PREVENTION OF NOCTURNAL HYPOGLYCEMIA IN ADULTS WITH TYPE 1 DIABETES UNDERGOING INTENSIVE MANAGEMENT

Maria Kalergis

School of Dietetics and Human Nutrition,
McGill University, Montreal

November 2002

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements of the degree of
Doctor of Philosophy

PREFACE

This thesis examines strategies for the prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management and the impact of one of these strategies on catecholamine response and symptom awareness to experimentally-induced hypoglycemia.

Chapter 1 provides the rationale and objectives of this doctoral research. A comprehensive review of the literature on type 1 diabetes, hypoglycemia, and prevention of nocturnal hypoglycemia is presented in chapter 2. The findings of this doctoral research are presented in the form of three manuscripts in chapters 3-5. Chapter 3 examines the impact of four different bedtime snack compositions on the prevention of nocturnal hypoglycemia using a randomized, controlled, crossover, inpatient study design. Chapter 4 extends the findings of chapter 3 in a nine month randomized, controlled, crossover trial comparing the efficacy of three treatment strategies on prevention of nocturnal hypoglycemia in free-living adults with type 1 diabetes. Chapter 5 compares the impact of one of the strategies employed in chapter 4 on catecholamine responses and symptom awareness to hypoglycemia using an experimental model of clinical hypoglycemia. The thesis ends with chapter 6 which provides a summary of the findings from chapters 3-5 and an overall conclusion.

ABSTRACT

The objectives of this research were to determine the impact of 4 different bedtime snack compositions on prevention of nocturnal hypoglycemia and to determine whether optimized titration and delivery of bedtime insulin using multiple daily injections of insulin (MDI) or continuous subcutaneous insulin infusion (CSII) could prevent nocturnal hypoglycemia in the absence of bedtime snacks. We also sought to determine whether 3 months of CSII therapy would improve catecholamine response and symptom awareness to experimentally-induced hypoglycemia. The need for and the most appropriate composition of bedtime snacks were dependent on the glycemic level at bedtime. No bedtime snacks were necessary at bedtime glycemic levels > 10 mmol/L. At bedtime glycemic levels between 7-10 mmol/L , a standard snack and cornstarch-containing snack worked best and at bedtime glycemic levels < 7mmol/L, a standard and protein-rich snack were most effective. Despite optimized titration and delivery of bedtime insulin, including the use of CSII, "the gold standard" of nocturnal insulin replacement, the incidence of nocturnal hypoglycemia over 181 nights was 54 episodes per 100 patient-nights. However, there was a substantial reduction, by 36% ($p=0.17$), in the incidence of nocturnal hypoglycemia with the use of bedtime snacks. Therefore bedtime snacks, tailored to the bedtime glycemic level, are recommended for all adults undergoing intensive management with MDI or CSII. Although, 3 months of CSII therapy did not improve catecholamine response and symptom awareness to experimentally-induced hypoglycemia, it did not deteriorate the responses either. Therefore, CSII therapy is a viable option in intensive management of adults with type 1 diabetes.

RÉSUMÉ

Les objectifs de cette recherche étaient de déterminer l'impact de 4 compositions différentes de collations au coucher sur la prévention des hypoglycémies nocturnes et de déterminer si la livraison optimisée de l'insuline au coucher en utilisant les injections multiples d'insuline (MDI) ou l'infusion sous-cutanée continue d'insuline (pompe à insuline) pourraient empêcher l'hypoglycémie nocturne en l'absence de collations au coucher. Nous avons également cherché à déterminer si 3 mois de thérapie avec la pompe amélioreraient la réponse des catécholamines et la reconnaissance des symptômes d'hypoglycémie. Le besoin de collation et la composition la plus appropriée de celles-ci au coucher dépendaient du niveau glycémique au coucher. Aucune collation au coucher n'était nécessaire aux niveaux glycémiques >10 mmol/L. Aux niveaux entre 7-10 mmol/L, une collation standard ou une collation avec fécule de maïs étaient les plus efficaces et aux niveaux glycémiques < 7mmol/L, une collation standard ou une collation riche en protéines étaient les plus efficaces. Malgré la livraison optimisée de l'insuline au coucher, même avec la pompe, l'incidence d' hypoglycémies nocturnes (n=181 nuits) fut de 54 épisodes par 100 patient-nuits. Cependant, il y avait une réduction substantielle, de 36% (p=0.17), de l'incidence d'hypoglycémie nocturne avec l'utilisation des collations au coucher. Par conséquent les collations au coucher sont recommandées pour tous les adultes traités par insulinothérapie intensive avec MDI ou pompe. Bien que 3 mois de thérapie avec pompe n'aient pas amélioré la réponse des catécholamines et la reconnaissance des symptômes d'hypoglycémie, il n'y a pas eu de détérioration non plus. Par conséquent, la thérapie par pompe est une option viable dans la thérapie intensive des adultes atteints d'un diabète de type 1.

THESIS GUIDELINES

This thesis uses a manuscript-based format consisting of three manuscripts as submitted or to be submitted for publication. In accordance with faculty regulations, the following five paragraphs are reproduced from the Guidelines for Thesis Preparation by the Faculty of Graduate Studies and Research.

> Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly-duplicated text of one or more published papers. These texts must be bound as an integral part of the thesis.
>
> If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all the requirements of the "Guidelines for Thesis Preparation." The thesis must include: A Table of Contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.

Additional material must be provided where appropriate (e.g. in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.

In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers.

ORIGINAL CONTRIBUTIONS

This doctoral research is original in regards to both the objectives proposed and the findings obtained.

There are several very important findings derived from the studies which comprise this doctoral research and which are considered a great advancement to knowledge in the area of prevention of nocturnal hypoglycemia in type 1 diabetes.

The design of the first study (chapter 3) is unique in that it is the first study to compare the efficacy of two macronutrient compositions: cornstarch and protein in the context of a bedtime snack against each other and against a clearly defined standard snack composition which is typical of that recommended in clinical practice. The study design is also unique in that meticulous attention was placed on consistency of the macronutrient compositions of the snacks so that only the variable of interest was isolated. In other words, the snacks were equivalent in all important aspects (e.g. Calories, fat and total available glucose) except for the variable of interest (ie- pure protein, raw cornstarch, cooked starch). As well, this is the first study to assess the role of bedtime snacks in the context of insulin lispro, an insulin analogue which is becoming the standard short-acting insulin for use in the clinical management of type 1 diabetes. Since studies have demonstrated reductions in the incidence of nocturnal hypoglycemia with the use of insulin lispro at supper instead of human regular insulin, some clinicians and investigators believe that bedtime snacks are no longer necessary.

Findings obtained from this first study (chapter 3) which are novel and considered an advancement to knowledge include the following:

1) A mediating effect of the bedtime blood glucose level with respect to the need for and composition of bedtime snacks. This is the first study to report that the need for a bedtime snack and the most appropriate composition is dependent on the blood glucose level at bedtime. Specifically, we found that a bedtime snack was not necessary if the bedtime blood glucose level was > 10 mmol/L. However, a bedtime snack is warranted for bedtime blood glucose levels < 10 mmol/L. A standard snack (defined as 2 starch + 1 protein exchange) is the most effective snack composition for bedtime blood glucose levels between 7-10 mmol/L and < 7mmol/L. A protein-enriched snack (1 starch + 3 protein exchanges) is most effective at bedtime blood glucose levels < 7mmol/L and a cornstarch-containing snack (1 starch + 14g raw cornstarch + 1 protein exchange) is most effective between 7-10 mmol/L.

2) Despite the use of lispro insulin, our findings confirmed that bedtime snacks are warranted, but only at bedtime blood glucose levels < 10 mmol/L.

3) In this study we observed a higher cut-off (ie- 10 mmol/L) for the bedtime blood glucose level than that reported in previous studies to be protective against nocturnal hypoglycemia (ie- approximately 7 mmol/L).

4) This is the first study to clearly delineate an important role of protein as part of a bedtime snack in the prevention of nocturnal hypoglycemia. For the equivalent amount of Calories and less carbohydrate, the protein-rich snack was equally effective as the standard snack in preventing nocturnal hypoglycemia.

5) Unlike all previous studies, we did not find that the use of raw cornstarch was superior than the other bedtime snack compositions in the prevention of nocturnal hypoglycemia, especially at bedtime blood glucose levels < 7 mmol/L.

The findings of the above study, specifically the use of bedtime snacks according to the bedtime glycemic level, were used in the design of the second study: the outpatient study (chapter 4). In designing the second study (chapter 4), our goal was to determine whether meticulous or optimized titration and delivery of bedtime insulin, using all available means proven to be effective to date, would be able to prevent nocturnal hypoglycemia without the use of bedtime snacks. In order to accomplish this goal, we designed a study whereby we compared the efficacy of three strategies used in the context of intensive management on prevention of nocturnal hypoglycemia. Specifically, we compared continuous insulin infusion (CSII), the "gold standard" of basal insulin replacement, especially for nocturnal control (without the use of bedtime snacks) to 2 strategies using multiple daily injections of insulin or MDI (with and without bedtime snacks). In all cases, insulin lispro was used. The design of the study is therefore unique in that it is the first study to compare these approaches, especially the role of CSII in prevention of nocturnal hypoglycemia. Furthermore, in this study continuous glucose monitoring technology was used to determine the incidence of nocturnal hypoglycemia. Therefore, this is also the first study to determine the incidence of nocturnal hypoglycemia in free-living individuals.

It is also one of the first studies to use continuous glucose monitoring technology as a tool to optimize titrations of insulin dose, specifically bedtime insulin.

Findings derived from this study (chapter 4) which are considered an advancement to knowledge include the following:

1) The incidence of nocturnal hypoglycemia in free-living adults with type 1 diabetes is determined for the first time to be 54 episodes per 100 patient-nights. In total, 98 episodes occurred over 181 nights in 97% of individuals. With respect to the strategies: 25 episodes occurred with strategy 1 (MDI with bedtime snack); 39 episodes occurred with strategy 2 (MDI with no bedtime snacks) and 34 episodes occurred with strategy 3 (CSII, no bedtime snacks). In comparison to strategy 2 which had the highest incidence, there was a 36% reduction in the incidence of nocturnal hypoglycemia with strategy 1 (MDI with bedtime snacks) which had the lowest incidence.

2) Although strategy 1 had the lowest incidence of nocturnal hypoglycemia, the duration of nocturnal hypoglycemia was significantly longer with strategy 1 compared to strategies 2 and 3 (319 ± 36 min versus 183 ± 27 min and 136 ± 28 min respectively, $p<0.001$).

3) This is the first study to document that the use of bedtime snacks, in comparison to strategies which did not include bedtime snacks, did not negatively impact on long-term glycemic control (HbA_{1c}), lipid profile, body weight, body composition or psychosocial adaptation, including quality of life.

4) Predictors or correlates of nocturnal hypoglycemia were identified for the first time and include: baseline and most recent HbA_{1c} level, bedtime blood glucose and morning blood glucose level.

The final study (chapter 5) was a sub-study of the outpatient study (chapter 4). The rationale behind the design of the final study (the hypoglycemic clamp study) was based on previous findings which have shown that avoidance of hypoglycemia, including nocturnal hypoglycemia, can ameliorate the defenses to ensuing hypoglycemia which appear to become attenuated over the natural course of type 1 diabetes and may be due to hypoglycemia itself.

Findings derived from this study (chapter 5) which are considered an advancement to knowledge include the following:

1) We found that our group of participants, with a mean duration of diabetes of 20.8 years, had catecholamine and symptom responses similar to that of healthy, non-diabetic individuals prior to CSII therapy.

2) Although, 3 months of CSII therapy did not improve catecholamine and symptom responses (as these were already normal), it did not deteriorate them either, as was the case in an earlier study.

3) Three levels of awareness during 40 minutes of hypoglycemia were identified for the first time. Participants were classified, post priori, as being completely unaware, partially aware and fully aware. Important observations were made among the 3 levels of awareness and catecholamine and symptom responses and cognitive function, some of which reached statistical significance.

In summary this doctoral thesis has made significant contributions to the existing literature in the areas of prevention of nocturnal hypoglycemia, CSII therapy and counterregulation to hypoglycemia in adults with type 1 diabetes undergoing intensive management.

CONTRIBUTIONS OF AUTHORS

Conception and Design

The Candidate was responsible for the conception and design of all the studies, including the protocol for the hypoglycemic clamp study, with input from the thesis supervisor, Dr. Jean-François Yale. Dr. Alicia Shiffrin, Dr. Réjeanne Gougeon and Dr. Peter JH Jones provided feedback with respect to the design of the studies during committee meetings.

Acquisition of Data

The candidate was solely responsible for the acquisition of all the data and for the management of all the studies.

Analysis and Interpretation of Data

The candidate was responsible for the data analyses and interpretation of the data with input from the thesis supervisor, Dr. Jean-François Yale.

Drafting of Manuscripts

The candidate was solely responsible for drafting all the manuscripts.

Critical Revision of Manuscripts

The thesis supervisor, Dr. Jean-François Yale, Dr. Alicia Shiffrin, Dr. Réjeanne Gougeon and Dr. Peter JH Jones reviewed all manuscripts and provided critical feedback.

CONTRIBUTIONS OF AUTHORS

Statistical Expertise

The candidate was solely responsible for decisions regarding sample size and the use of appropriate statistical analyses with input from the thesis supervisor, Dr. Jean François Yale, and a statistician when warranted

Obtaining Funding

The candidate was solely responsible for initiating and writing the operating grant for this doctoral research which was successfully funded by the Canadian Diabetes Association. The candidate served in the capacity of co-investigator in this grant application. The thesis supervisor, Dr. Jean-François Yale, Dr. Alicia Schiffrin and Dr. Réjeanne Gougeon reviewed the grant proposal and provided feedback.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Jean-François Yale, for providing me with a very nurturing and stimulating research environment. He is truly a role model as a human being, researcher, clinician and supervisor. I thank him very much for giving me the independence and confidence that I needed to successfully carry out the studies which comprise this doctoral research. I also extend my gratitude to my co-supervisor, Dr. Peter JH Jones and other members of my supervisory committee: Dr. Réjeanne Gougeon and Dr. Alicia Schiffrin for their advice and support. I would also like to thank the staff of the Clinical Investigation Unit and the Metabolic Day Centre. In particular, I wish to thank Dr. Sara Meltzer, MD who has been very involved with our studies and who provided feedback with respect to abstract and manuscript submissions. I am also grateful to Dr. Irene Strychar of the Université de Montréal for the support she has provided me through the years. I would like to extend a special thank you to the entire staff of the McGill Nutrition and Food Science Centre for their support and encouragement. I thank Josie Plescia for her patience and for her invaluable assistance with entry of the references for this thesis. I would like to thank Dr. Errol B. Marliss, the director of the McGill Nutrition and Food Science Centre, for his support and words of wisdom over the years and invaluable input regarding the third study (chapter 5) of this thesis. Finally, I wish to thank my family and friends who have encouraged me and kept me going throughout this journey. I especially would like to thank my husband, Richard, who has been my "rock" and who, as a person living with type 1 diabetes, has taught me to appreciate the personal side of this disorder. I dedicate this thesis to him.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Type 1 diabetes is defined as a chronic disease characterized by hyperglycemia due to destruction of the pancreatic beta cells, usually leading to an absolute insulin deficiency (Meltzer et al 1998; American Diabetes Association 2002). As such, individuals afflicted with this disorder must rely on exogenous insulin in order to survive.

In 1993 the landmark study, the Diabetes Control and Complications Trial (DCCT) provided unequivocal evidence that attainment of glycemic control as close to normal is necessary for the prevention and progression of chronic complications associated with type 1 diabetes which include: retinopathy, nephropathy, neuropathy and cardiovascular disease (The DCCT Research Group 1993). Attainment of optimal glycemic control , in the DCCT, was achieved via intensive management which consisted of intensive insulin therapy: multiple daily injections of insulin (MDI) and continuous subcutaneous insulin infusion (CSII); intensive nutritional counseling; frequent self-monitoring of blood glucose and frequent contact with the healthcare team (The DCCT Research Group 1995). Although, intensive management proved to be successful in achieving its goal of reducing the incidence and progression of chronic complications, intensive management was a also associated with a 3-fold increased risk of developing severe hypoglycemia and an increased risk of weight gain (The DCCT Research Group 1993). Severe hypoglycemia (defined as an episode requiring assistance to treat and associated with a blood glucose level <2.8 mmol/L) was found to occur primarily during sleep, especially overnight, between midnight and 8am (The DCCT Research Group

1991); and usually without warning (The DCCT Research Group 1991; The DCCT Research Group 1997). Despite, the adverse consequences of intensive management, the conclusion of the DCCT was that intensive management, with the goal of attaining glycemic control as close to normal as possible, should be implemented in the majority of individuals with type 1 diabetes, recognizing hypoglycemia as a major obstacle which future investigators must try to address (The DCCT Research Group 1993).

Hypoglycemia continues to be a major barrier to the attainment of optimal glycemic control in type 1 diabetes (Yale 2001). Part of the reason why hypoglycemia, specifically nocturnal hypoglycemia, is problematic is due to the inherent limitations of current insulin preparations to mimic normal physiology. In particular, current insulin preparations which are used for basal insulin replacement, particularly for overnight control (eg NPH and Ultralente) usually peak at the same time insulin requirements are at their nadir and begin to wane shortly thereafter, therefore predisposing the individual to both nocturnal hypoglycemia and morning (fasting) hyperglycemia (Bolli et al 1993, Lepore et al 2000). In addition to the limitations of current insulin preparations, individuals with type 1 diabetes, due to the nature of their disease, have compromised defenses to ensuing hypoglycemia (Gerich 1988; Bolli and Fanelli 1999). These compromised defenses include: diminished counterregulatory hormone responses to hypoglycemia (Bolli et al 1985; Gerich 1988; Bolli and Fanelli 1999), impaired awareness of hypoglycemia (Gold et al 1994; Cryer 1994), and alterations in the glycemic levels at which counterregulatory hormones are normally secreted and typical warning symptoms are perceived (Amiel et al 1988; Maran et al 1995).

These compromised defenses may have a common etiology: hypoglycemia itself (Cryer 1992). The theory of hypoglycemia-associated autonomic failure posits that antecedent hypoglycemia can reduce counterregulatory hormone responses and symptom awareness to subsequent hypoglycemia (Cryer 1992; Cryer 2001). Support for this theory is derived from studies which demonstrate that antecedent hypoglycemia, including nocturnal hypoglycemia, can diminish counterregulatory hormone responses and symptoms to ensuing hypoglycemia (Davis et al 1992; Ligenfelser et al 1993; Veneman et al 1993; Davis et al 1997).

Therefore, individuals with type 1 diabetes, due to the nature of their disease and reliance on exogenous insulin replacement which is far from ideal, are predisposed to an increased risk of hypoglycemia which in turn predisposes to more hypoglycemia leading to a vicious cycle, whereby hypoglycemia begets hypoglycemia (Cryer 1994; Cryer 2001). Furthermore, it has been recently shown that sleep itself causes a further diminution of the catecholamine response to hypoglycemia (Jones et al 1998).

Despite the fact that nocturnal hypoglycemia is recognized as a major obstacle in the management of type 1 diabetes, there is a paucity of scientific evidence regarding the frequency of its occurrence and potential strategies for its prevention. Strategies for prevention of nocturnal hypoglycemia, to date, have focused on the use of more physiologic insulin preparations (Ahmed et al 1998; Heller et al 1999) and insulin delivery regimens (Kanc et al 1998; Fanelli et al 2002) and on the use of bedtime snacks (Schiffrin and Suissa 1987; Whincup and Milner 1987; Bendtson et al 1988; Vervoort et al 1996), with emphasis on specific bedtime snack compositions (Ververs et al 1992; Kaufman and Devgan 1996; Kaufman et al 1996; Saleh and Cryer 1997; Axelsen et al

1999). However, strategies for prevention of nocturnal hypoglycemia have not been adequately addressed in any North American clinical practice guidelines (Meltzer et al 1998; American Diabetes Association 2002; Yale et al 2002) including in the recently published evidence-based guidelines for the prevention and management of hypoglycemia, due to a lack of available scientific data (Yale et al 2002).

Therefore, the main goal of the following three studies, which comprise this doctoral dissertation, was to address the urgent need for more research in the area of prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management and thus advance the knowledge base in this very important and lacking area.

1.1 Research Objectives and Hypotheses

Objective 1: To assess the impact of different bedtime snack compositions on prevention of nocturnal hypoglycemia, without compromising overnight and morning (fasting) glycemic control.

Hypothesis 1: A bedtime snack which provides a continuous (cornstarch) or a delayed (protein) source of glucose will be more effective at preventing nocturnal hypoglycemia than a standard snack composition

Objective 2: To determine the impact of optimized titration and delivery of bedtime insulin using CSII and MDI, in the absence of bedtime snacks, on prevention of nocturnal hypoglycemia compared to optimized titration and delivery of bedtime insulin using MDI in the context of bedtime snacks, without compromising metabolic control and quality of life, in free-living adults with type 1 diabetes undergoing intensive management.

Hypothesis 2: Optimized titration and delivery of bedtime insulin using CSII will result in less nocturnal hypoglycemia compared to MDI (with or without bedtime snacks)

Objective 3: To determine the impact of optimized titration and delivery of bedtime insulin using CSII, the "gold standard" of nocturnal insulin replacement, on catecholamine response and symptom awareness to experimentally-induced hypoglycemia.

Hypothesis 3: Optimized titration and delivery of bedtime insulin using CSII will result in improved catecholamine response and symptom awareness to experimentally-induced hypoglycemia

These research objectives and hypotheses have been addressed in the form of three distinct studies which are described in the manuscripts which are found in chapters 3, 4 and 5.

1.2 References

American Diabetes Association: Clinical practice recommendations 2002. Diabetes Care 25 (suppl 1): s1-s147, 2002

Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 37: 901-907, 1988

Ahmed ABE, Home PD: The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. Diabetes Care 21: 32-37. 1998

Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. J Int Med 245: 229-236, 1999

Bendtson I, Kverneland A, Pramming S, Binder C: Incidence of nocturnal hypoglucemia in insulin-dependent diabetic patients on intensive therapy. Acta Med Scand 223: 543-548, 1988

Bolli G, De Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. Diabetes 32: 134-141, 1983

Bolli GB, Fanelli CG: Physiology of glucose counterregulation to hypoglycemia. Endocrinol Metab Clin North Am 28 (3): 467-93, 1999

Cryer PE, Fisher JN, Shamoon H: Hypoglycemia: Technical Review. Diabetes Care 17 (7): 734-755, 1994

Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a viscious cycle. Diabetes 41: 1335-1340, 1992

Cryer PE: Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 281: E1115-E1121, 2001

Davis MR, Mellman M, Shamoon H: Further defects in counter-regulatory responses induced by recurrent hypoglycemia in IDDM. Diabetes 41: 1335-1340, 1992

Davis SN, Shavers C, Mosqueda-Garcia R,Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. Diabetes 46 (8): 1328-1335, 1997

Gerich JE: Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37: 1608-1617, 1988

Gold AE, MacLeod KM, Frier BM: Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 17 (7): 697-703, 1994

Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia in IDDM children. Diabetes Care 338: 1657-1662, 1998

Heller SR, Amiel S, Mansell P, UK Lispro Study group: Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 22 (10): 1607-1611, 1999

Kanc K, Janssen MJ, Keulen ETP, Jacobs MAJM, Popp-Snijders C, Snoek FJ, Heine RJ: Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen imporves counterregulatory hormonal responses and warning symptoms of hypoglcyemia in IDDM. Diabetologia 41: 322-329, 1998

Kaufmann F, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type 1 diabetes. J Diab and Comp 10: 84-87, 1996

Kaufman FR, Halvorson M, Kaufman ND: A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at Diabetes Camp. Diab Res Clin Pract 1: 1-5, 1996

Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 49 (12): 2142-2148, 2000

Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UM, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. Diabetes 42: 610-618. 1993

Maran A, Crepaldi C, Tiengo A, Grassi G, Vitali E, Pagano G, Bistoni S, Calabrese G, Santeusanio F, Leonetti F, Ribaudo M, Di Mario U, Annuzzi G, Genovese S, Riccardi G, Previti M, Cucinotta D, Giorgino F, Bellomo A, Giorgino R, Poscia A, Varalli M: Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter analysis. Diabetes Care 25 (2): 347-52, 2002

Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D: 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ 159 (suppl 8): s1-s29, 1998

Saleh T, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes 20 (8): 1236-1236, 1997

Schiffrin A, Suissa S: Predicting nocturnal hypoglycemia in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Am J Med 82: 1127-1132, 1987

The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90: 450-459, 1991

The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 329: 977-986, 1993

The DCCT Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 18 (3): 361-76, 1995

The DCCT Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes 46 (2): 271-86, 1997

Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of Hypoglycemia Unawareness by Asymptomatic Nocturnal Hypoglycemia. Diabetes 42: 1233-1237, 1993

Yale JF: Hypoglycemia, In: Evidenced-Based Diabetes Care, Gerstein HC, Haynes RB, Editors. 2001, BC Decker Inc: Hamilton/London. p. 380-395.

Yale JF, Begg I, Gerstein H, Houlden R, Jones H, Maheux P, Pacaud D. 2001 Canadian Diabetes Association Clinical Practice Guidelines for the prevention and management of hypoglycemia in diabetes. Can J Diabetes 26 (1): 22-35, 2002

CHAPTER 2

LITERATURE REVIEW

This literature review is comprised of three major topics which provide the needed background to support the rationale for the studies which follow and are presented in chapters 3-5.

The literature review begins with section 2.1 which provides a comprehensive overview of type 1 diabetes including current definition, classification and etiology of type 1 diabetes, followed by an extensive review of the management of type 1 diabetes including issues regarding insulin replacement, intensive management and the most current clinical practice guidelines. In section 2.2, the main obstacle in the management of diabetes, hypoglycemia, is addressed in a comprehensive review which includes definition, classification, etiology and risk factors for hypoglycemia followed by the reasons for increased risk of hypoglycemia in type 1 diabetes, particularly nocturnal hypoglycemia. The chapter ends with a critical review on the prevention of nocturnal hypoglycemia in type 1 diabetes.

This literature review is based on original research, review articles, meta-analyses and the most recent evidence-based guidelines in the management of diabetes and hypoglycemia. Articles published in English since 1966 were identified using MEDLINE, CINAHL and PUBMED. Other pertinent articles identified by perusing the reference list in the articles obtained by the indices aforementioned, were also obtained for inclusion in this review. Preference was given to "landmark" studies irrespective of year since publication and to more recent studies, within the past 10 years.

2.1 Type 1 Diabetes Mellitus

2.1.1 Definition and Classification of Type 1 Diabetes Mellitus

Diabetes is defined as a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both (Meltzer et al 1998). This definition encompasses all forms of diabetes including: type 1 diabetes, type 2 diabetes, gestational diabetes and other specific types (Meltzer et al 1998).

In 1995, an international expert committee working under the auspices of the American Diabetes Association (ADA) was established to review the National Diabetes Data Group's (NDDG's) 1979 classification and diagnostic criteria for diabetes (Meltzer et al 1998).

The classification of the various forms of diabetes is currently based on etiology, not on insulin treatment. Therefore, according to the new classification system the old terms of "insulin-dependent diabetes mellitus" (IDDM) and "non-insulin-dependent diabetes mellitus" (NIDDM) should be eliminated and replaced by "type 1" and "type 2" diabetes (using Arabic rather than Roman numerals) (Meltzer et al 1998). In accordance with this new classification system, type 1 diabetes encompasses diabetes that is primarily a result of pancreatic beta-cell destruction. This form includes cases due to an autoimmune process and those for which the etiology of beta-cell destruction is unknown (Meltzer et al 1998).

Type 1 diabetes is therefore defined as a chronic disease characterized by hyperglycemia due to destruction of the pancreatic beta cells, usually leading to an absolute insulin deficiency (Meltzer et al 1998; American Diabetes Association 2002). As such, individuals afflicted with this disorder must rely on exogenous insulin in order to survive. Type 1 diabetes was also formerly referred to as juvenile-onset diabetes (American Diabetes Association 2002). Although type 1 diabetes usually develops before 30 years of age, it can occur at any age (Lawson and Muirhead 2001).

2.1.2 Etiology of Type 1 Diabetes

The etiology of type 1 diabetes is multifactorial, with genetics playing a significant role (Lawson and Muirhead 2001). Type 1 diabetes is also a polygenic disorder, with at least 15 different genes contributing in varying degrees. However, the single most important genetic determinant in type 1 diabetes is the histocompatibility locus (HLA) on chromosome six, in particular HLA-DR and HLA-DQ alleles (Lawson and Muirhead 2001).

The discordance in the development of type 1 diabetes in identical twins (30%) indicates that the etiology is only partly genetic, suggesting that other factors may play a role. Risk factors for which evidence exists include dietary triggers (cow's milk, caffeine, and nitrites), enterovirus infections during childhood and perhaps during pregnancy, and possibly psychosocial events in early childhood (Lawson and Muirhead 2001). Most individuals with type 1 diabetes have immune-mediated disease caused by cellular-mediated autoimmune

destruction of the insulin-producing beta cells of the pancreas. However, there is a small group of individuals with type 1 diabetes who have no evidence of autoimmunity or other known etiology; this condition is referred to as "idiopathic type 1 diabetes" (Lawson and Muirhead 2001).

2.1.3 Incidence and Prevalence of Type 1 Diabetes

There is extremely wide geographic and racial variability in the incidence of type 1 diabetes. Incidence rates worldwide vary 40-fold, between 0.6 per 100,000 per year in Mexico and Korea to 35.3 per 100,000 per year in Finland. Furthermore, type 1 diabetes is much more common in Caucasians than in Blacks, Asians, or Hispanics (Lawson and Muirhead 2001).

Currently, the diagnosis of diabetes has been made in approximately 5% of Canadians or 1.5 million people (Meltzer et al 1998). Approximately 10% of these cases (150,000) represent type 1 diabetes with the remainder being type 2. This number is expected to reach 3 million by the year 2010 (Meltzer et al 1998).

There is a large body of evidence supporting an environmental influence on the development of type 1 diabetes (Lawson and Muirhead 2001). The incidence of type 1 diabetes appears to be much higher in northern than in southern hemispheres (Lawson and Muirhead 2001). There has been a high positive correlation found between incidence and latitude and a negative correlation between incidence and average yearly temperature (Lawson and Muirhead 2001).

Type 1 diabetes is rare before 6 months of age. After 9 years of age, the incidence rises sharply, peaking between 9 and 13 years, with a decline in incidence thereafter (Lawson and Muirhead 2001). The incidence of type 1 diabetes after age 30 varies depending on the diagnostic criteria used but was found to be 9.6 per 100,000 per year when strict criteria were used in a population-based study in Coppenhagen (Lawson and Muirhead 2001).

Incidence rates in males and females are similar overall, although type 1 diabetes is more common in males than in females < 7 years of age and more common in females than in males from 7 to 13 years of age, with similar rates for males and females thereafter (Lawson and Muirhead 2001).

2.1.4 Presentation and Diagnosis of Type 1 Diabetes

The clinical presentation of type 1 diabetes ranges from mild nonspecific symptoms or no symptoms to coma (Lawson and Muirhead 2001). At presentation, most patients are thin and have experienced weight loss, polyuria (frequent urination), polydipsia (increased thirst) and fatigue. These are the classical symptoms of diabetes which are caused by marked hyperglycemia (American Diabetes Association 2002). In addition to the classical symptoms aforementioned, approximately 25% of individuals with type 1 diabetes also present with ketoacidosis (Lawson and Muirhead 2001) which is not very common in the presentation of type 2 diabetes (American Diabetes Association 2002).

The diagnosis of diabetes in non pregnant individuals can be made in three ways (Meltzer et al 1998; American Diabetes Association 2002). The diagnostic criteria and the glucose thresholds (based on laboratory measurements of venous plasma samples) are as follows:

- Symptoms of diabetes plus a casual plasma glucose value ≥ 11.1 mmol/L

OR

- A fasting plasma glucose (FPG) ≥ 7.0 mmol/L

OR

- A plasma glucose value in the 2-h sample (2hPG) of the oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L

A confirmatory test must be done in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation (Meltzer et al 1998). Casual is defined as any time of the day, without regard to the interval since the last meal. Fasting is defined as no caloric intake for at least 8 hours (Meltzer et al 1998).

Previous diagnostic criteria were based on a fasting plasma glucose value of ≥ 7.8 mmol/L. However, this level was found to lack sensitivity as a significant proportion of individuals, who would have otherwise been diagnosed with diabetes had they underwent a 2-h 75g oral glucose tolerance test, remained undiagnosed (Meltzer et al 1998). The diagnostic threshold of 11.1 mmol/L used for the 2-h sample in the oral glucose tolerance test (OGTT) is based on the risk of developing microvascular complications (Meltzer et al 1998).

A recent re-evaluation of population studies suggests that a fasting plasma glucose threshold of 7.0 mmol/L correlates most closely with a 2hFPG level of 11.1 mmol/L and best predicts the development of microvascular disease (Meltzer et al 1998).

2.1.5 Management of Type 1 Diabetes

Prior to the discovery of insulin (Banting and Best 1922), type 1 diabetes was often a fatal condition (Bliss M 2002). Over the past 8 decades, insulin has evolved to the point where human insulin, produced by recombinant DNA technology, is standard therapy for people with diabetes who require insulin (Meltzer et al 1998).

a) Insulin Replacement

The goal of insulin replacement by exogenous insulin is to mimic the normal physiology of endogenous insulin secretion that would occur in individuals without diabetes (Simpson and Toth 2002). Insulin is normally secreted from pancreatic beta cells in response to changes in the concentration of plasma glucose as will be discussed in more detail in section 2.2.

Conventional insulin formulations are typically grouped into rapid, intermediate and long acting preparations according to their action profiles (Simpson and Toth 2002). The onset and duration of action of conventional insulin preparations are modified by the addition of zinc and protamine to human insulin (Simpson and Toth 2002). These substances act to stabilize the insulin

structure and delay absorption from subcutaneous injection sites (Simpson and Toth 2002). Rapid-acting or short-acting insulin is used primarily for postprandial glycemic control whereas intermediate and long acting insulin is used primarily for basal replacement (Lepore et al 2000). Short-acting insulin consists of human regular insulin which has an onset of action of 0.5-1 hour, peak activity at approximately 2-4 hours and a maximum duration of 6-8 hours. Intermediate-acting insulin, which includes the insulin preparations: NPH and Lente, has an onset of action of about 2-4 hours, peak activity at 4-12 hours and a maximum duration of 16-24 hours. Long acting insulin which consists of the preparation Ultralente has an onset of activity of 4-6 hours, peaks at 8-24 hours and has a maximum duration of 24-30 hours (Simpson and Toth 2002). In a recent study in type 1 diabetes, it was shown that the peak action of NPH insulin, which is commonly used as a basal insulin, particularly overnight, has a peak activity at 4.5 hours followed by waning (Lepore et al 2000).

The pharmacokinetics of injected insulin are dependent on several factors which include: type and concentration of insulin, dose, injection technique, site of injection (Binder et al 1984).

After injection, insulin is absorbed into the blood stream by which it reaches its target tissue and its sites of degradation (Binder et al 1984). The rate of absorption depends on the physical state of insulin, the volume injected, the insulin concentration, blood flow and the presence or absence of degradation at the site of injection (Binder et al 1984). The absorption rate is significantly correlated to blood flow. For example, the rate of absorption is higher from the

abdominal area compared to the femoral area due to differences in blood flow. The slowing effect of smoking on absorption of regular insulin is likely related to to a reduction in blood flow secondary to peripheral vasoconstriction induced by smoking (Binder et al 1984).

Although human insulin formulations have been a mainstay of insulin replacement, they have not been able to mimic normal physiology (Simpson and Toth 2002). Some of the reasons given to explain why conventional insulin preparations have been unable to mimic physiological insulin secretion include: slow and variable absorption from subcutaneous injection sites, antibody binding, nonphysiological route of delivery (ie- not via portal vein as per endogenous insulin), inadequacy of current basal preparations to provide smooth 24-hour coverage and finally, difficulty in estimating the required amount of insulin prior to each meal (Simpson and Toth 2002).

Some of the problems described above are being addressed with the development of insulin analogues.

i) Insulin Analogues

Insulin in concentrated solutions associates as dimers and hexamers resulting in a lag phase in the absorption of regular human insulin (Madsbad 2002; Simpson and Toth 2002). The formation of hexamers is considered a rate-limiting step in the absorption of insulin (Simpson and Toth 2002). Strategies to reduce this self-association include development of insulin analogues (Simpson and Toth 2002). Genetic manipulation of insulin's amino acid sequence has produced several analogues that have significantly reduced self-association and remain as monomers in solution (Simpson and Toth 2002).

Insulin lispro was the first rapid-acting insulin analogue to be approved for use in Canada, under the brand name Humalog ®. Insulin lispro differs from regular human insulin by only 2 amino acids, with the sequence of proline and lysine amino acids near the COOH-terminal of the B-chain being reversed (Simpson and Toth 2002). Insulin lispro has an onset of action of 0.25-0.5 hours, a peak action at 0.5-1.5 hours and a duration of 3-4 hours (Hopkins 2002). Several studies comparing insulin lispro with regular human insulin have demonstrated improved postprandial glycemic control and reduced frequency of hypoglycemia (Anderson et al 1997; Jacobs et al 1997; Zinman et al 1997; Ahmed and Home 1998; Heller et al 1999) including nocturnal hypoglycemia (Ahmed and Home 1998; Heller et al 1999). Improvements in long-term glycemic control (HbA_{1c}) with insulin lispro compared to regular insulin have been demonstrated in some studies (Zinman et al, 1997; Jacobs et al 1997; Ebeling et al 1997; Tsui et al 1998) but not in others (Anderson et al 1997; Heller et al 1999;

Renner et al 1999). Since insulin lispro has a shorter duration of action than human regular insulin, adequate basal insulin coverage becomes more pertinent with the use of insulin lispro (Ebeling et al 1997; Lalli et al 1999). Insulin lispro has also been shown to be the preferred insulin for use in continuous subcutaneous insulin infusion (CSII) or insulin pump therapy (Renner et al 1999, Hanaire-Broutin 2000; Tsui et al, 2001). Furthermore, insulin lispro has been associated with increased treatment satisfaction and no negative impact on weight gain (Ebeling et al 1997) or counterregulatory hormone responses (Tsui et al 1998), despite improved glycemic control (Ebeling et al 1997; Tsui et al 1998).

Insulin aspart is the second rapid-acting insulin analogue approved for use in Canada and Europe under the brand name NovoRapid®, and in the United States under the brand name NovoLog® (Simpson and Toth 2002). In this insulin analogue, the amino acid proline on the B-chain is replaced with aspartic acid. Preliminary clinical studies in type 1 diabetes comparing human regular insulin with aspart have demonstrated lower postprandial hyperglycemia and slightly improved HbA_{1c} (Simpson and Toth 2002).

The first long acting insulin analogue, insulin glargine is currently approved for use in Canada and the U.S. under the brand name Lantus ®, but is not yet available in Canada. Compared to human regular insulin, there are 3 modifications to the insulin glargine molecule. Glycine replaces asparagine at position 21 on the A-chain and 2 arginine amino acids are added to the COOH-terminal of the B-chain (Simpson and Toth 2002). The modifications that are made, in this case, retards the absorption from subcutaneous injection sites

resulting in a basal supply of insulin similar to normal basal release patterns from the pancreas (Simpson and Toth 2002). Preliminary studies have shown that compared to NPH insulin, glargine insulin is relatively peakless and closely mimics insulin delivery by continuous subcutaneous insulin infusion, the gold standard of basal insulin replacement (Lepore et al 2000; Madsbad 2002). In a multicentre, randomized study in type 1 diabetes comparing insulin glargine with NPH insulin, there was a slight improvement in HbA_{1c} with insulin glargine and a significant reduction in fasting blood glucose and nocturnal hypoglycemia (Ratner et al 2000). In his review of the literature on insulin analogues, Madsbad (Madsbad 2002) concludes that studies with insulin glargine, thus far, appear to indicate that insulin glargine is relatively peakless with a long duration of action (> 24 hours) and with little day-to-day variation in absorption (Madsbad 2002). Furthermore, insulin glargine appears to cause less hypoglycemia, especially during the night, compared with intermediate NPH insulin (Madsbad 2002).

The development of new insulin preparations, with more physiological action profiles, is one major step to improving the replacement of insulin in type 1 diabetes. Another very important step with respect to optimizing insulin replacement is in regards to insulin delivery regimens, particularly in the context of intensive management.

b) Intensive Management

i) The Diabetes Control and Complications Trial (DCCT)

The Diabetes Control and Complications Trial (DCCT) is a landmark study which revolutionized the management of type 1 diabetes. The DCCT was a randomized, controlled trial which consisted of 1,441 individuals with type 1 diabetes, aged 13-39 years, from 29 centres in the U.S. and 3 centres in Canada. The goal of the study was to compare intensive versus conventional management on the prevention and progression of complications, namely retinopathy (The DCCT Study Group 1993; The DCCT Study Group 1995). Intensive management was comprised of several important components including intensive insulin therapy which consisted of multiple daily injections of insulin or MDI (3 or more injections of insulin per day) or continuous subcutaneous insulin infusion (CSII) via an external insulin pump. Species of insulin used included animal (pork, beef) and human insulin, with the use of the latter increasing as the study progressed (The DCCT Research Group 1995). Intensive management was also associated with specific glycemic targets. Goals for blood glucose levels, measured at least four times per day, were as follows: fasting and pre-meal (4-7mmol/L), postprandial <10mmol/L and 3:00am (measured weekly) > 3.6 mmol/L and HbA_{1c} < 6.05% ((The DCCT Research Group 1995). No glycemic goals were established for conventional management. The primary goals of conventional management were: absence of symptoms attributable to hyperglycemia or hypoglycemia, absence of ketonuria, and maintenance of normal growth and development (The DCCT Research Group 1993; The DCCT

Research Group 1995). After a mean follow-up of 6.5 years (range: 3 to 9 years), intensive management resulted in a significant improvement in glycemic control compared to conventional management (mean HbA_{1c}: 7.0 versus 9.0 respectively, $p<0.001$). Although less than 5% of individuals were able to attain normal glycemic control (HbA_{1c} <6.05%), the glycemic control achieved with intensive management resulted in substantial and significant reductions in the development and progression of chronic complications (The DCCT Research Group 1993) Intensive management reduced the mean risk of retinopathy, in the primary prevention group, by 76% (95% CI: 62 to 85%) and progression of retinopathy by 54% (95% CI: 39 to 66%). Each 1.0 unit decrease in HbA_{1c} represents a reduction in the development of retinopathy of approximately 36%. Furthermore, there is no glycemic threshold (short of normal glycemia) below which there is no risk for complications (The DCCT Research Group 1993). Intensive management also significantly reduced the risk of nephropathy and neuropathy (The DCCT Research Group 1993) and the development of hypercholesterolemia (The DCCT Research Group 1993). Intensive management with CSII resulted in improved HbA_{1c} compared to MDI (6.8% vs. 7.0% respectively, $p<0.05$). However, given the non-random assignment of these two modes of insulin delivery any conclusion drawn must be viewed with caution.

Intensive management consisted of more than just intensification of insulin delivery. Intensive management also consisted of several important components which are described below.

ii) Components of Intensive Management

Blood Glucose Monitoring

Frequent monitoring of blood glucose was a key feature in the intensive management group. Participants were instructed to perform a minimum of 4 tests per day consisting of 3 pre-meal and one bedtime sample and a test at 3:00 am once per week. A variety of commercially available glucose meters were used during the trial, including meters with memory as they became available (The DCCT Research Group 1995). HbA_{1c} levels were measured monthly with a goal of attaining an HbA_{1c} level of <6.05%. In contrast, participants in the conventional management group were instructed to perform at least one capillary test per day and had HbA_{1c} levels measured every 3 months, the results of which both the investigator and participant were blinded to unless the HbA_{1c} exceeded 13.3%, at which time prompt corrective action was required (The DCCT Research Group 1995).

Nutritional Intervention

Nutritional counseling was conducted by registered dietitians at each center. The goals of diet composition were similar for the two groups and consisted of a prescribed caloric level to achieve and maintain 90-120% of ideal body weight and/or support normal growth and development. Diet composition goals were 10-25% of calories from protein, 30-35% of calories from fat and 45-55% of calories from carbohydrate with ≤ 25% of carbohydrate from simple sugars. All participants were also instructed in the Step I diet of the National Cholesterol Education Program with further counseling and advice on the Step II diet and cholesterol lowering medication, if necessary (The DCCT Research Group 1995). Exercise was encouraged according to the individual's interest and physical fitness. Participants were taught to adjust insulin doses and diet to accommodate exercise with emphasis placed on avoidance of hypoglycemia (The DCCT Research Group 1995).

In addition to the conventional nutritional counseling outlined above, participants in the intensive group received more frequent and detailed instruction on the role of diet in attaining normoglycemia. Centres had the choice of a variety of nutritional strategies which were individualized to each participant's needs and preferences. The main emphasis of nutritional counseling was the attainment of glycemic goals which took precedence over other dietary goals (The DCCT Research Group 1993; The DCCT Research Group 1995). Specific nutritional interventions, which primarily focused on carbohydrate consistency, included: healthy food choices, the ADA exchange system, carbohydrate counting

using insulin to carbohydrate ratios, total available glucose (TAG) (The DCCT Research Group 1993). Although the study design precluded comparisons among the specific nutrition interventions that were used, the key feature that they all had in common, was flexibility with respect to adjustments of insulin for food intake (The DCCT Research Group 1993).

Flexibility with respect to adjustments of insulin for food intake was also identified as being very important in a randomized, controlled study which compared three treatment approaches used in intensive management of adults with type 1 diabetes (Kalergis et al 2000).

The important role that diet played in the attainment of glycemic goals in the DCCT is highlighted in a study which identified specific diet behaviours that were conducive to better glycemic control (Delahanty and Halford 1993). The study identified four diet-related behaviours that were associated with maintenance of lower HbA_{1c} levels: adherence to diet, prompt treatment of hyperglycemia, avoidance of overtreatment of hypoglycemic reactions with food, and avoidance of extra snacks (Delahanty and Halford 1993). Two other behaviours were also identified that resulted in lower HbA_{1c} levels, albeit to a lesser degree: adjusting insulin for food intake and consistency in taking the prescribed bedtime snack (The DCCT Research Group 1993). The average HbA_{1c} among intensively managed patients who reported that they followed these specific diet-related behaviours was 0.25 to 1.0 unit lower than among participants who did not follow these behaviours (Delahanty and Halford 1993).

In addition to the above components, people in the intensive group also received very frequent contact with the study team including weekly telephone contact and monthly clinic visits. The purpose of the visits and telephone contact was to review glycemic control, reinforce goals and principles of intensive management, and adjust treatment regimen which included insulin scales, diet, exercise and glucose monitoring to achieve glycemic goals (The DCCT Research Group 1995).

The DCCT provided very convincing evidence that intensive management, with the goal of attaining glycemic control as close to normal as possible, prevents the development and progression of chronic complications. However, intensive management as carried out in the DCCT, was also associated with two major adverse consequences: increased risk of severe hypoglycemia and weight gain.

ii) Consequences of Intensive Management

Severe Hypoglycemia

Intensive management was associated with a 3-fold increased risk of developing severe hypoglycemia compared to conventional management (The DCCT Research Group 1993).

Severe hypoglycemia was defined as an episode with symptoms consistent of hypoglycemia, in which the patient required the assistance of another person and which was associated with a blood glucose level < 2.8 mmol/L or prompt recovery after oral carbohydrate, glucagon injection or intravenous glucose (The DCCT Research Group 1997).

There were a total of 3,788 episodes of severe hypoglycemia (requiring assistance); 1,027 of these episodes were associated with coma and/or seizure (The DCCT Research Group 1997). A total of 65% of patients in the intensive group versus 35% of patients in the conventional group had at least one episode of severe hypoglycemia by the end of the study. The overall rates were 61.2 episodes per 100 patient-years in the intensive group versus 18.7 episodes per 100 patient-years in the conventional group, with a relative risk of 3.28 (The DCCT Research Group 1997). In the feasibility phase of the study, it was shown that a substantial proportion (approximately 40%) of severe hypoglycemic episodes occurred during the night (between midnight and 8:00am) in both treatment groups (The DCCT Research Group 1991). Furthermore, more than half of the episodes occurred during sleep and without warning symptoms (The DCCT Research Group 1991).

Subgroups and significant risk factors were identified for increased risk of severe hypoglycemia and included male gender, adolescents, subjects with no residual insulin (C-peptide) or with a prior history of severe hypoglycemia (The DCCT Research Group 1997). Within both treatment groups, patients who experienced severe hypoglycemia were at increased risk of subsequent episodes. Approximately 30% of individuals in both groups experienced a second episode within 4 months following the first episode of severe hypoglycemia (The DCCT Research Group 1997). The number of prior severe hypoglycemic episodes was the strongest predictor of risk of future episodes, followed closely by the current HbA_{1c} value. However, after adjustment of the current HbA_{1c} level, intensive management was still associated with a significantly increased risk of hypoglycemia, indicating that the increased risk with intensive treatment is not completely explained by differences in HbA_{1c} values (The DCCT Research Group 1997). Patients who used higher insulin doses (U/kg) at baseline also had significantly higher rates of hypoglycemia in both treatment groups. The rates of hypoglycemia were also examined within clinics. In all but two clinics, there was a greater risk of hypoglycemia among patients treated intensively. In 19 of the 29 centres, the relative risk for intensive vs. conventional treatment was > 2 (The DCCT Research Group 1997). Despite the increased number of severe hypoglycemic episodes with intensive management, there were no changes in cognitive function based on serial neuropsychological testing (The DCCT Research Group 1993).

Aside from a significantly increased risk of severe hypoglycemia, intensive management was also associated with increased weight gain.

Weight Gain

Intensive management was associated with an increase of 33% in the mean adjusted risk of becoming overweight (>120% ideal body weight). Intensive management consisted of 12.7 cases of overweight per 100 patient-years versus 9.3 in the conventional group (The DCCT Research Group 1993). At five years, participants in the intensive group had gained a mean of 4.6 kg more than participants receiving intensive management (The DCCT Research Group 1993).

The increased weight gain was already apparent during the first year of the feasibility phase (The DCCT Research Group 1988). Participants in the intensive group gained significantly more weight than those in the conventional group (mean 5.1kg versus 2.4 kg respectively, $p<0.0001$) (The DCCT Research Group 1988). Furthermore, participants with one or more severe hypoglycemic episodes gained more weight than intensively treated subjects with no severe episodes. A higher baseline HbA_{1c} level and greater decrements in HbA_{1c} during intensive management were both associated with greater weight gain (The DCCT Research Group 1988).

The reasons for and composition of weight gain associated with intensive management were presented in a study shortly after the DCCT results were announced (Carlson and Campbell 1993). In this study of 6 adults with type 1 diabetes, weight gain secondary to intensive management was identified as being

associated with an increase in fat mass and largely due to improved glycemic control (ie- decrease in glycosuria). A total of 70% of the weight gain was associated with a decrease in glycosuria with the remainder due to a reduction in 24-h energy expenditure (related to a decrease in futile cycling) (Carlson and Campbell 1993).

A recent study presented the results with respect to the influence of intensive management on body weight and body composition in the DCCT cohort (The DCCT Research Group 2001). The approximately 5 kg gain in weight, on average, with intensive management represented excess increases in body mass index (BMI) of 1.5 kg/m^2 among men and 1.8 kg/m2 among women (The DCCT Research Group 2001). Major weight gain (BMI increase $\geq$ 5 kg/m^2) was associated with higher percentages of both body fat and fat-free mass, whereas among participants without major weight gain, intensive management was associated with greater fat-free mass with no difference in adiposity. Therefore, the additional weight gain with intensive therapy appears to include both lean tissue as well as fat mass (The DCCT Research Group 2001).

The increased weight gain with intensive management can not be explained by ingestion of excess calories since both groups had similar and not significantly different intakes of calories and macronutrients (The DCCT Research Group 1995). The increase in weight with intensive management is likely due to improved glycemic control (Carlson and Campbell 1993). Patients initiated on intensive management should therefore be advised of the possibility of weight gain so that appropriate precautions can be taken.

Despite the limitations associated with intensive management, the conclusions of the DCCT indicated that the benefits to be gained with intensive management outweigh the risks. Therefore, intensive management is recommended for most individuals with type 1 diabetes, with the goal of maintaining glycemic status as close to normal as is safely possible (The DCCT Research Group 1993). It was further concluded that the challenge for future investigators is to develop treatment methods that will afford the benefits of improved glucose control with reduced risk of hypoglycemia (The DCCT Research Group 1997).

The DCCT provided convincing evidence that it may be possible to obtain good, although not normal, glycemic control in relatively young, highly motivated individuals. Intensive therapy in not highly selected individuals, followed in a typical clinical setting for four years resulted in a mean HbA_{1c} level of 7.8 (7.1 to 8.4), higher than the level attained in the DCCT. Therefore, the full benefits of intensive therapy may be difficult to realize in typical clinical settings where the resources that were available to the DCCT are limited.

Intensive management in the DCCT consisted of either multiple daily injections of insulin (MDI) or continuous subcutaneous insulin infusion (CSII) via an external insulin pump (The DCCT Research Group 1993; The DCCT Research Group 1995). Although, comparisons between these two modes of insulin delivery were limited by the non-random assignment of these groups, it was shown that CSII resulted in a significantly lower HbA_{1c} level compared to MDI (The DCCT Research Group 1995).

Since the publication of the DCCT results (The DCCT Research Group 1993), CSII is gaining momentum as a mode of insulin delivery in the context of intensive management of type 1 diabetes.

iv) Continuous Subcutaneous Insulin Infusion (CSII)

CSII, often called insulin pump therapy, was first developed primarily as a research tool in 1976 (Pickup and Keen 2002). By the early 1980's, it had been adapted in several countries as an alternative form of routine treatment in type 1 diabetes (Pickup and Keen 2002). Approximately 25 years after its introduction, CSII is now widely used in clinical practice. There are now estimated (largely from pump sales) to be > 200,000 individuals with diabetes worldwide using CSII for their everyday treatment, with > 130,000 in the U.S. alone (Pickup and Keen 2002). However, in some countries such as the U.K. there are only a few hundred users, but growing pressure from the patients is likely to increase its availability (Pickup and Keen 2002). In Canada, there is also a relatively small number of individuals using insulin pump therapy, although exact estimates are not currently available.

In a comprehensive review of insulin pump therapy, Lenhard and Reeves outline some of the misconceptions, advantages and disadvantages of CSII therapy (Lenhard and Reeves 2001). Some of the misconceptions that both patients and even some health care providers have with respect to insulin pump therapy include: need for surgery, pump viewed as an artificial pancreas, possible

to ignore diet, no need to self- monitor blood glucose, complete elimination of hypoglycemia and hyperglycemia (Lenhard and Reeves 2001).

Surgery is not required for external insulin pumps. A catheter is used which is manually inserted into the subcutaneous tissue, typically in less than 5 minutes (Lenhard and Reeves 2001). An insulin pump is not an artificial pancreas (ie- insulin pumps need to be programmed to give the appropriate dose of insulin) (Lenhard and Reeves 2001). In all the available models, the basal or background insulin can be pre-programmed. However, insulin required to cover meals or "on demand" must be programmed as needed. As such, patients can not ignore their diets or meal plans because they must still be able to co-ordinate insulin dose with food intake if they are to reap the maximum benefits of insulin pump therapy. As well, patients on insulin pump therapy must monitor their blood glucose levels as much if not usually more frequently than needed with MDI. Although there is good evidence that CSII will provide better glycemic and metabolic control than MDI, with fewer glycemic excursions, it will not completely eliminate hypoglycemia and hyperglycemia (Lenhard and Reeves 2001).

Some of the advantages of CSII compared to MDI therapy include: improved glycemic control, reduction in the rates of severe hypoglycemia and improved lifestyle flexibility (Lenhard and Reeves 2001).

With respect to glycemic control, a recent meta-analysis of 12 randomized controlled trials from 1975-2000 indicates that insulin pump therapy results in improved glycemic control compared to MDI but the difference is relatively small (approximately 0.5% for HbA_{1c} and 1 mmol/L for blood glucose concentration)

(Pickup et al 2002). The improved control during CSII was achieved with a mean reduction in total daily insulin dose by 14%. Even though the reduction in HbA_{1c} appears to be modest, the DCCT demonstrated that there is no glycemic threshold (short of normal glycemia) below which there is no risk for complications (The DCCT Research Group 1993). Therefore, any improvement in glycemic control is regarded as important. Moreover, the majority (10/12) of the trials were conducted in the 1980's. Only two trials were conducted later (one in 1990 and the other in 2000) (Pickup et al 2002). Significant improvements with respect to insulin pump technology and catheters have been made since the 1980's, therefore more recent studies are urgently needed. In contrast to the study conducted in 2000 which utilized insulin lispro with both MDI and CSII (Hanaire-Broutin et al 2000), a more recent study which was not included in the above meta-analysis, indicated that there was no significant difference in glycemic control between MDI versus CSII, with the use of insulin lispro (Tsui et al 2001). One non-randomized study found improved glycemic control, as indicated by HbA_{1c}, in adolescents who chose CSII compared to similar group who chose MDI as their mode of intensive therapy (Boland et al 1999).

With respect to the rates of severe hypoglycemia, earlier studies had shown that the risk of hypoglycemia with CSII was greater or similar as MDI (White et al 1983). More recently, however, it has been shown that severe hypoglycemia may be reduced by as much as 4-fold with CSII compared to MDI (Bode et al 1996). Severe hypoglycemia has now become an accepted indication for initiation of CSII therapy (Lenhard and Reeves 2001).

Furthermore, this decrease in hypoglycemic events has been accompanied by increases in self-reported warning symptoms and some of the counterregulatory hormone responses to hypoglycemia (Kanc et al 1998).

Lifestyle flexibility may be one of the most important reasons patients choose insulin pump therapy (Lenhard and Reeves 2001). One study found that adolescents who used CSII were able to cope better with their diabetes compared to those who used MDI (Boland et al 1999). However, a more recent study in adults found no significant difference with respect to quality of life with CSII compared with MDI (Tsui et al 2001).

Some disadvantages associated with CSII include: increased risk for diabetes ketoacidosis (DKA), catheter site infection and contact dermatitis.

Diabetes Ketoacidosis (DKA) is a potentially fatal condition marked by alterations in blood pH concentrations and dehydration as a result of inadequate insulinization (American Diabetes Association 2002). Since there is no subcutaneous depot of long-acting insulin with CSII, if the flow of insulin is interrupted, ketonemia and DKA can develop rapidly and more frequently with CSII than with MDI (Lenhard and Reeves 2001). However, many times the interruption of insulin is a result of patient error and inadequate training, particularly when patients do not take the emergency steps necessary in the event of unexplained hyperglycemia (Lenhard and Reeves 2001). In the DCCT, the rates of DKA were no different between conventional versus intensive management (MDI or CSII) (The DCCT Research Group 1995).

The most common complication associated with CSII is infection at the infusion site and is the most common cause for discontinuation of CSII (Lenhard and Reeves 2001). The annual rate of catheter infection has been estimated at 7.3 to 11.3 events per 100 patient-years of follow-up (The DCCT Research Group 1995).

Occasional cases of contact dermatitis, usually as a result of the components of the infusion sets and tape, are known to occur. In very rare cases, the contact dermatitis persists despite changing the type of tape and/or catheter, and is so severe that CSII must be discontinued (Lenhard and Reeves 2001).

With respect to other concerns such as weight gain, there was no difference in weight gain between patients using CSII and those using MDI in the DCCT (The DCCT Research Group 1995).

To minimize the risk of infection, it is advised that patients change their catheter and infusion site every 2 to 3 days. The application of local antibiotic ointment to mild infections will usually cure them, and creams with aloe, vitamin E, or corticosteroids may be helpful for contact dermatitis (Lenhard and Reeves 2001). To minimize the risk of ketoacidosis, patients must check their blood glucose levels at least 4 times per day and take appropriate action if there is unexplained hyperglycemia (blood glucose > 13 mmol/L).

Self-monitoring of blood glucose (SMBG) is therefore a very important component for successful and safe management with CSII. SMBG is also an integral component of diabetes management in general, especially intensive management.

c) Self-Monitoring of Blood Glucose (SMBG)

SMBG has been identified as an integral component of diabetes management (Meltzer et al 1998; American Diabeets Association 2002). Major clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as an important component of their interventions (American Diabetes Association 2002). For example, in the Diabetes Control and Complications Trial, SMBG played a critical role especially in the intensive management group (The DCCT Research Group 1995).

SMBG allows patients to evaluate their individual response to therapy and assess if glycemic targets are being achieved (American Diabetes Association 2002). Results of SMBG are useful in preventing hypoglycemia and adjusting medications, diet and physical activity (Meltzer et al 1998; American Diabetes Association 2002). Individuals with type 1 diabetes often use pre-meal and bedtime tests, as well as intermittent post-meal testing to adjust their insulin doses (Meltzer et al 1998).

According to the American Diabetes Associations 1996 consensus statement on SMBG, health care providers should use SMBG data to make clinical decisions concerning nutritional and pharmacological management of

diabetes as well as to teach patients how to make self-care management decisions (American Diabetes Association 1996).

However, in order for SMBG to be useful to the patient and health care team, the data obtained must be both accurate and reliable. Accuracy will depend on the glucose meters used and on quality assurance practices. The reliability of the data will depend on the reliability of the patient's reporting of their results.

i) Accuracy of Glucose Meters

The introduction of glucose meters in the 1980's revolutionized the management of diabetes. Individuals afflicted with diabetes no longer had to rely on urine tests of glycemia which only detect glucose when the level in the blood surpasses the renal threshold, usually > 10 mmo/L (American Diabetes Association 2002).

There are currently several models of glucose meters available, all with different specifications.

In a recent study, we assessed the accuracy of various glucose meters over a variety of blood glucose values, ranging from 2.5 to 16 mmol/L. We compared plasma blood glucose results obtained with 5 commonly used glucose meters with results obtained via the reference method (Beckman Analyzer, Fullerton, CA) using Clarke's error grid analysis for evaluating clinical accuracy (Clarke et al 1987). The results obtained indicated that with all 5 meters 100% of the estimations were clinically accurate (zones A and B). However, all meters tended

to underestimate blood glucose concentrations in the hypoglycemic range (2.8-4.0 mmol/L) by a range of 5 to 22 % (unpublished observations).

Optimal use of SMBG data obtained by glucose meters also requires appropriate quality assurance (Meltzer et al 1998). Verification of accuracy of glucose meters is required at least annually (Meltzer et al 1998). Verification of accuracy consists of comparing a sample of capillary blood obtained by the glucose meter with a simultaneous laboratory measurement of a fasting venous blood sample (Meltzer et al 1998).

Clinicians rely on SMBG results from all patients with diabetes, in order to make periodic adjustments of therapy. In addition to the accuracy of the glucose meters utilized, the effectiveness of these adjustments also depends on the reliability of the information provided by the patient.

ii) Reliability of Reporting SMBG Results

The issue of reliability of reporting was first assessed in the late 1980's, with the availability of memory-equipped glucose meters. In 1984, Mazze and colleagues were the first to publish results which assessed accuracy of SMBG reports by comparing them to meter-downloaded results (Mazze et al 1984). Over a 2 week period they evaluated SMBG logbooks of 19 adults with type 1 diabetes who were unaware of the memory capacity of the glucose meters. Findings revealed that 26% of patient entries differed from the meter memory and that approximately 75% of patients significantly reported lower than actual values. Since this study was published, other studies (Zeigler et al 1989; Hoskins et al

1988; Gonder-Frederick et al 1988) have confirmed these results, including in patients using insulin pump therapy (Zeigler et al 1989) and those with gestational diabetes (Hoskins et al 1988). However, when subjects were aware that their results were being compared to the meter memory, accuracy of reporting increased (Mazze et al 1985).

Since the publication of the aforementioned studies, the issue of accuracy of reporting has not since been adequately addressed, especially in the context on intensive management.

In a more recent study, we addressed this issue in both adults with type 2 diabetes undergoing conventional management and adults with type 1 diabetes undergoing intensive management. We found that there is still a problem regarding accuracy of reporting more than a decade since the first study was published. Specifically, we found that approximately 20% of patients in both groups were very inaccurate in their reporting (< 50% of their entries were accurate) and this pattern did not appear to improve over time. Furthermore, we found relationships between accuracy of reporting and glycemic control, quality of life and self-efficacy in subjects with type 1 diabetes. Individuals who were classified as being very reliable in their reporting (> 90% of values accurate) had optimal glycemic control; were more satisfied and less worried (quality of life) and more confident (self-efficacy) with their diabetes self-management (Kalergis et al 1999).

Self-monitoring of blood glucose is a fundamental tool for individuals with type 1 diabetes on intensive management. However, even though it is performed very frequently, these intermittent or "spot" checks of blood glucose are not sufficient to detect and reflect daily variations in the individual glucose profiles (Boland et al 2001; Kochinsky and Heinemann 2001; Maran et al 2002). In particular, it is difficult to obtain information on the nocturnal period. This is partly related to patient adherence, which appears to be very poor with respect to monitoring blood glucose overnight (The DCCT Research Group 1995; Kanc et al 1998) and partly due to the lack of knowledge regarding the exact occurrence of nocturnal hypoglycemic episodes. Furthermore, conventional glucose monitoring or SMBG is considered inconvenient and invasive (Kochinsky and Heinemann 2001; Maran et al 2002).

d) Continuous Blood Glucose Monitoring

For the past 30 years numerous attempts have been made to develop continuous glucose monitors or glucose sensors (Kochinsky and Heinemann 2001). The dream was finally realized in 1999 with the introduction of the first continuous glucose monitor: the continuous glucose monitoring system (CGMS, Medtronic/MiniMed, Sylmar, CA). The CGMS was approved for use in Canada in 2000. It is considered to be minimally invasive as it requires puncturing of the skin for insertion. It is worn in a similar fashion as an insulin pump (ie- via subcutaneous insertion of a small cannula). The cannula is referred to as a glucose electrode or glucose sensor as it is enzymatically coated with glucose

oxidase. The glucose sensor is connected to a monitor by a cable which sends electric current from the sensor to the monitor where it is translated into glucose values (Kochinsky and Heinemann 2001). The CGMS provides glucose readings every 5 minutes for up 288 readings per day and can be worn for up to 3 days at a time. The glucose sensor measures glucose in the interstitial fluid compartment. Under physiological conditions there is a free and rapid exchange of glucose molecules between blood plasma and interstitial fluid. Therefore, changes in blood glucose and interstitial glucose are strongly correlated. However, the changes of glucose levels in the two compartments do not occur at the same time; they occur with a delay reported to be between a few seconds and 15 minutes (Kochinsky and Heinemann 2001).

Preliminary post-marketing research comparing the CGMS with results obtained by glucose meters via SMBG indicate a very strong correlation (r=0.91) with almost all the values (96%) falling within clinically acceptable regions (zones A and B), as assessed by Clarke's error grid analysis (Gross et al 2000). Similar results were obtained by a recent multicenter study using another, but similar, glucose sensing system (Maran et al 2002). In this study, interstitial glucose was compared with venous blood samples as analyzed using the reference standard method (Beckman, Fullerton, CA) (Maran et al 2002). Results obtained showed a very strong correlation ($r = 0.91$, $p<0.001$) between the interstitial glucose and venous blood glucose with 97% of the data being clinically acceptable (zones A and B using the error grid analysis) (Maran et al 2002).

Furthermore, preliminary studies have demonstrated improved glycemic control in type 1 diabetes with the use of the CGMS as a tool to optimize therapy (Bode et al 1999; Boland et al 2001).

The development of noninvasive glucose sensors is also on the horizon and appears to be very promising (Klonoff 1997) with the first such system: Glucowatch Biographer, currently available in the U.S. (Pitzer et al 2001).

e) Clinical Practice Guidelines

The goal of the management of type 1 and type 2 diabetes is to control metabolic abnormalities in order to prevent both acute (hyperglycemia and hypoglycemia) and chronic complications (retinopathy, neuropathy, nephropathy, cardiovascular disease) without negatively impacting on quality of life (Meltzer et al 1998).

In type 1 diabetes, glycemic control will depend on coordination of insulin doses, food intake and physical activity.

i) Glycemic Targets

The following represents the glycemic targets for adults and adolescents with both type 1 and type 2 diabetes (Meltzer et al 1998).

	Ideal	Optimal	Sub-optimal	Inadequate
*Glycated Hb e.g. HbA1c (%)	≤100 4 -6	≤ 115 <7	116-140 7 – 8.4	>140 > 8.4
Fasting or pre-meal glucose level (mmol/L)	3.8-6.1	4-7	7.1-10	>10
1-2 h post-meal glucose level (mmol/L)	4.4-7	5-11	11.1-14	>14

* represents the % of the upper limit of normal.

The ideal (normal, non-diabetic) range is also presented but the realistic goal for management is to attain optimal control. Sub-optimal control is attainable in the majority of people with diabetes but may not be adequate to prevent complications. Levels in the inadequate category are related to markedly increased risk of long-term complications and thus require reassessment and readjustment of therapy (Meltzer et al 1998).

In addition to the above glycemic target, the American Diabetes Association (American Diabetes Association 2002) also includes specific glycemic targets for bedtime as follows:

	Normal	Goal	Additional action suggested
Plasma glucose values (mmol/L)	< 7	6-8	<6 or >10

Additional action suggested depends on the individual patient circumstances. Such actions may include enhanced diabetes self-management education, co-management with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation of or increase in SMBG, or more frequent contact with the patient (American Diabetes Association 2002).

ii) Lipid Targets

Targets for plasma lipid levels for people with diabetes are based on a 10 year risk of developing cardiovascular complications and is calculated from the number of major risk factors an individual possess. Targets are as follows (Meltzer et al 1998):

Risk factors	10 yr risk %	LDL-cholesterol mmol/L	Total: HDL cholesterol ratio	TG mmol/L
CAD or 3 or more other risk factors	>40	<2.5	<4	<2.0
2 other risk factors	20-40	<3.5	<5	<2.0
1 other risk factor	10-20	<4.0	<6	<2.0
no other risk factor	0-10	<5.0	<7	<3.0

Diabetes counts as 1 major risk factor. Other major risk factors include: family history of premature CAD, smoking, hypertension, low HDL (≤ 0.9 mmol/L) and age over 30 years for both men and women (Meltzer et al 1998).

According to the new American Medical Association guidelines on the detection, evaluation and treatment of high blood cholesterol, diabetes now counts as equivalent to CAD (American Medical Association 2001).

iii) Nutrition Guidelines

Nutrition guidelines for people with diabetes are very similar as those for the general population, with some modifications. The goals of nutrition that apply to all people with diabetes are as follows (ADA 2002):

1) Attain and maintain optimal metabolic outcomes including:

- blood glucose levels as close to normal as is safely possible to prevent or reduce the risk for complications of diabetes.
- a lipid and lipoprotein profile that reduces the risk for macrovascular disease.
- blood pressure levels that reduce the risk of vascular disease

2) Prevent and treat the chronic complications of diabetes. Modify nutrient intake and lifestyle as appropriate for the prevention and treatment of obesity, dyslipidemia, cardiovascular disease, hypertension, and nephropathy.

3) Improve health through healthy food choices and physical activity.

4) Address individual nutritional needs taking into consideration personal and cultural preferences and lifestyle while respecting the individual's wishes and willingness to change.

With respect to guidelines for macronutrient composition, individuals with diabetes are encouraged to consume a wide variety of food with the majority of energy from carbohydrate (55-60%); 15-20% of energy as protein and <30% from fat (American Diabetes Association 2002). The Canadian guidelines differ from the American guidelines in that they include a restriction for added sugars of no more than 10% of total daily caloric intake (Wolever et al 1998).

Nutritional counseling must be tailored to the needs of the individual and must be considerate of a number of factors including: the type of diabetes, lifestyle, socioeconomic issues, presence of obesity, progression of beta-cell dysfunction, type of treatment, personal preferences and nature of any complications (Meltzer et al 1998).

Although the guidelines provide several important goals regarding the management of diabetes, hypoglycemia, and in particular nocturnal hypoglycemia, which represents a major acute complication in type 1 diabetes is not adequately addressed in either the Canadian or American clinical practice guidelines (Meltzer et al 1998; American Diabetes Association 2002). Furthermore, the need or composition of bedtime snacks is not addressed at all (Meltzer et al 1998; Wolever et al 1998; American Diabetes Association 2002).

Canada recently released the first evidence-based guidelines on the prevention and management of hypoglycemia in diabetes (Yale et al 2002). Advice given to reduce the risk of asymptomatic nocturnal hypoglycemia consists of periodical monitoring of overnight blood glucose at a time that corresponds to the peak action time of the overnight insulin and consumption of a bedtime snack with at least 15g carbohydrate and protein if the bedtime blood glucose level is under 7 mmol/L (Yale et al 2002). The level of evidence used to support this recommendation was Grade D, consensus (Yale et al 2002).

The level of evidence given for the aforementioned recommendation is a clear indication that there is a paucity of scientific data with respect to nocturnal hypoglycemia which, as indicated by the DCCT, is a major obstacle in the intensive management of type 1 diabetes.

The following section (2.2) will provide more insight into the issue of hypoglycemia and will provide some of the more pertinent reasons as to why it is such a major obstacle for people living with type 1 diabetes.

2.2 Hypoglycemia

Hypoglycemia has been described as the "Achille's Heel" in the management of type 1 diabetes (Pacaud et al 2002). It is a major obstacle to the attainment of the optimal glycemic control which is required to prevent the chronic complications associated with type 1 diabetes (The DCCT Research Group 1993). Hypoglycemia itself is not a disease. It is a biochemical sign indicating that some condition has caused an imbalance between rates of release of glucose into the circulation and rates of glucose removal from circulation, so that the latter exceeds the former (Gerich 1988).

2.2.1 Definition of Hypoglycemia

The precise definition of hypoglycemia remains the subject of debate (Yale 2001). Clinically, hypoglycemia is best documented by the presence of Whipple's triad which consists of symptoms compatible with hypoglycemia, a low plasma glucose concentration, and relief of symptoms after plasma glucose is raised (Cryer et al 1994). Biochemically, hypoglycemia is defined as a plasma glucose concentration of $\leq$ 2.8 mmol/L. Clinically, however, this may not be a useful definition as it may underestimate the true frequency of hypoglycemia in type 1 diabetes (Yale 2001). Furthermore, this definition may not be appropriate from a physiological point of view given that the first counterregulatory mechanism, the suppression of endogenous insulin secretion, is already activated at a plasma glucose concentration of ~ 4.2 to 4.0 mmol/L (Bolli et al 1999). A more conservative definition, as suggested by Bolli and colleagues (Bolli et al

1999) is any decrease in plasma glucose concentration below 4.2 mmol/L. This definition is not only more precise, from a physiological point of view, but may be more clinically relevant for people with type 1 diabetes in order to establish lower limits of plasma glucose control (Bolli et al 1999), especially with intensive management where the risk for recurrent hypoglycemia is high (The DCCT Research Group 1993). The current Canadian guidelines for prevention and management of hypoglycemia in diabetes propose a level of 4.0 mmol/L as a cut-off for clinical use in patients treated with insulin or insulin secretagogues (Yale et al 2002)

2.2.2 Classification of Hypoglycemia

The severity of hypoglycemia can be classified, according to clinical manifestations and the ability to self-treat, as: mild, moderate and severe (Yale et al 2002). Mild hypoglycemia is associated with the presence of autonomic symptoms and individuals are able to self-treat (Yale et al 2002). Moderate hypoglycemia is associated with autonomic and neuroglycopenic symptoms and the individual is also able to self-treat (Yale et al 2002). Autonomic symptoms are those manifested as a cause of activation of the sympathetic nervous system and include, in order of percent incidence: trembling, palpitations, sweating, anxiety, hunger, nausea and tingling (Hepburn et al 1991; Yale 2001). Neuroglycopenic symptoms are those manifested in response to decreased levels of glucose to the brain and include, in order of percent incidence: difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty

speaking, headache, dizziness and tiredness (Hepburn et al 1991; Yale 2001). With severe hypoglycemia, the individual requires the assistance of another person and unconsciousness may occur (Yale et al 2002). Since the publication of the DCCT results, the standard definition of severe hypoglycemia used by clinicians and investigators is an episode which requires assistance to treat and is associated with a plasma glucose concentration of <2.8 mmol/L (The DCCT Research Group 1993).

2.2.3 Frequency of Hypoglycemia in Adults with Type 1 Diabetes

a) Mild and Moderate Hypoglycemia

The best estimates of the frequency of mild or moderate symptomatic hypoglycemia are derived from a recent population-based cohort study (Allen et al 2001). This study demonstrated the frequency of hypoglycemia to be ~ 2 episodes per week. Over a lifetime, this translates to thousands of episodes per given person. The majority (~65%) of subjects were on intensive management and had a mean baseline HbA_{1c} of 11.5% (Allen et al 2001). Similar findings in terms of frequency of mild/moderate hypoglycemia episodes have been reported in adults with type 1 diabetes on conventional management (Pramming et al 1991 in Cryer 1994).

b) Severe Hypoglycemia

The best estimates of severe hypoglycemia are derived from the Diabetes Control and Complications Trial (The DCCT Research Group 1991, The DCCT Research Group 1993; The DCCT Research Group 1997), whereby intensive management was associated with a 3-fold increased risk of severe hypoglycemia compared to conventional management (The DCCT Research Group 1993; The DCCT Research Group 1997). The overall rates of severe hypoglycemia were 61.2 episodes per 100 patient-years in the intensive group versus 18.7 episodes per 100 patient-years in the conventional group (The DCCT Research Group 1993; The DCCT Research Group 1997). Furthermore, more than half (~55%) of episodes occurred during sleep, with a significant proportion (~43%) occurring during the nocturnal period, between midnight and 8am, in both treatment groups (The DCCT Research Group 1991). Moreover, more than half (~51%) of subjects in both groups did not recognize warning symptoms during episodes which occurred while they were awake. Overall, 70% of the episodes of severe hypoglycemia occurred during sleep or without apparent warning symptoms (The DCCT Research Group 1991).

i) Risk Factors for Severe Hypoglycemia

Conventional risk factors for treatment-induced hypoglycemia are based on the premise that absolute or relative insulin excess is the sole determinant of risk and include: error in insulin administration (eg. excessive dose, ill-timed, wrong type of insulin), decreased availability of exogenous glucose (eg. missed meal or snack or overnight fast), increased glucose utilization (eg. exercise), decreased production of endogenous glucose (eg. alcohol ingestion), increased insulin sensitivity (eg. effective intensive therapy, weight loss, post-exercise) and decreased insulin clearance (eg. progressive renal insufficiency) (Cryer 1994). However, the findings from the DCCT indicate that these conventional risk factors only explain a minority of episodes of severe hypoglycemia, with only a missed meal being more frequent ($p<0.05$) on a hypoglycemia day compared to a non hypoglycemia day (The DCCT Research Group 1991; Cryer 1994).

The most important and significant risk factors for severe hypoglycemia, as determined by relative risk (RR) in the DCCT (The DCCT Research Group 1991), include: previous severe hypoglycemia RR= 2.54 (95% CI 1.67 to 3.88); a longer duration of diabetes, 9-12 years RR= 1.72 (95% CI 1.07 to 2.77); a higher baseline HbA_{1c} RR= 1.20 per 1% increase (95% CI 1.04 to 1.39); a lower most-recent HbA_{1c} RR= 1.43 per 1% decrease (95% CI 1.17 to 1.76); and a higher baseline insulin dose RR= 1.11 per 0.1 u/kg higher (95% CI 1.03 to 1.19) (Cryer 1994; Yale 2001).

A lower baseline HbA_{1c} or better glycemic control has also been confirmed to be an important risk factor in children with type 1 diabetes (Daneman et al 1989; Davis et al 1997). However, not all studies have confirmed an association between glycemic control and risk of severe hypoglycemia (Mühlhauser et al 1985; Bergada et al 1989; Bott et al 1997).

Aside from the risk factors identified in the DCCT (The DCCT Research Group 1991), two other important independent risk factors for severe hypoglycemia include: hypoglycemia unawareness, which is described in detail later on in this review and autonomic neuropathy (Meyer et al 1998). Hypoglycemia unawareness, defined as a loss of early warning symptoms to ensuing hypoglycemia (Mokan et al 1994), increases the risk of severe hypoglycemia (Gold et al 1994; Strachan and Frier 2002) by approximately 6-fold, from 50 to 280 episodes per 100 patient-years (Gold et al 1994). Autonomic neuropathy, defined as defects in both heart rate and systolic blood pressure changes with standing (Yale 2001), is associated with an approximately 2-fold increased risk of severe hypoglycemia (Meyer et al 1998).

Individuals with type 1 diabetes are at increased risk for severe hypoglycemia, partly due to inadequacies of current insulin preparations to mimic the normal physiology of insulin requirements as discussed in section 2.1 and partly due to impaired defenses against developing hypoglycemia as discussed below.

2.2.4 Counterregulation to Hypoglycemia

a) Normal Physiology of Glucose Homeostasis

In individuals without diabetes plasma glucose homeostasis is maintained by a careful balance between insulin and glucagon (Gerich 1988). In humans, plasma glucose is maintained within a narrow range (~3.6 to 7.8 mmol/L) in both the fasting and fed state because of a tightly regulated balance between glucose production and use (Bolli and Fanelli, 1999). This tight control of plasma glucose is related to the fact the human brain has an almost exclusive need for glucose which can reach 100g or ~ 555 mmol per day in an adult (Bolli and Fanelli, 1999). The brain can utilize other substrates for energy such as lactate and ketones. However, in everyday life, these alternate substrates are of minor importance (Bolli and Fanelli 1999). The high energy requirements of the brain coupled with its low energy reserves renders its function almost totally dependent on a continuous supply of glucose from the arterial circulation (Bolli and Fanelli 1999). The transport of circulating glucose into cerebral cells is an insulin-independent process that requires the presence of facilitative glucose transport proteins such as GLUT 1 and GLUT 3 (Bolli and Fanelli 1999). Under normal circumstances, the rate-limiting step for glucose uptake is phosphorylation within the cerebral cell by the enzyme hexokinase. However, when the plasma glucose concentration falls, the glucose carrier protein systems through the blood-brain barrier become the rate-limiting step (Bolli and Fanelli 1999).

In both the fed and fasted states, insulin is the main factor in the regulation of glucose production and use (Bolli and Fanelli 1999). As the plasma glucose concentration increases following a meal, glucose enters the pancreatic ß-cells via the GLUT 1 and GLUT 2 transporters, is phosphorylated by glucokinase initiating a sequence of events culminating in the release of insulin (Gerich 1988). Insulin acts to restore normoglycemia in 3 ways (Gerich 1988): 1) it decreases hepatic glucose production by diminishing both glycogenolysis and gluconeogenesis; 2) it increases glucose uptake by skeletal muscle and adipose tissue; it diminishes the delivery of the gluconeogenic precursors alanine and glycerol to the liver. As a result of these responses, plasma glucose concentrations normally return to baseline values within several hours (Gerich 1988).

b) Normal Physiology of Counterregulation to Hypoglycemia

i) The Counterregulatory System

The counterregulatory system is located in different organs but is primarily found in the brain (Bolli and Fanelli 1999). When the brain senses a fall in plasma glucose levels, a series of reactions is initiated which lead to secretion of adrenocorticotropic hormone (ACTH) which leads to cortisol secretion and neural stimulation of the adrenal medulla and adrenergic nerve endings which lead to catecholamine secretion (Bolli and Fanelli 1999). The counterregulatory system is also located in the pancreatic islets, which respond directly to the low blood glucose levels and also to central neurogenic signals (Bolli and Fanelli 1999).

A decline in the plasma glucose concentration, even as little as ~0.6 to 0.8 mmol/L, is sufficient to blunt endogenous insulin secretion (Bolli and Fanelli 1999). The ability to suppress insulin is an important component of the response to hypoglycemia and is considered the first defense mechanism against falling plasma glucose levels (Gerich 1988, Cryer 1994). Normally, at arterial plasma glucose concentrations of < 3 mmol/L, insulin secretion is completely suppressed (Gerich 1988).

Following the suppression of endogenous insulin secretion, the second defense mechanism against falling plasma glucose levels is via the glucose counterregulatory hormones.

ii) Conterregulatory Hormones

The counterregulatory hormones, in order of importance, are as follows: glucagon, the catecholamines (epinephrine and norepinephrine), cortisol and growth hormone (Gerich 1988, Cryer 1993; Bolli and Fanelli 1999). The counterregulatory hormones can be classified according to their action profile as rapid-acting and slow-acting (Bolli and Fanelli 1999). Glucagon and the catecholamines are rapid-acting hormones which are critical for counterregulation of the early phase of hypoglycemia (Bolli and Fanelli 1999). Growth hormone and cortisol are referred to as slow-acting hormones because their effects do not become evident until after at least 3 hours of hypoglycemia (Bolli and Fanelli 1999).

Glucagon

Glucagon plays a primary role among the glucose counterregulatory hormones (Cryer 1993; Gerich 1988). It acts only in the liver, increasing glucose production by stimulating both glycogenolyis and gluconeogenesis (Gerich 1988). Severe hypoglycemia has been shown to occur with isolated impairment of glucagon responses in both individuals without diabetes and individuals with type 1 diabetes, even in the context of increased catecholamine secretion (Bolli and Fanelli 1999). This observation supports the relative importance of glucagon and suggests that increased catecholamine secretion can not fully compensate for impaired glucagon response (Bolli and Fanelli 1999).

Epinephrine

Epinephrine stimulates glucose production and limits glucose utilization via both direct and indirect actions. Epinephrine, acting via beta adrenergic receptors, has similar hepatic effects as those of glucagon. Indirect actions, mediated via alpha adrenergic stimulation, include suppression of insulin secretion and increase in glucagon production (Gerich 1988).

Norepinephrine

Norepinephrine is a catecholamine neurotransmitter with metabolic effects that are thought to be similar to, and act through the same mechanisms as, those of epinephrine (Bolli and Fanelli 1999). However, the norepinephrine concentration during hypoglycemia is increased to a lesser extent compared to epinephrine (Mitrakou et al 1991).

Cortisol

Cortisol secretion antagonizes the effects of insulin thus limiting both stimulation of glucose utilization and suppression of glucose production (Gerich 1988). However, these effects only occur after several hours of hypoglycemia (Bolli and Fanelli 1999). Its role in glucose production may be via an increase in gluconeogenesis by way of increased lipolysis (Bolli and Fanelli 1999).

Growth Hormone

Like cortisol, growth hormone is also not important until after several hours of hypoglycemia, usually 3 to 4 hours (Bolli and Fanelli 1993). Also like cortisol, growth hormone acts to counterregulate hypoglycemia, by increasing glucose production and limiting its use through an increase in the levels of glycerol and free fatty acids (Bolli and Fanelli 1999).

Other factors which may play very important roles in restoring plasma glucose levels include substrates such as free fatty acids and glucose itself, which have been described as the third mechanism in the counterregulation to hypoglycemia (Bolli and Fanelli 1999).

Free Fatty Acids

In a late phase of hypoglycemia, at least 50% of the effects of catecholamines on the production and use of glucose are mediated by stimulation of lipolysis (Bolli and Fanelli 1999). Free fatty acids, released via lipolysis, support glucose production via gluconeogenesis (Gerich 1988) and inhibit glucose oxidation (Randle et al 1963).

Glucose (Hepatic Autoregulation)

When the plasma glucose concentration is extremely low, as in the case of severe hypoglycemia, endogenous glucose production increases independently of hormone levels (Gerich 1988; Bolli and Fanelli 1999). This mechanism is referred to as "hepatic autoregulation" and requires severe hypoglycemia before it can be activated. It is believed to be an emergency backup system to protect the brain when other counterregulatory factors have failed to restore normoglycemia (Bolli and Fanelli 1999).

iii) Glycemic Thresholds for Counterregulation

Studies have identified glycemic levels or thresholds at which counterregulatory hormones are secreted and at which characteristic symptom responses and cognitive impairment occur (Mitrakou et al 1991). In individuals without diabetes, the following thresholds have been identified in response to hypoglycemia. However, these levels vary between individuals (Yale 2001) Endogenous insulin secretion is suppressed by the pancreas at plasma glucose concentrations of approximately 4.2 mmol/L (Gerich 1988; Mitrakou et al 1991; Bolli and Fanelli 1999). The release of counterregulatory hormones: glucagon, epinephrine, cortisol and growth hormone begins at plasma glucose concentrations of about 3.6 mmol/L (Gerich 1988; Mitrakou et al 1991; Bolli and Fanelli 1999). These hormonal responses begin well before the onset of symptoms of hypoglycemia (Mitrakou et al 1991; Cryer 1993). Initial symptoms, mediated by catecholamine secretion, include: sweating, anxiety, palpitations, tremor and hunger and occur at approximately 3.3 mmol/L (Gerich 1988; Mitrakou et al 1991). These symptoms are also referred to as autonomic symptoms and constitute an important protective response in people with diabetes, warning them to ingest food (Yale 2001). As the plasma glucose level continues to fall, to about 2.8 to 3.1 mmol/L, symptoms indicative of neuroglycopenia or cognitive impairment become manifest and include: difficulty concentrating, confusion, dizziness, fatigue, blurred vision (Gerich 1988; Mitrakou et al 1991). More severe neurological symptoms occur with progressive hypoglycemia. Lethargy begins at plasma glucose level between 2.5 to 2.8

mmol/L; coma ensues at a plasma glucose concentration of about 1.7 mmol/L, convulsions can occur at about 1.1 mmol/L; and death shortly thereafter (Gerich 1988).

The knowledge base about glucose counterregulation is derived from studies utilizing experimental models of hypoglycemia.

c) Experimental Models of Hypoglycemia

i) Model of Acute Hypoglycemia

In the model of acute hypoglycemia, an intravenous bolus dose of insulin is given in order to induce hypoglycemia. In this model, plasma insulin peaks to supraphysiologic levels and wanes rapidly causing an abrupt decrease in plasma glucose. Recovery of glucose occurs during the subsequent waning of insulin. The conclusions derived from this type of model, however, do not reflect the clinical situation of hypoglycemia induced by hyperinsulinemia over an extended period of time. The majority of the pioneering studies in the area of glucose counterregulation are based on the acute model of hypoglycemia (Bolli and Fanelli 1999). The relative importance of the counterregulatory hormones, based on this model of hypoglycemia, indicate that glucagon is of primary importance followed by the catecholamines which only play a critical role when the response of glucagon is deficient. Cortisol and growth hormone do not appear to be involved (Bolli and Fanelli 1999).

ii) Model of Prolonged Hypoglycemia

Clinical hypoglycemia which occurs in individuals with diabetes given subcutaneous insulin or insulin seretagogues differs from the acute model. Clinical hypoglycemia usually develops gradually, may last for several hours, and is reversed slowly (Bolli and Fanelli 1999). In the model of prolonged or clinical hypoglycemia, induced by low-dose continuous infusion of insulin to reproduce the clinical situation, there is no waning of insulin and thus no recovery of glucose despite increased levels of counterregulatory hormones. Therefore, in this model, the counterregulatory mechanisms are not evaluated in terms of glucose recovery but in terms of their response, and thus by extension, ability to prevent severe hypoglycemia (Bolli and Fanelli 1999).

Using this model, the relative importance of the counterregulatory hormones indicates that all hormones are important and play a role in glucose recovery at different times (early or late phase) and via different mechanisms as previously described such as increase in glucose production, suppression of glucose use, or both (Bolli and Fanelli 1999).

d) Pathophysiology of Counterregulation in Type 1 Diabetes

i) Impaired Counterregulatory Hormone Response

The first defense mechanism to falling plasma glucose levels, suppression of endogeonous insulin, is absent in individuals with type 1 diabetes who are dependent on exogenous insulin in order to survive (Gerich 1988; Bolli and Fanelli 1999). Therefore, the main defense against hypoglycemia in individuals with type 1 diabetes is release of counterregulatory hormones. The glucagon response to hypoglycemia, although normal at the onset of diabetes, becomes markedly impaired or absent within the first 5 years after diagnosis (Bolli et al 1983). It is important to note, however, that the glucagon response to other stimuli is largely intact, thus leading to speculation that the underlying defect may be related to insulin deficiency (Cryer 2001). Support for the hypothesis that the glucagon reponse to hypoglycemia may be related to signaling between the pancreatic beta and alpha cells (Cryer 2001) is derived from studies in type 2 diabetes which demonstrate an intact glucagon response to hypoglycemia (Levy et al 1998). Given an absent glucagon response, individuals with type 1 diabetes become largely dependent on sympathoadrenal responses, especially epinephrine secretion and action, for appropriate counterregulation to hypoglycemia (Cryer 2001, Yale 2001). However, after several years the epinephrine response also becomes attenuated (Cryer 2001) for reasons that are unclear but may be related to hypoglycemia itself (Cryer 1992; Cryer 2001). Individuals with impairments in both glucagon and epinephrine have been shown to have a significantly increased risk of developing severe hypoglycemia (Boden et al 1981). Furthermore, it has

been shown that intensive therapy significantly increases the risk of developing severe hypoglycemia in individuals with impaired glucagon and epinephrine responses (White et al 1983; Simonson et al 1985; Amiel et al 1988; Kinsley et al 1995) by as much as 25-fold (White et al 1983). Moreover, sleep itself has been shown to decrease counterregulatory hormone responses in both individuals with and without type 1 diabetes (Jones et al 1998). The specific mechanism (s) for this decrease have not been identified but may be part of a general reduction in sympathetic activity that occur during stages 3 and 4 of non-REM sleep (Jones et al 1998). This sleep stage predominates during the first third of the nighttime-sleep cycle, the time when patients with diabetes are most prones to severe hypoglycemia (Jones et al 1998). This may explain why the majority of severe hypoglycemic episodes seem to occur during sleep (The DCCT Research Group 1991, The DCCT Research Group 1993; The DCCT Research Group 1997).

Individuals with type 1 diabetes depend on epinephrine secretion for appropriate perception of symptoms associated with hypoglycemia (Kinseley et al 1995). Therefore, secondary to diminished counterregulatory hormone responses to hypoglycemia, specifically decreased epinephrine secretion, individuals with type 1 diabetes often suffer from a condition known as hypoglycemia unawareness or impaired awareness of hypoglycemia.

ii) Hypoglycemia Unawareness

Hypoglycemia unawareness has been defined as a lack of appropriate autonomic warning symptoms before development of neuroglycopenia (Mokan et al 1994). A more precise physiological definition is an absence of autonomic symptoms at a blood glucose level of ~ 3 mmol/L (Janssen et al 2000). An estimated 25% of patients overall and as much as 50% of those with longstanding diabetes (> 15 years) have the clinical syndrome of hypoglycemia unawareness (Gold et al 1994; Cryer 1994). Affected individuals with this condition no longer have the warning (autonomic) signals that previously allowed them to recognize hypoglycemia and act (ie- ingest food) to prevent its progression to severe hypoglycemia (Cryer 1994; Yale 2001). Individuals with hypoglycemia unawareness have been shown to have a 6-fold increased risk of developing severe hypoglycemia compared to individuals who retain normal awareness (Gold et al 1994). They have also been shown to have more moderate hypoglycemic episodes than individuals with intact awareness (Clarke et al 1995). The etiology of hypoglycemia unawareness, however, remains unclear but is associated with an increased duration of diabetes (>10 years) and better glycemic control (HbA_{1c} <9%) (Mokan et al 1994), especially an $HbA_{1c} \leq 7\%$ (Amiel et al 1988). The impact of tighter glycemic control on the etiology of hypoglycemia unawareness has also been confirmed by other investigators (Kinseley et al 1995).

The mechanism associated with glycemic control and awareness to hypoglycemia may be related to the altered glycemic thresholds for counterregulatory hormone and symptom responses to hypoglycemia in individuals with type 1 diabetes, especially in those with tight glycemic control

iii) Altered Glycemic Thresholds for Counterregulation

Long-term glycemic control, as defined by HbA_{1c}, alters the glycemic thresholds for counterregulatory hormone and symptom responses to hypoglycemia in individuals with type 1 diabetes (Amiel et al 1988; Maran et al 1995). Poor glycemic control (HbA_{1c} >9%) is associated with lower glycemic thresholds (higher plasma glucose level) for initiation of hormone secretion and symptom response and tight glycemic control (HbA_{1c} ≤7%) is associated with higher glycemic thresholds (lower plasma glucose level) for hormone secretion and symptom response (Amiel et al 1988). Similar findings have been observed in individuals without diabetes (Mitrakou et al 1991; Fanelli et al 1995) and in those with type 2 diabetes (Levy et al 1998). The clinical implication of these findings is that individuals with type 1 diabetes, who achieve optimal or tight glycemic control via intensive management, will have counterregulatory hormone responses and onset of symptoms to a hypoglycemic stimulus at much lower plasma glucose concentrations, often at levels associated with neuroglycopenia and cognitive impairment (Amiel et al 1988). Therefore, individuals with increased glycemic thresholds are less likely to act in a timely manner to ensuing hypoglycemia. By definition, individuals with increased glycemic thresholds

have hypoglycemia unawareness or impaired awareness of hypoglycemia and are therefore at an increased risk of developing severe hypoglycemia (Gold et al 1994; Strachan and Frier 2002).

The above abnormalities in the counterregulation to hypoglycemia in individuals with type 1 diabetes, namely: impaired counterregulatory hormone response, hypoglycemia unawareness and altered glycemic thresholds may have a common etiology: hypoglycemia itself. These phenomenon has been coined "hypoglycemia-associated autonomic failure" (Cryer 1992; Cryer 2001).

iv) Hypoglycemia-Associated Autonomic Failure

The concept of hypoglycemia-associated autonomic failure (HAAF) posits that recent antecedent hypoglycemia causes both defective glucose counterregulation by reducing the epinephrine response and hypoglycemia unawareness by reducing the autonomic symptom response (Cryer 2001). HAAF was initially a theoretical construct proposed by Dr. Philip E. Cryer in 1992 (Cryer 1992) as a way of explaining the observation that defective hormonal response, hypoglycemia unawareness and elevated glycemic thresholds in response to hypoglycemia tended to cosegregate (ie- occurr in the same individuals) with type 1 diabetes. This concept, whereby hypoglycemia begets hypoglycemia, leading to a vicious cycle (Cryer 1992) has received support from several studies which have demonstrated that antecedent hypoglycemia, including nocturnal hypoglycemia, can diminish the hormonal response to subsequent hypoglycemia (Davis et al 1992; Ligenfelser et al 1993; Veneman et al 1993;

Davis et al 1997) in both individuals with diabetes (Maris et al 1992; Ligenfelser et al 1993) and without diabetes (Veneman et al 1993; Davis et al 1997). Further support of this concept is derived from studies demonstrating that counterregulatory hormone responses and symptom awareness can be improved with avoidance of hypoglycemia (Fanelli et al 1993; Fritche et al 2001; Kanc et al 1998), including avoidance of nocturnal hypoglycemia (Kanc et al 1998, Fanelli et al 2001; Fritche et al 2001).

The exact mechanism (s) by which hypoglycemia may predispose to hypoglycemia by altering glycemic thresholds and diminishing counterregulatory hormone response and symptom awareness remain unclear. In his review of the literature on possible mediators of hypoglycemia-associated autonomic failure, Cryer outlines two predominant hypotheses which have been proposed and include: cerebral adaptation and increased beta adrenergic sensitivity (Cryer 2001). Support for the first hypothesis of increased cerebral adaptation comes from studies demonstrating an increase in GLUT-1 mRNA and protein with chronic hypoglycemia in rodents (Simpson et al 1999 in Cryer 2001). As well, studies conducted in individuals with type 1 diabetes demonstrate preserved brain glucose uptake during hypoglycemia (Boyle et al 1995 in Cryer 2001). However, a recent study (Cranston et al 2001) demonstrated diminished brain glucose uptake in individuals with hypoglycemia unawareness compared to those with intact awareness.

The second hypothesis proposed to explain hypoglycemia-associated autonomic failure pertains to increase in beta adrenergic sensitivity via cortisol release (Cryer 2001). Support for this hypothesis comes from studies conducted by Davis and colleagues which propose that cortisol (rather than hypoglycemia) is responsible for HAAF (Davis et al 1997 in Cryer 2001). Indeed, cortisol has been shown to up-regulate beta receptors during hypoglycemia (Gerich 1988) and this may be the reason why some individuals with type 1 diabetes have intact awareness but diminished counterregulatory hormone response to hypoglycemia (Fritche et al 2001). However, with continued episodes of hypoglycemia, the maximally enhanced beta adrenergic sensitivity decreases and hypoglycemia unawareness developes, likely due to exhausted beta receptor upregulation (Fritche et al 2001). Reversal of hypoglycemia unawareness by avoidance of hypoglycemia, mediated by improved beta adrenergic sensitivity, was recently confirmed in a study by Fritche and colleagues (Fritche et al 2001). Furthermore, this hypothesis may explain why it may be possible to reverse the defect of hypoglycemia unawareness but not necessarily counterregulatory hormone response with avoidance of hypoglycemia (Dagogo-Jack et al 1994; Fritche et al 2001).

The concept of hypoglycemia-associated autonomic failure provides sound argument of the dangers of hypoglycemia and the need for its prevention.

2.2.5 Consequences of Hypoglycemia

Other consequences of hypoglycemia include impairments in cognitive function and psycho-social adaptation including quality of life.

Recent studies demonstrate that antecedent hypoglycemia can attenuate several aspects of cognitive function during subsequent hypoglycemia in individuals without diabetes (Hvidberg et al 1996; Fruhwald-Schultes et al 2000; Lobmann et al, 2001; McAulay et al 2001). Studies conducted in individuals with diabetes have also demonstrated similar results (Fanelli et al 1998; Lobmann et al 2001). However, unlike counterregulatory hormone and symptom responses, cognitive function does not appear to be associated with altered glycemic thresholds (Hvidberg et al 1996). Although studies have shown that antecedent hypoglycemia can cause cognitive impairment in the short term (Hvidberg et al 1996; Fanelli et al 1998; Fruhwald-Schultes et al 2000; Lobmann et al, 2001; McAulay et al 2001), there is no evidence, thus far, in adults of any long term impairment in neuropsychological function (Yale 2001) even in the context of increased frequency of severe hypoglycemia during intensive management (Reichard et al 1991; Austin et al 1999) including coma (Kramer et al 1998). Although these results are reassuring, definitive answers will only come from long-term prospective studies (Yale 2001).

Aside from cognitive impairment, hypoglycemia is also associated with a negative impact on quality of life (Rubin 2002) and increased levels of fear of hypoglycemia (Gold et al 1994) which may limit attempts to maintain optimal glycemic control which is required for prevention of the long-term complications associated with type 1 diabetes (The DCCT Research Group 1993).

This review of the literature on hypoglycemia provides clear evidence of the significant consequences of hypoglycemia in adults with type 1 diabetes who, due to the nature of their disease, have compromised defenses to ensuing hypoglycemia. Furthermore, hypoglycemia itself diminishes the already compromised defense system leading to a vicious cycle whereby hypoglycemia begets hypoglycemia. Other significant consequences of hypoglycemia include cognitive impairment and a negative impact on quality of life. Therefore, efforts to prevent hypoglycemia, primarily nocturnal hypoglycemia, must be a priority in adults with type 1 diabetes undergoing intensive management.

2.3 Prevention of Nocturnal Hypoglycemia

2.3.1 Nocturnal Glycemic Control in Type 1 Diabetes

In order to understand why nocturnal hypoglycemia is highly prevalent in people living with type 1 diabetes and why it is of utmost priority to prevent this complication, one must appreciate the complexities of nocturnal glycemic control and regulation in individuals with type 1 diabetes.

In individual without diabetes, plasma glucose concentrations remain virtually the same during the night and early morning. The rate of glucose production by the liver decreases in the early part of the night, soon after 2400, remains fairly stable until 0600 and finally increases slightly until 0900 (Bolli et al 1993). The reasons for the decrease in the rate of hepatic glucose production soon after midnight are not clear (Bolli et al 1993). The increased plasma glucose between 0600 and 0800, which is associated with an increased insulin secretion, is often referred to as the "dawn phenomenon." Therefore, there is an increased sensitivity to insulin soon after midnight and diminished insulin sensitivity at dawn (Bolli et al 1993). However, in individuals without diabetes this is of no consequence as there is continuous background insulin which restrains hepatic glucose production and prevents development of fasting hyperglycemia (Bolli et al 1993).

The overnight insulin requirements of individuals with type 1 diabetes resembles those of individuals without diabetes in that there is a decrease in insulin requirement in the early part of the night and subsequent increase at dawn (Bolli et al 1993). However, individuals with type 1 diabetes are dependent on exogenous insulin and thus on inherent pharmocokinetics of current insulin preparations (Bolli et al 1993). Current insulin preparations which are used for nocturnal glycemic control in type 1 diabetes include NPH and Ultralente insulin which tend to peak at that same time insulin requirements are at their nadir and begin to wane when insulin requirements are increased (Binder et al 1984, Lepore et al 2000) thus predisposing individuals with type 1 diabetes to nocturnal hypoglycemia and fasting hyperglycemia (Bolli et al 1993).

Aside from the limitations associated with the non-physiological replacement of insulin, two other factors complicate nocturnal glycemic control and are obstacles to intensive management of individuals with type 1 diabetes: the dawn phenomenon and the Somogyi effect.

a) The Dawn Phenomenon

The dawn phenomenon is defined as an increase in insulin requirements at dawn (0600 to 0800), in the absence of preceding or concomitant insulin deficiency (Bolli et al 1993).

Since the term "dawn phenomenon" was first coined by Maria Ines Schmidt in 1981, it has become common practice to refer to any early morning hyperglycemia in individuals with type 1 diabetes, in the absence of nocturnal hypoglycemia, as the dawn phenomenon (Bolli et al 1993).

In 1991, a study by Pereillo and colleagues characterized the dawn phenomenon in individuals with type 1 diabetes (Pereillo et al 1991). They found that the dawn phenomenon was very common, occurring in 89% of a total of 114 individuals with type 1 diabetes (Pereillo et al 1991). However, the magnitude (20% increase in insulin requirements between 2400 and 0700) was much less than previous reports (Pereillo et al 1991). Also, they found that several factors mediate the magnitude of the dawn phenomenon including: the level of glycemic control, state of counterregulation to hypoglycemia, duration of diabetes and insulin sensitivity (Pereillo et al 1991). Good glycemic control, achieved via intensive management, inadequate counterregulation to hypoglycemia, a longer duration of diabetes and a higher insulin sensitivity were all associated with an attenuated dawn phenomenon. Conversely, poor glycemic control, adequate counterregulation, a shorter duration of diabetes and a decreased insulin sensitivity were all associated with an exaggerated dawn phenomenon (Pereillo et al 1991).

The conclusions of this study indicate that the dawn phenomenon is a very frequent event in individuals with type 1 diabetes, its magnitude is much lower than initially indicated, it is highly reproducible from day to day and it is influenced by factors such as duration of diabetes, quality of antecedent glycemic control, state of the counterregulation system to hypoglycemia, and insulin sensitivity (Pereillo et al 1991).

In the context of continuous background insulin, the contribution of the dawn phenomenon to fasting hyperglycemia is modest, only ~1.5 to 2 mmol/L (Bolli et al 1993). However, in the everyday life of people living with type 1 diabetes, the dawn phenomenon is associated with waning of the evening insulin. Attempts to correct this waning, and thus decrease fasting hyperglycemia, by increasing the dose of the evening insulin are often counter-productive as they result in unacceptably high rates of nocturnal hypoglycemia (Bolli et al 1993).

Aside from the contributions of the dawn phenomenon and more importantly insulin waning to fasting hyperglycemia, the counterregulatory hormone response to hypoglycemia may play an important role. The exxaggerated counterregulatory hormone response to nocturnal hypoglycemia is often referred to as the "rebound" or "Somogyi" effect (Bolli et al 1993).

b) Somogyi Effect

In 1938, Somogyi postulated that the hyperglycemia that he often observed in his patients with type 1 diabetes following an episode of insulin-induced hypoglycemia was a result of an "activation" of glycogenolytic mechanisms (Somogyi 1938 in Bolli et al 1993). He had observed that glycosuria which was absent in the early night hours became relevant in the early morning. His hypothesis was supported by his observation that a decrease in the evening insulin dose resulted in reduction of glycosuria in the early morning (Somogyi 1938 in Bolli et al 1993). The concept that "hypoglycemia begets hyperglycemia" gained wide popularity in the 1950's and is still popular today, despite a lack of supportive evidence (Bolli et al 1993). Gale and colleagues were the first to propose that the waning of insulin rather than counterregulatory hormones (ie-Somogyi effect) was responsible for fasting hyperglycemia (Gale et al 1980 in Bolli et al 1993). In contrast, several studies, which have monitored plasma glucose levels overnight, have found that as a rule nocturnal hypoglycemia is often followed by low, not high, fasting blood glucose levels (Gale and Tattersall 1979; Bendtson et al 1988; Lerman et al 1988; Stephenson and Schernthaner 1989; Vervoort et al 1996). However, as pointed out by Bolli, these obesrvations do not invalidate the existence of the Somogyi effect, as the modern era of insulin replacement is condusive to "overinsulinization" and hence the rarity of the "rebound" or Somogyi effect (Bolli et al 1993). In fact, the "rebound" or Somogyi effect following nocturnal hypogycemia is evident later on in the day, usually after breakfast, increasing plasma glucose levels by ~ 4 mmol/L and may

last up to 10 hours after hypoglycemia (Bolli et al 1993). Furthermore, insulin regimens which result in low depots, such as MDI or CSII (Lepore et al 2001) may accelerate this problem of a "delayed Somogyi effect" or what is referred to as "post-hypoglycemia insulin resistance" (Bolli et al 1993).

Given the complexities of nocturnal glycemic control coupled with limitations in current insulin preparations and regimens, individuals with type 1 diabetes are faced with an increased risk of nocturnal hypoglycemia and deterioration of morning and daytime glycemic control. Furthermore, in the context of intensive management, which strives to attain optimal glycemic control, individuals with type 1 diabetes, with already compromised defenses against hypoglycemia, are at an even greater risk for nocturnal hypoglycemia.

2.3.2 Consequences of Nocturnal Hypoglycemia

Nocturnal hypoglycemia is feared for three main reasons. First, it can easily lead to severe hypoglycemia, as clearly demonstrated in the DCCT where almost half of the severe episodes occurred between midnight and 8am (The DCCT Research Group 1991; The DCCT Research Group 1993). Part of the reason why severe hypoglycemia is more likely to occur during the night is due to further diminution of the counterregulatory hormone responses to hypoglycemia with sleep itself (Jones et al 1998). Second, nocturnal hypoglycemia can lead to impaired counterregulation and hypoglycemia unawareness (Veneman et al 1993) which can significantly increase the risk for severe hypoglycemia at any time of the day (Gold et al 1994; Strachan and Frier 2002) and thus lead to a vicious cycle

whereby hypoglycemia begets hypoglycemia (Cryer 1994, Cryer 2001). Finally, nocturnal hypoglycemia can deteriorate glycemic control later on in the day via the mechanism of post-hypoglycemia insulin resistance (Bolli et al 1993) thus making the pursuit of optimal glycemic control, which is required to reduce the long-term complications of diabetes (The DCCT Research Group 1993), more elusive. Other significant consequences associated with nocturnal hypoglycemia include deterioration in well-being and increased fatigue the next day (King et al 1998).

Therefore, nocturnal hypoglycemia is a significant problem for individuals with type 1 diabetes, especially in the context of intensive management. However, despite the fact that nocturnal hypoglycemia remains an obstacle for the attainment of optimal glycemic control, little evidence exists as to the exact frequency of its occurrence, especially in free-living individuals.

2.3.3 Frequency of Nocturnal Hypoglycemia in Type 1 Diabetes

In 1979, Gale and Tattersall first documented the incidence of nocturnal hypoglycemia in insulin-treated individuals (Gale and Tattersall 1979). 39 poorly controlled individuals, ages 9 to 66 years, who were on conventional management, participated in an overnight metabolic study to assess the incidence of nocturnal hypoglycemia, defined as a blood glucose < 2 mmol/L. Their results indicated that nocturnal hypoglycemia was very common, occurring in 56% of patients and lasted longer than 3 hours in the majority (17/22) of patients, with a

mean of 5 hours (Gale and Tattersall 1979). Furthermore, the majority of patients (11/17) did not experience any symptoms (Gale and Tattersall 1979).

Since the publication of this landmark study (Gale and Tattersall 1979) more than 20 years ago, there has been a paucity of studies in the area of nocturnal hypoglycemia, especially in adults, despite the fact that nocturnal hypoglycemia has been identified as a major barrier to optimal glycemic control in both children and adults with type 1 diabetes (The DCCT Research Group 1993; Yale 2001).

In 1987, Schiffrin and Suissa assessed the incidence of nocturnal hypoglycemia (blood glucose < 3.6 mmol/L).in 20 youth, aged 13 to 20 years, with type 1 diabetes on intensive management using CSII (Schiffrin and Suissa 1987). Participants were free-living and collected capillary blood glucose readings at home at designated time points during the night. Six nights (nocturnal blood glucose profiles) were collected per patient and formed the unit of analysis. The authors found that the incidence of nocturnal hypoglycemia was 13% of nights (or nocturnal profiles) (Schiffrin and Suissa 1987). They also found that the incidence of nocturnal hypoglycemia can be significantly reduced via consumption of an "extra" snack (6-8oz of milk) when blood glucose values at 10:30pm were < ~7 mmol/L. Therefore, the authors concluded that the bedtime blood glucose value, specifically at ~10:30 pm may be a useful predictor of nocturnal hypoglycemia and that consumption of an "extra" snack has the potential to minimize the risk of nocturnal hypoglycemia (Schiffrin and Suissa 1987). Whincup and Milner confirmed the findings of Schiffrin and Suissa in 102 children, aged 3 to 16 years

with type 1 diabetes managed by conventional therapy (Whincup and Milner 1987). They also demonstrated that a blood glucose value < 7 mmol/L at 10:00pm is the best predictor of nocturnal hypoglycemia and that ingestion of an "extra" snack consisting of 10g carbohydrate (source unspecified) was sufficient to reduce the incidence nocturnal hypoglycemia. However, no details were provided as to the extent of this reduction (Schiffrin and Suissa 1987; Whincup and Milner 1987).

In adults with type 1 diabetes, the incidence of nocturnal hypoglycemia (blood glucose < 3mmol/l), in the context of intensive therapy, was first documented by Bendtson and colleagues (Bendtson et al 1988). 48 adults, aged 20-53 years undergoing intensive therapy using MDI (n=23) or CSII (n= 25) participated in this inpatient overnight study (Bendtson et al 1988). The results of this study indicated that 7/23 (30%) of patients in the MDI groups and 11/25 (44%) of patients in the CSII group experienced at least one episode of nocturnal hypoglycemia during the night (Bendtson et al 1988). Furthermore, the total number of nocturnal hypoglycemic episodes was significantly higher with CSII compared with MDI (42 of 225 vs. 16 of 207 respectively, $p<0.025$). They also found a longer duration of nocturnal hypoglycemia with CSII compared to MDI (mean of 4 hours vs. 2 hours respectively, $p<0.05$). The bedtime blood glucose was a significant predictor of nocturnal hypoglycemia. The mean bedtime blood glucose value of individuals who experienced nocturnal hypoglycemia was 7.8 mmol/L vs. 11.1 mmol/L for individuals who did not experience nocturnal hypoglycemia (Bendtson et al 1988). A bedtime blood glucose < 6 mmol/L was

associated with a risk of 100% of nocturnal hypoglycemia in the MDI group. However, the bedtime blood glucose level was not a useful predictor in the CSII group (Bendtson et al 1988). As well, baseline glycemic control (HbA_{1c}) and morning glycemia were not found to be associated with nocturnal hypoglycemia (Bendtson et al 1988).

The most recent study assessing the incidence of nocturnal hypoglycemia (blood glucose < 3mmol/l) in adults with type 1 diabetes undergoing intensive management with MDI using regular human insulin before meals and NPH at bedtime was conducted by Vervoort and colleagues (Vervoort et al 1996) 31 adults, ages 19 to 67 years participated in this inpatient, overnight study. The investigators found 12 episodes of nocturnal hypoglycemia over a total of 31 patient-nights (39 episodes per 100 patient-nights). Nocturnal hypoglycemia occurred in 29% of nights and in 35% of patients (Vervoort et al 1996). Furthermore, they found that the majority (67%) of the episodes were asymptomatic and tended to either occur very early in the night (between 11pm and 1am) or very early in the morning (between 4am and 7:30am), with no episodes observed at 3am, the time most clinicians advice patients to test their blood glucose if nocturnal hypoglycemia is suspected (Vervoort et al 1996). The median duration of nocturnal hypoglycemia was found to be 1 hour with a range of 0.5 to 1.5 hours (Vervoort et al 1996). In this study they also found that the bedtime blood glucose value was predictive of nocturnal hypoglycemia in the early night but not in the early morning. A bedtime (11pm) blood glucose value of ≤ 7.5 mmol/L, similar to the level observed in previous studies (Schiffrin and

Suissa 1987; Whincup and Milner 1987; Bendtson et al 1988), was found to be predictive of nocturnal hypoglycemia in the early part of the night. Moreover, consumption of a bedtime snack (composition unspecified) was protective against nocturnal hypoglycemia in the early night but had no impact on early morning hypoglycemia. A bedtime blood glucose level > 7.5 mmol/L was never followed by early night hypoglycemia irrespective of whether or not a bedtime snack was consumed (Vervoort et al 1996). A fasting blood glucose level < 5.5 mmol/L was associated with early morning hypoglycemia. The authors concluded that early night hypoglycemia is likely due to the extended action of regular short-acting insulin and early morning hypoglycemia is due to the NPH insulin (Vervoort et al 1996). In this study, no association with baseline glycemic control (HbA_{1c}) was found with nocturnal hypoglycemia in agreement with a previous study in intensive management (Bendtson et al 1988).

The evidence presented thus far clearly describes the magnitude of the problem of nocturnal hypoglycemia in the context of intensive management. However, all the previous aforementioned studies were either conducted in "artificial conditions" (ie- not free-living) (Gale and Tattersall 1979; Bendtson et al 1988; Vervoort et al 1996) or relied on self-reported data of nocturnal hypoglycemia (The DCCT Research Group 1993; Schiffrin and Suissa 1987; Whincup and Milner 1987). As most studies have demonstrated that the majority of nocturnal hypoglycemic episodes are asymptomatic (Gale and Tattersall 1979; Bendtson et al 1988; Vervoort et al 1996), relying on self-reports may grossly underestimate the true frequency of nocturnal hypoglycemia. Moreover, patients

may not be able to adhere well with requests for data collection during the night, as was the case in the DCCT (The DCCT Research Group 1993) and a recent study whose goal was to assess the efficacy of CSII on nocturnal hypoglycemia but could not do so due to the lack of available data (Kanc et al 1998). Therefore, detection of nocturnal hypoglycemia, especially in free-living conditions, has presented a challenge in determining the true frequency of nocturnal hypoglycemia in type 1 diabetes mellitus.

2.3.4 Detection of Nocturnal Hypoglycemia in Type 1 Diabetes

a) Continuous Glucose Monitoring Technology

The advent of the first marketed continuous glucose monitor: the continuous glucose monitoring system (CGMS, Medtronic/MiniMed Inc, Sylmar, CA) in 1999 has enabled the possibility of detecting asymptomatic nocturnal hypoglycemia in free-living conditions (Kochinsky and Heinemann 2001). As previously described in section 2.1, preliminary studies have indicated improvements in glycemic control with the use of this technology (Bode et al 1999). By providing glucose readings every 5 minutes, for up to 288 reading per day, a very precise picture of the 24-hour glycemic profile can be obtained. Hence, the possibilities for very precise titrations of insulin, especially for overnight control, are such that it may be possible to prevent nocturnal hypoglycemia without compromising on the pursuit of optimal glycemic control. This technology may therefore prove to be a very useful tool in the prevention of nocturnal hypoglycemia in the context of intensive management.

Strategies for prevention of nocturnal hypoglycemia are based on providing more physiological replacement of insulin via the use of more "physiological" insulin preparations (ie- insulin analogues) or via the use of more "physiological" insulin delivery regimens (ie- MDI and CSII) and on the use of bedtime snacks, with an emphasis on specific bedtime snack compositions, namely raw cornstarch and protein.

2.3.5 Strategies for Prevention

a) Insulin Analogues

Insulin analogues, such as the short-acting insulin lispro and more recently aspart, have been marketed as being more physiological (Lepore et al 2000, especially for postprandial glycemic control (Anderson et al 1997; Jacobs et al 1997; Zinman et al 1997; Ahmed and Home 1998; Heller et al 1998). The shorter action profile of the insulin analogues (eg. Insulin lispro) compared to human regular insulin have been shown to be ideal for handling the glycemic excursions following a meal, especially dinner, without causing nocturnal hypoglycemia due to the extended action as has been the case with human regular insulin (Ahmed et al 1998; Heller et al 1999). Studies comparing insulin lispro with human regular insulin have shown reductions in the frequency of hypoglycemia (Anderson et al 1997; Jacobs et al 1997; Zinman et al 1997; Ahmed and Home 1998; Heller et al 1998) including nocturnal hypoglycemia (Ahmed et al 1998; Heller et al 1999). In fact, a recent study demonstrated that the incidence of nocturnal hypoglycemia could be reduced by 70% when insulin lispro is used at supper instead of regular

insulin in the setting of intensive insulin therapy (Heller et al 1999). Aside from the short-acting insulins, the new long-acting basal insulin analogue: insulin glargine, has already shown promise in providing more physiological basal insulin replacement, especially for overnight (Lepore et al 2000) and is being compared to CSII, the "gold standard" of basal insulin replacement (Bolli et al 1993, Lepore et al 2000; Madsbad).

b) Insulin Regimens

i) Multiple Daily Injections of Insulin (MDI)

It was first suggested by Bolli and colleagues that splitting the evening dose of insulin (ie- short-acting insulin at dinner and longer-acting at bedtime) may be an important strategy in preventing nocturnal hypoglycemia in individuals with type 1 diabetes (Bolli et al 1993). The rationale for such a suggestion is based on studies which show that when NPH insulin is injected at dinner, it results in excess plasma insulin bioavailability at around midnight, a time at which humans, including individuals with type 1 diabetes, are more insulin sensitive (Bolli et al 1993; Lepore et al 2000). The injected insulin subsequently begins to wane at dawn, a time of reduced insulin sensitivity (Bolli et al 1993). Therefore, in theory moving the injection of NPH insulin from dinner to bedtime may prevent nocturnal hypoglycemia and fasting hyperglycemia. This hypothesis was recently tested in a randomized, controlled, outpatient study of 22 adults with type 1 diabetes undergoing intensive management (Fanelli et al 2002). Participants received regular insulin before meals and NPH insulin either at

supper or at bedtime for 4 months. The primary end point, on which sample size calculations were based, was a reduction of 50% in nocturnal hypoglycemia (≤ 4mmol/L). Participants were instructed to measure blood glucose values before each insulin injection, at bedtime and at 3 am every other day. At the end of each 4 month period, long-term glycemic control, as assessed via HbA_{1c}, was also determined as well as awareness to hypoglycemia and thresholds for counterregulatory hormone and symptom responses via a stepped-hypoglycemic clamp study (Fanelli et al 2002). At the end of the study, 308 and 301 blood glucose values were collected at 3am from the supper and bedtime NPH groups respectively. The results of the study indicated the 90 hypoglycemic episodes had occurred during the supper NPH periods versus 28 episodes during the bedtime NPH periods, a reduction of 62% with NPH given at bedtime instead of at supper, $p<0.001$. Furthermore, the fasting plasma glucose value was significantly ($p<0.05$) lower with in the NPH at bedtime group vs. NPH at supper and the HbA_{1c} was also better in the NPH at bedtime group compared to the NPH at supper group (mean 7.0 % vs. 7.5% respectively, $p=0.004$). The glycemic thresholds for catecholamine and symptom responses were also lower (ie- occurred at higher plasma glucose concentrations) with NPH given at bedtime rather than at supper (Fanelli et al 2002). In conclusion, this study clearly demonstrated that the simple move of giving NPH at bedtime instead of at supper with the short-acting insulin significantly (~60%) decreases the incidence of nocturnal hypoglycemia, improves long-term glycemic control and catecholamine and symptom responses to hypoglycemia (Fanelli et al 2002). The authors also

speculated on what might occur had a short-acting insulin analogue (lispro or aspart) been used at dinner instead of human regular insulin (Fanelli et al 2002). Further research is required to answer this question.

ii) Continuous Subcutaneous Insulin Infusion (CSII)

In their seminal article on nocturnal glycemic control in type 1 diabetes, Bolli and colleagues suggested that continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is the "gold standard" for basal insulin replacement, particularly for overnight glycemic control (Bolli et al 1993). Almost a decade later, CSII is still being regarded as the "gold standard" for basal insulin replacement against which all basal insulin preparations, including the latest basal insulin analogue: glargine insulin, are compared (Lepore et al 2000). With the use of only short-acting insulin, the variability of insulin absorption is much less with CSII compared to MDI (Bolli et al 1993; Lepore et al 2000). Furthermore, all current insulin pumps allow for programming of variable basal rates, so that it is possible to provide a lower rate of insulin at the time where requirements are the lowest (ie- midnight to 4 am) and a higher rate to meet increased needs (ie- at dawn or after breakfast) (Bolli et al 1993; Lenhard et al 2001; Lepore et al 2002).

Substitution of CSII for bedtime NPH insulin has demonstrated improved catecholamine and symptom response to experimentally-induced hypoglycemia likely due to a reduction of nocturnal hypoglycemia (Kanc et al 1998). However, due to a lack of available data during the overnight period, the authors could not

draw firm conclusions regarding nocturnal hypoglycemia (Kanc et al 1998). Instead, the results of the study indicated that CSII vs. NPH at bedtime was superior in reducing the frequency of daytime hypoglycemic episodes and improving catecholamine and symptom responses to experimentally-induced hypoglycemia (Kanc et al 1998).

The use of insulin lispro in CSII has also been shown to be superior to CSII with human regular insulin in reducing the frequency of hypoglycemia, including self-reported nocturnal hypoglycemia, in adults with type 1 diabetes undergoing intensive management without deteriorating overall glycemic control or counterregulatory hormone response and symptom awareness to experimentally-induced hypoglycemia (Tsui et al 2001).

Aside from strides that have been made in the quest to attain physiological replacement of insulin, another important strategy in the prevention of nocturnal hypoglycemia is the provision of an exogenous source of glucose, especially at a highly vulnerable period (ie- overnight).

c) Bedtime Snacks

The efficacy of a bedtime snack in the prevention of nocturnal hypoglycemia in type 1 diabetes was first documented in the late 1980's (Schiffrin and Suissa 1987; Whincup and Milner 1987; Bendtson et al 1988), including in the context of intensive management (Schiffrin and Suissa 1987; Bendtson et al 1988). A more recent study also confirmed the importance of a bedtime snack in reducing the frequency of nocturnal hypoglycemia in adults with

type 1 diabetes undergoing intensive management (Vervoort et al 1996). As well, analyses conducted on the DCCT cohort revealed the importance of various diet behaviours, including consistency with consumption of the recommended bedtime snacks, in the attainment of optimal glycemic control (Delahanty and Halford 1993).

The aforementioned studies have provided evidence that bedtime snacks are very important for the prevention of nocturnal hypoglycemia. However, the type of snack or composition was not adequately specified in any of the studies (Schiffrin and Suissa 1987; Whincup and Milner 1987; Bendtson et al 1988, Vervoort et al 1996).

i) Composition of Bedtime Snacks

Raw (Uncooked) Cornstarch

In 1984, Chen and colleagues revolutionized the treatment of children with type 1 glycogen storage disease by demonstrating that the use of intermittent feedings (every 6 hours) with raw or uncooked cornstarch was a viable alternative to continuous nasogastric nocturnal infusion of glucose, the standard therapy in glycogen storage disease, for the prevention of hypoglycemia (Chen et al 1984). Cornstarch was able to maintain normoglycemia (blood glucose >3.9 mmol/L) for as long as 6 hours in most patients (Chen et al 1984). Subsequent studies confirmed the original findings of Chen and colleagues in children and adults with type 1 glycogen storage disease (Smit et al 1984; Wolfsdorf and Crigler 1997). The latter study, conducted in adults (Wolfsdorf and Crigler 1997) demonstrated

that a single dose of cornstarch equivalent to 1.76 g/kg was sufficient to maintain nocturnal glycemic levels > 3.9 mmol/L for ≥ 7 hours in most young adults with type 1 glycogen storage disease (Wolfsdorf and Crigler 1997).

In 1992 Ververs and colleagues were the first to assess the efficacy of raw cornstarch in the context of type 1 diabetes (Ververs et al 1993). They compared raw cornstarch versus a usual snack on prevention of nocturnal hypoglycemia (blood glucose ≤ 3 mmol/L) in 9 children, undergoing conventional management, via a crossover, inpatient metabolic study. Raw cornstarch was chosen on the basis that it had proven to be successful for the prevention of nocturnal hypoglycemia in children with type 1 glycogen storage disease (Chen et al 1984; Smit et al 1984). The usual snack was either fruit, biscuits or milk (quantities varied). The carbohydrate content of the evening usual snack, which ranged from 0.2 to 1.7g/kg body weight (median 0.4g/kg), was replaced by a similar quantity of raw cornstarch which was dissolved in water in the cornstarch condition. When the usual snack contained fat or protein, cheese was added to the cornstarch condition (Ververs et al 1992). The findings of the study indicated that raw cornstarch did not prevent nocturnal hypoglycemia in the dose used but blood glucose levels dropped more slowly than those after the usual or standard snack (Ververs et al 1992).

One major criticism of the study (Ververs et al 1992), as pointed out by Kaufmann and Devgan (Kaufman and Devgan 1996) was that cornstarch, which was dissolved in water, was given as the entire snack. Therefore, it did not contain

mono or disaccharides as did the usual snack even though the carbohydrate content of the two snack conditions was the same.

In 1996, Kaufman and Devgan devised a protocol in which 25%-50% of the carbohydrate content of the standard snack was replaced by raw cornstarch in 13 children and adolescents with type 1 diabetes, undergoing intensive management, via an inpatient, crossover study (Kaufman and Devgan 1996). The standard snack was determined to constitute 10% of the total daily Caloric intake of the participants and contain 50% of calories as carbohydrate, 30% from fat and 20% from protein (no other description of snack composition was provided). 25%-50% of the carbohydrate content of the evening snack was replaced by cornstarch, added to milk, during the cornstarch snack condition (5-15g cornstarch) (Kaufman and Devgan 1996). The results of the study indicated that the cornstarch snack significantly reduced the frequency of nocturnal hypoglycemic episodes compared to the standard snack without deteriorating overall glycemic control . Furthermore, the side effects of cornstarch (transient diarrhea, abdominal distension and increased flatulence) were not observed in this study (Kaufman and Devgan 1996) likely due to the smaller quantities of cornstarch used compared to those used in glycogen storage disease where these side-effects were observed (Chen et al 1984).

The participants in the study by Kaufman and Devgan (Kaufman and Devgan 1996) were very well controlled with a mean HbA_{1c} of 6.8%. The authors questioned whether similar benefits of cornstarch would be realized in a cohort of subjects with varying levels of glycemic control Therefore, a larger study was

devised by Kaufman and colleagues in order to assess the efficacy of raw cornstarch, substituted in a standard snack, on prevention of nocturnal hypoglycemia in 51 youth, ages 14 –22 years, with type 1 diabetes and with varying levels of glycemic control (Kaufman et al 1996). The standard snack was defined as 17g carbohydrate + 1 protein exchange in the form of a sugar-free jello pudding. Raw cornstarch (5g) replaced part of the carbohydrate content of the jello pudding. The results obtained confirmed those of the previous study (Kaufman and Devgan 1996) in that cornstarch, as part of the evening snack, significantly reduced the frequency of nocturnal hypoglycemia compared to an equivalent snack without cornstarch without deteriorating overall glycemic control (Kaufman et al 1996).

The studies by Kaufman and colleagues led to the development of a specially formulated snack bar which contained raw cornstarch and which was subsequently marketed as ZBar ™ (Baker Norton, Miami, Fla). The authors evaluated the efficacy of this special bar in 79 youth with type 1 diabetes and 9 control subjects who did not have diabetes. The bar with cornstarch was compared to a bar of equivalent macronutrient composition but without cornstarch. The results indicated that the cornstarch containing bar was superior to the bar without cornstarch in reducing the incidence of nocturnal hypoglycemia (Kaufman et al 1996).

In 1999 Axelsen and colleagues evaluated uncooked cornstarch in 12 adults with type 1 diabetes, undergoing intensive management, with regular insulin before meals and NPH at bedtime. Cornstarch was dissolved in a sugar-

free drink mix and was compared to placebo (sugar-free drink). Participants were provided these mixes and asked to consume them for 4 weeks at home. During the second and fourth weeks they were asked to record their blood glucose value at 3am every other night. Nine of the twelve participants were also evaluated at the end of each test period via an inpatient, overnight study where blood samples were collected every hour. The results of the study indicated that there was a significant reduction (> 50%) in the number of self-reported nocturnal hypoglycemic episodes with cornstarch compared to placebo (11 vs 3 episodes respectively, $P<0.05$) without adversely impacting on HbA_{1c} or lipid levels (Axelsen et al 1999). However, the authors cautioned that firm conclusions about the effectiveness of cornstarch in preventing nocturnal hypoglycemia in adults with type 1 could not be drawn due to the use of a carbohydrate-free placebo. In other words, this study demonstrates that raw cornstarch is better than placebo (no snack) in preventing nocturnal hypoglycemia. Whether or not it would be as effective as a standard or conventional snack remains to be clarified.

Aside from its proven effectiveness in the contexts of type 1 glycogen storage disease and type 1 diabetes, raw cornstarch has also been shown to be effective in the maintenance of plasma glucose concentrations in adults with postprandial hypoglycemic syndrome (Lozano et al 1990) and in adults with type 2 diabetes (Axelsen et al 1999).

All the above studies used standard cornstarch as opposed to high-amylose cornstarch (Behall and Howe 1995). The mechanism (s) by which raw cornstarch is able to provide a relatively continuous source of glucose for ≥ 7 hours

(Wolfsdorf and Crigler 1997) including overnight (Wolfsdorf and Crigler 1997, Axelsen et al 1999) are related to retarded digestion and absorption secondary to the uncooked nature of the starch (Björck et al 1994).

The goal for the ideal bedtime snack composition, in the management of type 1 diabetes, is to provide a source of overnight glucose, specifically at the time that the bedtime insulin peaks in order to prevent nocturnal hypoglycemia. At the same time, the ideal bedtime snack composition must not significantly deteriorate nocturnal glycemic control or morning (fasting) glycemia or have a negative impact on other metabolic parameters (eg. lipid profile). The ideal snack must also not have a negative impact on body composition or quality of life.

The above, aforementioned, studies provide evidence that raw cornstarch, substituted in an evening snack, has the potential to provide an ideal bedtime snack composition. However, body composition and quality of life were not evaluated in any of the studies to date.

Aside from raw cornstarch, the use of protein (or specific amino acids) in the prevention of nocturnal hypoglycemia in type 1 diabetes have also been evaluated.

Protein

The glycemic response of protein was first evaluated in 1936 in individuals with diabetes (Conn and Newburgh 1936) due to earlier findings that approximately 50% of ingested protein is converted to glucose (Janney 1916 in Conn and Newburgh 1936). Aside from providing substrate (amino acids) for gluconeogenesis (Sherwin and Felig 1981), the glycemic response to protein is also due to stimulation of glucose counterregulatory hormones such as glucagon (Krezowski et al 1986; Gannon et al 1988; Nuttall and Gannon 1990). Protein is also a potent stimulator of insulin (Nuttall and Gannon 1990). Therefore, protein appears to have a different glycemic raising potential depending on diabetes status. For example, the glycemic effect of protein in individuals without diabetes and those with type 2 diabetes is to maintain or reduce postprandial glycemic levels (Krezowski et al 1986; Gannon et al 1988; Nuttall and Gannon 1990). Conversley, as individuals with type 1 diabetes have no endogenous insulin, the glycemic effect of protein is to increase postprandial glycemia (Peters and Davidson 1993). The resultant glycemic level, in individuals with type 1 diabetes, will therefore depend on the supply and pharmacokinetics of exogenous insulin. However, the effect of protein on glycemic response only occurs after ~5 hours (Peters and Davidson 1993; Gray et al 1995). By providing glucose after several hours, especially close to the peak time of usual bedtime insulin preparations (Lepore et al 2000), protein may be an ideal snack composition in the prevention of nocturnal hypoglycemia in type 1 diabetes.

The first study to evaluate the role of protein on nocturnal glycemic control and regulation in type 1 diabetes was conducted by Winiger and colleagues (Winiger et al 1995). The protein content of the evening meal (ie-supper) on nocturnal glycemic control and regulation was evaluated in 8 adults with type 1 diabetes in an overnight metabolic study (Winiger et al 1995). In this study, participants were presented with two evening meal compositions in random order: low protein-high fat (5% protein, 60% fat) and high protein-low fat (35% protein, 30% fat). The authors measured plasma glucose levels as well as free insulin, glucagon, cortisol and growth hormone. They found that the protein meal increased plasma glucose levels for several hours during the night. Plasma glucose concentrations were significantly higher between 11pm and 4am ($p<0.02$) after the high protein meal compared to the low protein meal. They also found that the concentration of glucagon was also significantly ($p=0.023$) higher after the high protein meal compared to the low protein meal but did not find any significant differences between the two groups with respect to cortisol and growth hormone concentrations. The authors concluded that an increased protein content in the evening meal may provide a source of glucose for several hours during the night, likely via stimulation of glucagon, and that this may be an important strategy for prevention of nocturnal hypoglycemia in susceptible individuals.

Although the study by Winiger et al (Winiger et al 1995) was pivotal in demonstrating the important role of protein in nocturnal glycemic control and regulation, there were several important limitations in this study. First, the quantity of fat differed between the 2 groups and second, participants were not

provided with the option of consuming a bedtime snack, a practice that is relevant for the majority of people with type 1 diabetes (The DCCT Research Group 1995). Also, participants received an intravenous infusion of insulin overnight. Therefore, it is difficult to extrapolate these findings to the real-life conditions of individuals with type 1 diabetes who rely on subcutaneous injections of insulin and thus on the inherent limitations associated with such preparations (Lepore et al 2000).

The first study to assess the efficacy of an amino acid (alanine) compared to a standard snack at bedtime on prevention of nocturnal hypoglycemia in type 1 diabetes was conducted in 1997 (Saleh and Cryer 1997). Four treatment arms were assessed: usual snack, standard snack (240ml 2% milk + 1 slice toast, ~200 Kcal), alanine (40g plus 10g glucose, ~200Kcal); terbutaline (a β_2-adrenergic agonist). 15 individuals with type 1 diabetes for a mean duration of 8 years participated in this randomized, crossover inpatient study. Nine participants were on conventional insulin management of two injections of regular and NPH insulin. The findings of this study were that alanine and terbutaline were better able to prevent nocturnal hypoglycemia compared to a standard bedtime snack which was only effective during the first half of the night (Saleh and Cryer 1997).

Although protein continues to be recommended by clinicians in the bedtime snack composition of individuals with type 1 diabetes, the evidence thus far does not appear to be conclusive. For this reason, the role of protein in the bedtime snack of individuals with type 1 diabetes is a current source of controversy (Franz 2000) which can only be clarified by further research.

2.4 Overall Conclusion

This literature review has provided background on what type 1 diabetes is and the problems that arise due to a lack of insulin, the key hormone in metabolic regulation. Since individuals with type 1 diabetes must rely on exogenous insulin in order to survive, they are dependent on the inherent limitations of the pharmacokinetics of current insulin preparations and insulin delivery regimens.

In 1993 a landmark study, the Diabetes Control and Complications Trial (DCCT), unequivocally demonstrated that attainment of glycemic control as close to normal as possible is necessary to reduce the chronic complications associated with type 1 diabetes which include: retinopathy, nephropathy, neuropathy and cardiovascular disease. The attainment of "optimal" glycemic control was achieved via intensive management which consisted of intensive insulin therapy (multiple daily injections of insulin or MDI and continuous subcutaneous insulin infusion or CSII, also known as insulin pump therapy); intensive nutritional counseling, frequent self-monitoring of blood glucose (SMBG) of at least 4 times per day and frequent contact with the health care team (weekly telephone contact and monthly clinic visits). Although intensive management was able to significantly reduce the risk of chronic complications, intensive management also significantly increased the risk of severe hypoglycemia, which occurred primarily overnight.

Hypoglycemia, and more specifically nocturnal hypoglycemia, remains a major obstacle to the attainment optimal glycemic control. Some of the reasons

as to why individuals with type 1 diabetes are faced with an increased risk of hypoglycemia, and in particular, nocturnal hypoglycemia include: compromised hormonal defenses to ensuing hypoglycemia, impaired awareness of hypoglycemia and alterations of the blood glucose levels at which secretion of hormones and perception of warning symptoms to ensuing hypoglycemia occur. All of these problems are further exacerbated by inherent limitations in the pharmacokinetics of current insulin preparations and delivery regimens, especially during the nocturnal period. Moreover, sleep itself causes a further diminution of the catecholamine response to hypoglycemia. Therefore, prevention of nocturnal hypoglycemia is critical.

Despite the fact that nocturnal hypoglycemia is recognized as a major obstacle in the management of type 1 diabetes, there is a paucity of scientific evidence regarding the frequency of its occurrence and potential strategies for its prevention. Strategies for prevention of nocturnal hypoglycemia had not been addressed in any North American clinical practice guidelines until very recently. Canada was the first country in the world to develop specific evidence-based guidelines for the prevention and management of hypoglycemia. However, nocturnal hypoglycemia was not adequately addressed, even in this document, due to a lack of available scientific data.

Therefore, more research in the area of nocturnal hypoglycemia and in particular, prevention of nocturnal hypoglycemia, is urgently needed.

2.5 References

Ahmed ABE, Home PD: The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. Diabetes Care 21: 32-37, 1998

Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alessio D.J: Risk factors for frequent and severe hypoglycemia in type 1 diabetes. Diabetes Care 24 (11): 1878-1881, 2001

American Diabetes Association: Consensus statement on self-monitoring of blood glucose. Diabetes Care 19: s62-s66, 1996

American Diabetes Association: Clinical practice recommendations 2002. Diabetes Care 25 (suppl 1): s1-s147, 2002

American Medical Association: Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285: 2486- 2497, 2001

Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 37: 901-907, 1988

Anderson JH, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, DiMarchi R, Multicentre Insulin Lispro Group: Redcution of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes 46: 265-270, 1997

Austin EJ, Deary IJ: Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. Diabetes Care 22 (8): 1273-1277, 1999

Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. J Int Med 245: 229-236, 1999

Banting FG, Best CH: The internal secretion of the pancreas. J Lab Clin Med 8 (5): 251-266, 1922

Behall KM, Howe JC: Effect of long-term consumption of amylose vs. amylopectin starch on metabolic variables in human subjects. Am J Clin Nutr 61: 334-340, 1995

Bendtson I, Kverneland A, Pramming S, Binder C: Incidence of nocturnal hypoglucemia in insulin-dependent diabetic patients on intensive therapy. Acta Med Scand 223: 543-548, 1988

Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. Diabetes Care 4: 239-244, 1989

Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. Diabetes Care 7 (2): 188-199, 1984

Bjorck I, Granfeldt Y, Liljeberg H, Tovar J , Asp NG: Food properties affecting the digestion and absorption of carbohydrates. Am J Clin Nutr 59 (3 Suppl): 699S-705S, 1994

Bliss M, *The discovery of insulin*. 3 ed. 2000, Toronto: University of Toronto Press.

Bode BW, Gross TM, Thornton KR, Mastrototaro J.J: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. Diabetes Res Clin Pract 46 (3): 183-190, 1999

Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care 19 (4): 324-327, 1996

Boden G, Reichard GA, Jr , Hoeldtke RD, Rezvani I ,Owen OE: Severe insulin-induced hypoglycemia associated with deficiencies in the release of counterregulatory hormones. N Engl J Med 305 (20): 1200-1205, 1981

Boland E, Monsod T, Delucia M, Brandt CA, Fernando S ,Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care 24 (11): 1858-1862, 2001

Boland EA, Grey M, Oesterle A, Fredrickson L ,Tamborlane WV: Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. Diabetes Care 22 (11): 1779-1784, 1999

Bolli G, De Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. Diabetes 32: 134-141, 1983

Bolli GB, Fanelli CG: Physiology of glucose counterregulation to hypoglycemia. Endocrinol Metab Clin North Am 28 (3): 467-493, 1999

Bolli GB, Fanelli CG, Perriello G, De Feo P: Nocturnal blood glucose control in type 1 diabetes mellitus. Diabetes Care 16: 71-89, 1993

Bott S, Bott U, Berger M, Muhlhauser I: Intensified insulin therapy and the risk of severe hypoglycaemia. Diabetologia 40 (8): 926-32, 1997

Carlson MG, Campbell PJ: Intensive insulin therapy and weight gain in IDDM. Diabetes 42: 1700-1707, 1993

Chen YT, Cornblath M, Sidbury JB: Cornstarch therapy in type 1 glycogen-storage disease. N Engl J Med 310 (3): 171-175, 1984

Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W: Reduced awareness of hypoglycemia in adults with IDDM. Diabetes Care 18 (4): 519-522, 1995

Conn JW, Newburgh LH: The glycemic response to isoglucogenic quantities of protein and carbohydrate. J Clin Invest 15: 667-671, 1936

Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 10 (5): 617-621, 1987

Cranston I, Reed LJ, Marsden P.K , Amiel SA: Changes in regional brain (18)F-fluorodeoxyglucose uptake at hypoglycemia in type 1 diabetic men associated with hypoglycemia unawareness and counter-regulatory failure. Diabetes 50 (10) 2329-2336, 2001

Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a viscious cycle. Diabetes 41: 1335-1340, 1992

Cryer PE: Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. Enodocrinology and Metabolism Clinics of North America 28 (3): 495-499, 1999

Cryer PE: Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 281: E1115-E1121, 2001

Cryer PE, Fisher JN, Shamoon H: Hypoglycemia: Technical Review. Diabetes Care 17 (7): 734-755, 1994

Dagogo-Jack S, Rattarasarn C, Cryer PE: Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 43: 1426-1434, 1994

Davidson PC: Bolus and supplemental insulin, In: The Insulin Pump Therapy Book, Fredrickson L, Editor. 1995, MiniMed Technologies: Sylmar. p. 59-71.

Davis EA, Keating B, Byrne GC, Russell M, Jones TW: Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 20 (1): 22-25, 1997

Davis MR, Mellman M, Shamoon H: Further defects in counter-regulatory responses induced by recurrent hypoglycemia in IDDM. Diabetes 41: 1335-1340, 1992

Davis SN, Shavers C, Mosqueda-Garcia R, Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. Diabetes 46 (8): 1328-1335, 1997

Davis SN, Shavers C, Davis B, Costa F: Prevention of an increase in plasma cortisol during hypoglycemia preserves subsequent counterregulatory responses. J Clin Invest 100: 429-438, 1997

Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. Diabetes 42 (2): 341-344, 1993

Delahanty L.M, Halford BN: The role of diet behaviors in achieving improved glycemic control in intensively treated patients in the Diabetes Control and Complications Trial. Diabetes Care 16 (11): 1453-1458, 1993

Ebeling P, Jansson PA, Smith U, Lalli C, Bolli GB, Koivisto VA: Strategies toward improved control during insulin lispro therapy in IDDM. Importance of basal insulin. Diabetes Care 20 (8): 1287-1289, 1997

Esslinger K, Rochon G, Bonhomme S, Yale JF: Therapy of hypoglycemia by nurses on hospital wards: assessment of protocol knowledge. Can J Diabetes Care 25 (1): 14-21, 2001

Evans MI, Halter JB, Porte D: Comparison of double and single isotope enzymatic derivative methods for measuring catecholamines in plasma. Clin Chem 28: 764-770, 1978

Evans ML, Pernet A, Lomas J, Jones J, Amiel SA: Delay in onset of awareness of acute hypoglycemia and of restoration of cognitive performance during recovery. Diabetes Care 23 (7): 893-897, 2000

Fanelli C, Pampanelli S, Calderone S, Lepore M, Annibale B, Compagnucci P, Brunetti P, Bolli GB: Effects of recent, short-term hypeglycemia on responses to hypoglycemia in humans: relevance to the pathogenesis of hypoglycemia unawareness and hyperglycemia-induced insulin resistance. Diabetes 44: 515-518, 1995

Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P, Porcellati F, Scionti L, Santeusano F, Brunetti P, Bolli GB: Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most neuroendocrine responses to, smptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 42: 1683-1689, 1993

Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer P: Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. Diabetes 47: 1920-1927, 1998

Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB: Administration of neutral protamine hagedorn insulin at bedtime versus with dinner in type 1 diabeets mellitus to avoid nocturnal hypoglycemia and improve control. Ann Int Med 136 (7): 504-514, 2002

Folstein MF, Folstein SE, McHugh PR: Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-198, 1975

Franz M: Protein Controversies in Diabetes. Diab Spect 13 (3): 132-141, 2000

Fredrickson L Graff M, *MiniMed Certified Pump Trainer Manual for Insulin Pump Therapy*. 1998, Sylmar: MiniMed Inc.

Fritsche A, Stefan N, Haring H, Gerich J, Stumvoll M: Avoidance of hypoglycemia awareness by increasing b-adrenergic sensitivity in type 1 diabetes. Ann Int Med 134 (9): 729-736, 2001

Fruehwald-Schultes B, Born J, Kern W, Peters A, Fehm HL: Adaptation of cognitive function to hypoglycemia in healthy men. Diabetes Care 23 (8): 1059-1066, 2000

Gale EAM, Kurtz AB, Tattersall RB: In search of the somogyi effect. Lancet ii 279-282, 1980

Gale EAM, Tattersal RB: Unrecognized Nocturnal Hypoglycemia In Insulin-Treated Diabetics. The Lancet May 19: 1049-1052, 1976

Gannon MC, Nuttall FQ, Neil BJ, Westphal SA: The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. Metabolism 37 (11): 1081-10888, 1988

Gerich JE: Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37: 1608-1617, 1988

Gold AE, MacLeod K.M, Frier B.M: Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 17 (7): 697-703, 1994

Gonder-Frederick LA, Julian DM, Cox DJ, Clarke WL, Carter WR: Self-measurement of blood glucose. Accuracy of self-reported data and adherence to recommended regimen. Diabetes Care 11 (7): 579-585, 1988

Gray RO, Butler PC, Beers TR, Kryshak EJ, ,Rizza RA: Comparison of the ability of bread versus bread plus meat to treat and prevent subsequent hypoglycemia in patients with insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 81 (4): 1508-1511, 1996

Gross TM, Bode BW, Einhorn D, Kayne D.M, Reed JH, White NH, Mastrototaro JJ: Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. Diabetes Technol Ther 2 (1): 49-56, 2000

Haakens K, Dahl-Jorgenson K, Vaaler S, Aagenaes O, Mosand R, Hanssen KF: What happens in the long-term to the intensively treated IDDM pateinet?: a four year follow-up. Practical Diabetes International 12 (4): 178-181, 1995

Hanaire-Broutin H, Melki V, Bessiere-Lacombe S, Tauber JP, The Study group For The Development of Pump Therapy in Diabetes: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using lispor in type 1 diabetic patients on intensifeid treatment. Diabetes Care 23 (9): 1232-1235, 2000

Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 47: 223-226, 1991

Heller SR, Amiel S, Mansell P, UK Lispro Study group: Effect of the fast-acting insulin analog lispor on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 22 (10): 1607-1611, 1999

Hepburn DA, Deary IJ, Frier BM, Patrick AW, Quinn JD, Fisher BM: Symptoms of acute insulin-induced hypoglycemia in humans with and wtihout IDDM: factor-analysis approach. Diabetes Care 14 (11): 949-957, 1991

Herbel GH, Boyle PJ: Hypoglycemia: pathophysiology and treatment. Endocrinology and Metabolism Clinics of North America 29 (4): 725-743, 2000

Hess A, Beebe CA: Glycemic effect of a small amount of protein added to an evening snack in type 1 diabetes (abstract). Diabetes Care 22 (suppl 1): 306A, 1999

Hopkins M: Drug advances in the prevention and treatment of diabetes. A Diabetes Primer 1: s21-s29, 2002

Hoskins PL, Alford JB, Handelsman DJ, Yue DK, Turtle JR: Comparison of different models of diabetes care on compliance with self-monitoring of blood glucose by memory glucometer. Diabetes Care 11 (9): 719-24, 1988

Hvidberg A, Fanelli CG, Hershey T, Terkamp C, Craft S, Cryer PE: Impact of recent antecedent hypoglycemia on hypoglycemic cognitive dysfunction in nondiabetic humans. Diabetes 45 (8): 1030-1036, 1996

Jacobs M.A, Keulen ET, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine R J: Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. Diabetes Care 20 (8): 1279-1286, 1997

Janssen M.M, Snoek F J, Heine RJ: Assessing impaired hypoglycemia awareness in type 1 diabetes: agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycemia. Diabetes Care 23 (4): 529-532, 2000

Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM: Evaluation of the novel tanita body-fat analyser to measure body composition by comparison with a four-compartment model. British Journal of Nutrition 83: 115-122, 2000

Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia in IDDM children. Diabetes Care 338: 1657-1662, 1998

Kalergis M:"The evaluation of three treatment strategies in subjects with type 1 diabetes mellitus undergoing intensive diabetes management: metabolic, psycho-social and educational implications." Diss. McGill U: Montreal, 1996

Kalergis M, Aljaberi K, Schiffrin A, Meltzer S, Gougeon R, Yale JF: Frequency and duration of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management as determined by continuous glucose monitoring (abstract). Can J Diabetes Care 25: 156A, 2001

Kalergis M, Nadeau J, Yale JF: How accurate are self-monitoring of blood glucose diaries in type 1 and type 2 diabetes? (abstract). Diabetes 48 (suppl 1): 1520A, 1999

Kalergis M, Pacud D, Strychar I, Meltzer S, Jones PJH, Yale JF: Optimizing insulin delivery: assessment of three strategies in intensive diabetes management. Diabetes, Obesity and Metabolism 2: 299-305, 2000

Kalergis M. Schiffrin A, Gougeon R, Jones PJH, Yale JF: Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes mellitus undergoing intensive insulin management using lispro insulin ac meals: a randomized, placebo-controlled, crossover trial. Diabetes Care, In Press, 2002

Kalergis M, Schiffrin A, Gougeon R, Meltzer S, Jones PJH, Yale JF: "Impact of Optimized Titration and Delivery of Bedtime Insulin on Prevention of Nocturnal Hypoglycemia in Free-Living adults with type 1 Diabetes Undergoing Intensive Management: A Randomized, Controlled Trial Comparing MDI (with and without bedtime snacks) versus CSII. " Diss. McGill U: Montreal, 2002

Kanc K, Janssen MJ, Keulen ETP, Jacobs MAJM, Popp-Snijders C, Snoek FJ, Heine RJ: Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen imporves counterregulatory hormonal responses and warning symptoms of hypoglcyemia in IDDM. Diabetologia 41: 322-329, 1998

Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P: A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care 24 (12): 2030-2034, 2001

Kaufman FR, Halvorson M, Kaufman ND: A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at Diabetes Camp. Diab Res Clin Pract 1: 1-5, 1996

Kaufmann F, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type 1 diabetes. J Diab Compl 10: 84-87, 1996

Kaufmann FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P: A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care 24 (12): 2030-2034, 2001

Kaufmann FR, Halvorson M, Kaufmann N: A snack bar containing uncooked cornstarch to diminish hypoglycemia (abstract). Diabetes 200A, 1996

Kerr D: Continuous blood glucose monitoring: detection and prevention of hypoglycaemia. Int J Clin Pract Suppl (123): 43-6, 2001

King P, Kong MF, Parkin H, Macdonald IA ,Tattersall RB: Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM. Diabetes Care 21 (3): 341-350, 1998

Kinsley BT, Widom B, Simonson DC: Differential regulation of counterregulatory hormone secretion and symptoms during hypoglycemia in IDDM. Diabetes Care 18 (1): 17-26, 1995

Klonoff D. C.: Noninvasive blood glucose monitoring. Diabetes Care 20 (3): 433-437, 1997

Koivisto VA: The human insulin analogue insulin lispro. Ann Int Med 30: 260-266, 1998

Koschinsky T, Heinemann L: Sensors for glucose monitoring: technical and clinical aspects. Diabetes Metab Res Rev 17: 113-123, 2001

Kramer L, Fasching P, Madl C, Schneider B, Damjancic P, Waldhausl W, Irsigler K, Grimm G: Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. Diabetes 47 (12): 1909-1914, 1998

Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH: The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. Am J Clin Nutr 44 (6): 847-856, 1986

Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P, Cartechini MG, Bartocci L, Brunetti P, Bolli GB: Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 22 (3): 468-477, 1999

Lawson ML, Muirhead SE: What is type 1 diabetes?, In: Evidence-Based Biabetes Care, Gerstein HC, Haynes RB, Editors. 2001, BC Decker Inc: Hamilton/London. p. 124-150.

Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Déspres JP: A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. Am J Clin Nutr 64: 685-693, 1996

Lenhard MJ, Reeves GD: Continuous subcutaneous insulin infusion. Archives of Internal Medicine 161: 2293-2300, 2001

Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 49 (12): 2142-2148, 2000

Levy CJ, Kinsley BT, Bajaj M, Simonson D: Effect of glycemic control on glucose counterregulation during hypoglycemia in NIDDM. Diabetes Care 21 (8): 1330-1338, 1998

Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UM, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. Diabetes 42: 610-618, 1993

Linn T, Geyer R, Prassek S, Laube H: Effect of dietary protein intake on insulin secretion and glucose metabolism in insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 81 (11): 3938-3943, 1996

Lobmann R, Smid HG, Pottag G, Wagner K, Heinze HJ, Lehnert H: Impairment and recovery of elementary cognitive function induced by hypoglycemia in type-1 diabetic patients and healthy controls. J Clin Endocrinol Metab 85 (8): 2758-2766, 2000

Lozano R, Chalew SA , Kowarski AA: Cornstarch ingestion after oral glucose loading: effect on glucose concentrations, hormone response, and symptoms in patients with postprandial hypoglycemic syndrome. Am J Clin Nutr 52 (4): 667-670, 1990

Madsbad S: Insulin analogues: have they changed insulin treatment and improved glycaemic control? Diabetes Metab Res Rev 18 (suppl 1) s21-s28, 2002

Maran A, Crepaldi C, Tiengo A, Grassi G, Vitali E, Pagano G, Bistoni S, Calabrese G, Santeusanio F, Leonetti F, Ribaudo M, Di Mario U, Annuzzi G, Genovese S, Riccardi G, Previti M, Cucinotta D, Giorgino F, Bellomo A, Giorgino R, Poscia A , Varalli M: Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter analysis. Diabetes Care 25 (2): 347-352, 2002

Maran A, Lomas J, MacDonald IA, Amiel SA: Lack of preservation of higher brain function during hypoglycemia in patients with intensively-treated IDDM. Diabetologia 38: 1412-1418, 1995

Mazze RS, Pasmantier R, Murphy JA,Shamoon H: Self-monitoring of capillary blood glucose: changing the performance of individuals with diabetes. Diabetes Care 8 (3): 207-213, 1985

Mazze RS, Shamoon H, Pasmantier R, Lucido D, Murphy J, Hartmann K, Kuykendall V ,Lopatin W: Reliability of blood glucose monitoring by patients with diabetes mellitus. Am J Med 77 (2): 211-217, 1984

McAulay V, Deary IJ, Ferguson SC, Frier BM: Acute hypoglycemia in humans causes attentional dysfunction while nonverbal intelligence is preserved. Diabetes Care 24 (10): 1745-1750, 2001

Melki V, Hanaire-Broutin H: Indication of CGMS (Continuous Glucose Monitoring System) in the functionnal investigations of adult type 1 diabetic patients. Diabetes Metab 27 (1): 618-623, 2001

Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D: 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ 159 (suppl 8): s1-s29, 1998

Meyer C, Grobmann R, Mitrakou A, Mahler R, Veneman T, Gerich J, Bretzel RG: Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. Diabetes Care 21 (11): 1960-1966, 1998

Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J: Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. American Physiological Society E67-E74, 1991

Mokan M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, Gerich J: Hypoglycemia Unawareness in IDDM. Diabetes Care 17 (12): 1397-1403, 1994

Mühlhauser I, Berger M, Sonnenberg G, Koch J, Jorgens V, Schernthaner G, Scholz V, Padagogin D: Incidence and management of severe hypoglycemia in 434 adults with insulin-dependent diabetes mellitus. Diabetes Care 8 (3): 268-273, 1985

Nuttall FQ , Gannon MC: Metabolic response to egg white and cottage cheese protein in normal subjects. Metabolism 39 (7): 749-755, 1990

Pacaud D: Hypoglycemia: the achilles heel of the treatment of children with type 1 diabetes. Can J Diabetes 26 (3): 215-222, 2002

Perriello G, De Feo P, Torlone E, Fanelli C, Santeusanio F, Brunetti P, Bolli G B: The dawn phenomenon in type 1 (insulin-dependent) diabetes mellitus: magnitude, frequency, variability, and dependency on glucose counterregulation and insulin sensitivity. Diabetologia 34 (1): 21-28, 1991

Peters AL, Davidson MB: Protein and fat effects on glucose response and insulin requirements in subjects with insulin-dependent diabetes mellitus. Am J Clin Nutr 58: 555-560, 1993

Pickup J, Keen H: Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. Diabetes Care 25 (3): 593-598, 2002

Pickup J, Mattock M, Kerry S: Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 324: 1-5, 2002

Pitzer KR, Desai S, Dunn T, Edelman S, Jayalakshmi Y, Kennedy J, Tamada JA, Potts RO: Detection of hypoglycemia with the GlucoWatch biographer. Diabetes Care 24 (5): 881-885, 2001

Pramming S, Thorsteinsson B, Bedtson I, Ram B, Binder C: Nocturnal hypoglycemia in patients receiving conventional treatment with insulin. BMJ 291: 376-379, 1985

Randle P, Garland P, Hales C, Newsholme E: The glucose-fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus Lancet 1: 785-789, 1963

Ratner R , Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA for the US Study Group of Insulin Glargine in Type 1 Diabetes: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. Diabetes Care 23: 639-643, 2000

Reichard P, Berglund A, Britz A, Levander S, Rosenqvist U: Hypoglycaemic episodes during intensified insulin treatment: increased frequency but no effect on cognitive function. J Intern Med 229 (1): 9-16, 1991

Reichard P, Britz A, Rosenqvist U: Intensified conventional insulin treatment and neuropsychological impairment. BMJ 303: 1439-1442, 1991

Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R: Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. Diabetes Care 22 (5): 784-788, 1999

Rubiano F, Nunez C, Heymsfeld SB: A comparison of body composition techniques. Annals of the New York Academy of Sciences 904: 335-338, 2000

Rubin RR: Hypoglycemia and quality of life. Canadian Journal of Diabetes 26 (1): 60-63, 2002

Saleh T, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes 20 (8): 1236-1236, 1997

Schiffrin A, Suissa S: Predicting nocturnal hypoglycemia in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Am J Med 82: 1127-1132, 1987

Sherwin RS Felig P: Effect of glucagon on amino acid metanolism and gluconeogenesis, In: Glucagon: Physiology, pathophysiology, morphology of pancreatic A-cells. 1981, Elsevier: New York. p. 256-271.

Simonson DC, DeFronzo RA: Indirect calorimetry: methodological and interpretative problem, editorial review. The American Physiological Society 258: E399-413, 1990

Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS: Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type 1 diabetes. Ann Int Med 103: 184-190, 1985

Simpson SH, Toth EL: Expanding the options in insulin therapy: a review of insulin analogues. Can J Diabetes 26 (3): 195-205, 2002

Smit GPA, Berger R, Ptasnick P, Moses SW, Fernandes J: The dietray treatment of children with type 1 glycogen storage disease with slow release carbohydrate Ped Res 65: 1507-1511, 1984

Somogyi M: Insulin as a cause of extreme hyperglycemia and instability. Wkly Bull St Louis Med Soc 32: 498-500, 1938

Strachan MWJ, Frier BM: Long-term effects of severe hypoglycemia in type 1 diabetes: Acquired hypoglycemia syndromes and associated morbidity. Canadian Journal of Diabetes 26 (I): 54-59, 2002

Sumner J, Baber C, Williams V: What do patients with type 1 diabeets know about hypoglycemia? Prac Diab Int 17 (6): 187-190, 2000

The DCCT Research Group: Weight gain associated with intensive therapy in the diabetes control and complications trial. The DCCT Research Group. Diabetes Care 11 (7): 567-73, 1988

The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90: 450-459, 1991

The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. New England Journal of Medicine 329: 977-986, 1993

The DCCT Research Group: Nutrition interventions for intensive therapy in the diabetes control and complications trial. J Am Diet Assoc 93 (7): 768-772, 1993

The DCCT Research Group: Effect of intensive diabetes treatment in the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: diabeets control and complications trial. J of Ped 125: 177-187, 1994

The DCCT Research Group: Adverse events and their association with treatment regimens in the diabetes control and complications trial. Diabetes Care 18 (11): 1415-1427, 1995

The DCCT Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 18 (3): 361-76, 1995

The DCCT Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes 46 (2): 271-86, 1997

The DCCT Research Group: Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the diabetes control and complications trial. Diabetes Care 24 (10): 1711-1721, 2001

Tsui E, Barnie A, Ross S, Parkes R, Zinman B: Intensive insulin therapy with insulin lispro: a randomized tial of continuous subcutaneous insulin infusion versus multiple daily injection. Diabetes Care 24 (10): 1722-1727, 2001

Tsui EYL, Chiasson JL, Tildesley H, Barnie A, Simkins S, Strack T, Zinman B: Counterregulatory hormone responses after long-term continuous subcutaneous insulin infusion with lispor insulin. Diabetes Care 21 (1): 93-96, 1998

Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of Hypoglycemia Unawareness by Asymptomatic Nocturnal Hypoglycemia. Diabetes 42: 1233-1237, 1993

Ververs MTC, Rouwe C, Smit GPA: Complex carbohydrates in the prevention of nocturnal hypoglycemia in diabetic children. Eur J Clin Nutr 47: 268-273, 1993

Vervoort G, Goldschmidt HMG, Van Doorn LG: Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple daily injection regimens. Diabetic Medicine 13: 794-799, 1996

Whincup G , Milner RD: Prediction and management of nocturnal hypoglycaemia in diabetes. Arch Dis Child 62 (4): 333-337, 1987

White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV: Identification of type 1 patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 508 (9): 485-491, 1983

Winiger G, Keller W, Laager R, Girard J, Berger W: Protein content of the evening meal and nocturnal plasma glucose regulation in type 1 diabetic subjects. Horm Res 44: 101-104, 1995

Wolever T, Barbeau MC, Charron S, Harrigan K, Leung S, Madrick B, Taillefer T, Seto C: Guidelines for the nutritional managment of diabetes mellitus in the new millenium: A position statement by the Canadian Diabetes Association. Canadian Journal of Diabetes 23 (3): 56-69, 1999

Wolfsdorf JI, Crigler JF: Cornstarch regimens for nocturnal treatment of young adults with type 1 glycogen storage disease. Am J Clin Nutr 65: 1507-1511, 1997

Yale JF: Hypoglycemia, In: Evidenced-Based Diabetes Care, Gerstein HC, Haynes RB, Editors. 2001, BC Decker Inc: Hamilton/London. p. 380-395.

Yale JF, Begg I, Gerstein H, Houlden R, Jones H, Maheux P, Pacaud D.: 2001 Canadian Diabetes Association Clinical Practice Guidelines for the prevention and management of hypoglycemia in diabetes. Can J Diabetes 26 (1): 22-35, 2001

Ziegler O, Kolopp M, Got I, Genton P, Debry G, Drouin P: Reliability of self-monitoring of blood glucose by CSII-treated patients with type I diabetes. Diabetes Care 12 (3): 184-188, 1989

Zinman B, Tildesley, Chiasson JL, Tsui E, Strack T: Insulin lispro in CSII: results of a double-blind crossover study. Diabetes 46 (3): 440-443, 1997

CHAPTER 3

Impact of Bedtime Snack Composition on Prevention of Nocturnal Hypoglycemia in Adults with Type 1 Diabetes Mellitus Undergoing Intensive Insulin Management Using Lispro Insulin AC Meals: A Randomized, Placebo-Controlled, Crossover Trial

Maria Kalergis, MSc., RD [1,3]; Alicia Schiffrin, MD [2]; Réjeanne Gougeon, PhD [1], Peter JH Jones, PhD[3]; Jean-François Yale, MD [1]

[1] From The McGill Nutrition and Food Science Centre, Royal Victoria Hospital, McGill University Health Centre, Montreal, QC

[2] From The Division of Endocrinology, Jewish General Hospital, Montreal, QC

[3] From The School of Dietetics and Human Nutrition, McGill University, Montreal, QC

Short Title: Impact of Bedtime Snack Composition on Prevention of Nocturnal Hypoglycemia

Key words: Nocturnal Hypoglycemia; Bedtime Snack Composition, Cornstarch, Protein, Intensive Management.

Journal

Diabetes Care, volume 26, Number 1, January 2003

3.1 ABSTRACT

OBJECTIVE – To determine the impact of 4 bedtime (HS) snack compositions on nocturnal glycemic control including frequency of hypoglycemia (<4mmol/L) and morning hyperglycemia (>10mmol/L) in adults with type 1 diabetes using lispro insulin before meals and NPH at bedtime.

RESEARCH DESIGN AND METHODS- Substitutions of 15g of carbohydrate for an equivalent amount of uncooked cornstarch or pure protein were compared to a standard snack: 2 starch + 1 protein exchange (control) and to no snack (placebo) in 15 adults using a randomized, cross-over design. All snacks were equivalent in kcal, fat and total available glucose. An I.V.facilitated hourly blood glucose sampling during the night (23h00 –07h00).

RESULTS- The glycemic level at bedtime(<7mmol/L; 7-10mmol/L and >10mmol/L) mediated the effects observed. A total of 14 hypoglycemic episodes, in 60% of patients, and 23 morning hyperglycemic episodes occurred over 50 nights. The majority of hypoglycemic episodes (10/14= 71%) occurred with no snack compared to any snack ($p<0.001$) and at HS levels of < 7 mmol/L ($p=0.05$). The standard and protein snacks resulted in no nocturnal hypoglycemia at all HS glucose levels ($p<0.001$). Only an HS glucose >10mmol/L was protective against hypoglycemia even in the absence of a snack ($p=0.05$). 46% of morning hyperglycemic episodes were associated ($r=0.37$, $p=0.07$) with this HS glucose level.

CONCLUSIONS- The need for and composition of an HS snack depends on the HS glucose such that no snack is necessary at >10mmol/L. At levels between 7-10mmol/L any snack is advised and at <7mmol/L, standard or protein snack is recommended.

3.2 INTRODUCTION

Nocturnal hypoglycemia is a significant problem for both children and adults (1-5) and with both conventional and intensive management regimens (6,7,8). The diabetes control and complications trial indicated that about 40% of episodes of severe hypoglycemia occurred primarily overnight between midnight and 8am in both conventional and intensive treatment arms (6,7,8). The etiology of nocturnal hypoglycemia is largely related to the inadequacy of current insulin preparations to mimic normal physiology, especially during the nocturnal period where insulin requirements often decrease at the same time that current basal insulin preparations (NPH or Ultralente) peak (9,10). Furthermore, nocturnal hypoglycemia is often asymptomatic (4,5) with up to 67% of episodes going unrecognized (4,5) and has been implicated in the development of hypoglycemia unawareness (11-15) and deterioration of daytime glycemic control (9). Moreover, it has recently been shown that sleep itself impairs counter-regulatory hormone secretion in response to hypoglycemia (16). Therefore, prevention of nocturnal hypoglycemia is imperative.

Although it is recommended that individuals with type 1 diabetes mellitus consume a bedtime snack in order to prevent nocturnal hypoglycemia, the need for a snack and its composition have largely been based on tradition rather than scientific evidence. It was not until the late 1980's that a few studies demonstrated that a bedtime snack is beneficial in reducing the incidence of nocturnal hypoglycemia in children (2, 17) and adults (4) with type 1 diabetes. More recently, the scientific community began to question the impact of bedtime snack composition on nocturnal glycemic control. Studies conducted in patients with glycogen storage disease have shown that raw cornstarch can

reduce the incidence of nocturnal hypoglycemia by providing a source of continuous glucose up to 7 hours (18,19, 20). With respect to type 1 diabetes, 5 studies to date have demonstrated that raw cornstarch can reduce the incidence of nocturnal hypoglycemia in children (21-24) and adults (25). Although protein is routinely recommended in the bedtime snack of individuals with type 1 diabetes, the validity of this recommendation remains to be established. Recent studies examining the role of protein at supper (26) and the efficacy of an amino acid infusion compared to a standard bedtime snack containing protein (27) also have demonstrated a lower incidence of nocturnal hypoglycemia in adults with type 1 diabetes. Although, the underlying mechanisms by which protein exerts its effect on glycemic control have yet to be fully elucidated, there is evidence to suggest that protein increases late plasma glucose response in type 1 diabetes (26-29), including overnight (26, 27, 29). As new insulin preparations, with more physiologic kinetic profiles, have become available, clinicians are beginning to question whether a bedtime snack is even necessary. Currently the use of lispro (Humalog; Eli Lilly, Indianapolis, IN) over regular insulin is being advocated in the management of type 1 diabetes as studies have shown less nocturnal hypoglycemia with lispro insulin compared to regular insulin, without deterioration of long term glycemic control (30-32). independent of basal insulin regimen (30).

Therefore the present study was undertaken to test the hypotheses that a bedtime snack is necessary in order to prevent nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management despite the use of lispro insulin at supper and that a bedtime snack composition with the potential to either provide a continuous source of glucose (uncooked cornstarch) or a delayed source of glucose (protein), especially at the time of the basal insulin peak, would result in a more favourable nocturnal glycemic profile including a reduced incidence of nocturnal hypoglycemia compared to a conventional or standard snack. The goal of our study was to assess, in adults with type 1 diabetes undergoing intensive insulin therapy with multiple daily injections of insulin consisting of lispro insulin before meals and NPH insulin at bedtime, the impact of 4 bedtime (HS) snacks: placebo (Pl) or no snack ; standard snack (S); cornstarch-containing snack (CS); protein-rich snack (Prot), on nocturnal glycemic control. Specific objectives of our study were: 1) to determine the nadir blood glucose concentration during the night ; 2) to determine the mean blood glucose concentration during the night (excluding baseline or bedtime value); 3) to determine the frequency of nocturnal hypoglycemia (blood glucose < 4mmol/L) and 4) to determine the frequency of morning hyperglycemia (blood glucose > 10mmol/L) with all 4 conditions.

3.3 RESEARCH DESIGN AND METHODS

3.3.1 Participants and methodology

The study, undertaken at the Clinical Investigation Unit (CIU) of The Royal Victoria Hospital, Montreal, Quebec, was approved by the Department of Medicine's Ethics Committee of the Royal Victoria Hospital. Most participants were referred by the Metabolic Day Centre of the Royal Victoria Hospital. Adults between 18-65 years of age, with endocrine diagnosis of type 1 diabetes for at least 3 years duration, intensively treated with 3 or more injections of insulin per day, for at least 1 year, including lispro insulin at supper, and a history (at least 1 known episode in the last month) of nocturnal hypoglycemia were considered for inclusion in the study. Patients were excluded if they had obesity (BMI > 35kg/m^2); evidence of significant hepatic or renal disease; pregnancy or concurrent participation in another study. Participants were hospitalized 4 times according to their order of randomization which was accomplished using sealed envelopes with a manually-derived randomization schedule. Participants were asked to complete all 4 conditions with a minimum of 3 days and a maximum of 3 weeks between study conditions. In an attempt to minimize interruption to their usual daily routine, participants were admitted to the CIU of the Royal Victoria Hospital at 21h00 where they stayed overnight until 7h00. Upon arrival, participants were weighed and asked to complete a 24 hour general recall questionnaire about the food they ate, the amount of insulin they used, their blood glucose readings and the type of activity they had done in the last 24 hours. Participants were also asked to complete one descriptive questionnaire on their history and management of hypoglycemia and were asked to keep their activity level and supper composition consistent during each visit. Adherence to

these recommendations was verified at each visit via administration of the 24 hour general recall questionnaire. An intravenous catheter was inserted in an antecubital vein and kept open by 0.9% saline solution for hourly blood sampling during sleep. Blood glucose was measured at 22h00 (baseline or bedtime value) as the blood glucose value at this time point has been shown to be predictive of nocturnal hypoglycemia (5, 33, 34). Participants took their usual dose of bedtime insulin at 22h00 and were presented with 1 of the following 4 snacks: 1) placebo snack (aspartame containing orange flavoured drink); 2) standard snack, defined as 2 starch + 1 protein exchange (2 slices of white bread + 1 ounce of cheddar cheese + placebo drink); 3) cornstarch-containing snack (similar to standard snack except 1 slice of white bread was replaced by 14 g of raw cornstarch dissolved in the placebo drink) ; 4) protein-rich snack (similar to standard snack except 1 slice of white bread was replaced by 15g pure protein in the form of an orange flavored drink supplied by Bariatrix Inc., Lachine, QC). All snacks contained comparable amounts of energy (kcal), fat and total available glucose (35) as illustrated in Table 1. All snacks were consumed within 10 minutes and the midway time point was chosen as a marker of when to start hourly blood sampling. Participants and the study nurse were blinded as to the exact composition of the snacks. This was accomplished by using an aspartame containing (crystal light®) orange flavored drink with each snack. The raw cornstarch (Bensons®) and protein powder were dissolved in 1 teaspoon of "crystal light" with water during the cornstarch and protein snack conditions. The crystal light mix was dissolved in water only during the standard and placebo snack conditions. The snacks were, therefore, similar in appearance and taste. Verification of blinding was performed at each visit by asking participants if they could guess the composition of their

snack. Blood samples were drawn every hour to measure glucose, starting at 23h00 until 7h00. A registered nurse and the study co-ordinator were on site during the night and an endocrinologist was on call for each study.

Our primary efficacy measures, on which sample size calculations were based, were *nadir glucose* (the lowest glucose level attained during the night, and *nocturnal hypoglycemia* (whole blood glucose concentration, as measured by the Elite® glucose meter, of less than 4 mmol/L , irrespective of symptoms). Secondary efficacy measures included : *overnight glucose* (the mean glucose level from 23h00 to 7h00); and *morning hyperglycemia* (blood glucose >10mmol/L at 7h00). Hypoglycemic episodes were treated with glucose tablets according to hospital protocol as described elsewhere (35). All the glucose values (including values following treatment of hypoglycemia) were included in the overnight glucose calculation.

3.3.2 Statistical analyses and power calculation

Data were analyzed using the Statistical Program for Social Sciences (SPSS version 9, SPSS Inc., Chicago, Illinois, 1999). All data obtained after randomization were included in the analyses. A one way Analysis of Variance (ANOVA), with Bonferroni adjustment for multiple comparisons, was used to assess differences among groups for the continuous variables (nadir and overnight glucose) according to 3 bedtime glucose categories as follows: 1) <7 mmol/L; 2) 7-10 mmol/L and 3) >10 mmol/L. Tukey's Honestly Significant Difference (HSD) was utilized to locate the differences. Chi-square analysis was used to assess frequency of nocturnal hypoglycemia and morning hyperglycemia according to the 3 categories of HS blood glucose. Pearson Product

Moment Correlations were used to assess relationships between bedtime glucose with nadir, mean and morning glucose concentrations. The 95% CIs and P values were calculated for all continuous estimates. A P value <0.025 was used to assess statistical significance for nadir and overnight glucose. A P value <0.05 represented statistical significance for all other measures.

A difference in nadir glucose of 2 mmol/L and a reduction in the frequency of hypoglycemia by at least 50% were considered clinically significant and were used to determine the sample size required to achieve a power of 80%.

3.4 RESULTS

3.4.1 Baseline demographic data

Fifteen adults (9 men and 6 women) aged 23 to 65 years, with type 1 diabetes ranging from 8 to 43 years participated in this randomized, cross-over, placebo-controlled trial. We conducted preliminary analyses when we reached 15 participants to confirm our power calculation at which point we concluded we had enough subjects to terminate the study. The majority of participants (9/15= 60%) completed all 4 conditions while 3 participants completed 3 conditions, 2 completed 2 conditions and 1 person completed 1 condition. The size of the groups at the end of the study were as follows: Standard (n=13); Cornstarch (n=14); Protein (n=12) and Placebo (n=11). There were no significant differences between full and partial completers. Only 1 participant did not continue the study after completing 2 conditions (CS and Prot) secondary to having a negative experience (ie-difficulty sleeping). A detailed description of the baseline characteristics of participants is presented in Table 2. Participants were weight stable and had a mean

body mass index of 25.6 kg/m^2 and a mean HbA1c of 8.2% (reference: 4-6%) at baseline. All took lispro insulin before meals and the majority of subjects (11/15) took NPH insulin at bedtime. All subjects gave their HS insulin in accordance to their usual routine, as recommended by their respective physician. The majority (60%) of subjects adjusted their HS insulin dose according to their bedtime blood glucose results using a sliding scale as recommended by their physician. Ten subjects always consumed a bedtime snack while 5 subjects never did. Of those who had a snack, only 3 subjects consumed a similar amount of carbohydrate and protein as that of the recommended "standard" snack. Five subjects consumed less carbohydrate and protein than the recommended "standard" snack and 2 subjects consumed more than the standard snack. On average, the carbohydrate content of the usual bedtime snacks was 14g ± 4.5 (range= 0g to 60g). The mean ± SE protein content was 0.53 ± 0.2 exchanges (range = 0 to 2 protein exchanges). Four out of the ten participants who consumed a bedtime snack never had any protein in their bedtime snack.

There was a total of 435 blood glucose values over 50 nights for comparison. The majority of results are presented according to 3 bedtime blood glucose categories: <7mmol/L (n=209); 7-10mmol/L (n=83) and >10mmol/L (n=143). These categories were established post priori secondary to the discovery of a significant mediating effect with the efficacy measures of interest. The mean blood glucose concentrations ± standard errors and range associated with these categories were as follows: < 7 mmol/L (5.1 ± 0.1, range= 3.6 to 6.8mmol/L); 7-10 mmol/L (8.3 ±0.1, range= 7.2-10mmol/L); >10 mmol/L (12.5 ± 0.1, range= 10.4 to 16.3mmol/L).

3.4.2 Nadir blood glucose

There was a significant correlation between HS blood glucose and the nadir glucose ($r= 0.56$, $p<0.001$). There was also a significant ($p<0.05$) relationship between HS snack composition and mean nadir glucose during the night, whereby having no snack resulted in a lower mean nadir glucose compared to any snack. The mean nadir blood glucose concentrations during the night, according to the 3 HS categories are presented in Table 3. The absence of a snack resulted in a lower nadir glucose value such that at an HS glucose < 7mmol/L, the mean nadir glucose was in the hypoglycemic range : 3.2mmol/L (95% CI: 2.6, 3.7, $p<0.05$). At HS blood glucose concentrations between 7-10mmol/L, having no snack was associated ($p=0.048$) with lower nadir glucose compared with the standard and protein snacks: 4.6mmol/L (95% CI, 3.1, 6.1) vs. 9.4 mmol/L (95% CI 6.9, 11.9) and 8.0mmol/L (95% CI, 0.7, 15.0) respectively. At >10mmol/L, there was a trend ($p=0.13$) indicating a lower nadir glucose with no snack compared to any snack.

3.4.3 Mean overnight glucose

There was a significant correlation between the bedtime blood glucose and the mean glucose during the night ($r=0.52$, $p<0.001$). There was also a significant ($p<0.025$) relationship between bedtime snack composition and mean blood glucose during the night, whereby having no snack resulted in a lower mean glucose compared to having any snack across all HS glucose levels. The mean blood glucose concentrations, according to the 3 categories described are presented in Table 3. At bedtime blood glucose concentrations of <7mmol/L and between 7-10 mmol/L, having no snack was associated with significantly ($p<0.001$) lower mean glucose compared with having any

snack. The protein snack was significantly ($p<0.001$) associated with the highest mean glucose compared to all other conditions at a bedtime glucose >10mmol/L.

3.4.4 Frequency of nocturnal hypoglycemia

There was a total of 14 hypoglycemic episodes over 50 nights, in 60% of patients. 80% of which were asymptomatic. The mean ± standard error and (range) associated with these episodes was: 3.4mmol/L ± 0.1 (2.6 to 3.9 mmol/L). There was a strong trend ($p=0.05$) between HS blood glucose and frequency of nocturnal hypoglycemia; whereby, the majority of hypoglycemic episodes (11/14= 79%) occurred at <7mmol/L. Two episodes occurred at HS glucose concentrations between 7-10 mmol/L and one episode occurred at >10mmol/L. There was a significant relationship ($p<0.001$) between snack composition and the frequency of nocturnal hypoglycemia, whereby the majority (10/14= 71%) of episodes occurred with no snack and 4 episodes were associated with the cornstarch snack. No hypoglycemic episodes were associated with the standard or protein snacks at any HS glucose level. At HS glucose concentrations <7mmol/L, the majority of episodes (8/11=73%) occurred with no snack and 3 episodes occurred with the cornstarch snack ($p<0.001$). Two episodes occurred at concentrations between 7-10mmol/L with no snack ($p=0.19$) and 1 episode occurred at HS glucose level >10mmol/L with cornstarch (NS, $p=0.50$).

3.4.5 Frequency of morning hyperglycemia

There was a total of 23 hyperglycemic episodes at 7h00 over 50 nights in 73% of patients. The mean ± standard error and (range) associated with these episodes was: 14.4mmol/L ± 0.6 (10.3 to 19.4). There was a trend indicating a correlation (r= 0.37, p=0.07) between HS blood glucose and morning hyperglycemia, whereby 46 % occurred at blood glucose concentrations >10mmol/L. At HS concentrations < 7mmol/L, there were 9 morning hyperglycemic episodes (38%) of which only 2 were preceded by hypoglycemia. A trend (p=0.13) indicated that the lowest incidence of morning hyperglycemia was associated with no snack (8%) versus any snack (S and CS=29%; Prot=33%).

3.4.6 Nocturnal profiles

Nocturnal profiles (or nights) containing one or more episodes of hypoglycemia, morning hyperglycemia (without nocturnal hypoglycemia) and neither one, expressed as a percentage of total nights, for each snack composition according to the 3 categories of bedtime glucose are presented in Figure 1. At blood glucose concentrations <7mmol/L, their was a strong trend (p=0.08) indicating that having no snack results in 67% of nights with one or more episodes of hypoglycemia but no morning hyperglycemia. At this HS glucose concentration both the standard and protein snacks resulted in no hypoglycemia (100% reduction) and an equivalent frequency of morning hyperglycemia (43% and 40% respectively). At bedtime glucose concentrations between 7-10mmol/L, having no snack resulted in 33% of nights with nocturnal hypoglycemia and no morning hyperglycemia. All 3 snack compositions resulted in no nocturnal hypoglycemia at this HS glucose

concentration with the standard and cornstarch snacks resulting in an equal frequency of morning hyperglycemia (50%) compared to 67% for the protein snack, p=0.60. A bedtime glucose concentration >10mmol/L resulted in no nocturnal hypoglycemia in the absence of a bedtime snack but a 50% frequency of morning hyperglycemia. The standard and cornstarch snacks resulted in morning hyperglycemia frequencies of 67% and 40% respectively while the protein snack was associated with a frequency of 100%, p= 0.29 at this HS glucose level.

3.5 CONCLUSIONS

Our study found that the need for a bedtime snack and the recommended composition are dependent on the blood glucose concentration at bedtime. This finding is extremely important as people living with type 1 diabetes have varying blood glucose values at bedtime which must be taken into consideration when deciding if and what bedtime snack is necessary. Despite the use of lispro insulin, only a bedtime glucose concentration >10mmol/L was protective against nocturnal hypoglycemia in the absence of a bedtime snack. This level of 10mmol/L is higher than that found to be protective previous studies (5,33,34). One explanation may be the fact that other studies involved different populations such as children (21-24, 33) or modalities of treatment such as conventional management (34). As well, all previous studies used regular insulin as their short acting insulin. For bedtime blood glucose <10mmol/L, a bedtime snack is necessary especially when the blood glucose concentration is <7mmol/L. A value of approximately 7 mmol/L has been reported as predictive of nocturnal hypoglycemia in previous studies (5,7,33,34). Both the standard and protein snacks were equally effective at this bedtime blood glucose concentration. The large, sustained rise in blood glucose that occurred with the protein snack (data not shown) was surprising and impressive. Although the mechanisms by which protein exerts its effect on glycemic response remain to be elucidated, this is likely due to the rise in plasma glucagon and/or other counter-regulatory hormones as a result of feeding protein to people with type 1 diabetes (37). This is a very important observation since there is current controversy regarding the impact and need for protein in the bedtime snack composition of people with type 1 diabetes (38). We believe our findings, in addition to those of a previous studies (27,29),

clearly demonstrate that protein is an appropriate alternative in the bedtime snack of individuals with type 1 diabetes since for the equivalent amount of calories and less carbohydrate, the protein rich snack was equally effective as the standard snack in preventing nocturnal hypoglycemia. Although this study was able to single out the effects of pure protein by keeping energy and nutrient composition consistent among groups, we cannot rule out the possibility of an additive or synergistic effect between protein and carbohydrate. Therefore, further research is encouraged to test the efficacy of a pure protein bedtime snack in the absence of carbohydrate. Unlike previous studies (21-25), we did not find that raw cornstarch was superior in the prevention of nocturnal hypoglycemia, especially at bedtime glucose concentrations <7mmol/L as evidenced by a 27% incidence of nocturnal hypoglycemia with the use of cornstarch at this HS glucose level. Cornstarch may release glucose too slowly to be effective at this level. However, at bedtime blood glucose concentrations between 7-10 mmol/L we found that cornstarch was equally effective as the standard and protein snacks in preventing nocturnal hypoglycemia. A possible explanation as to why the cornstarch snack was not more effective than the other conditions, in the present study, is that this is the first study to identify a mediating effect of bedtime blood glucose and the first study in adults to compare raw cornstarch against a clearly defined "standard snack" representative of that recommended in clinical practice. For example, in 2 of the 5 previous studies cornstarch was only compared to placebo (21, 25). Furthermore, the amount of carbohydrate contained in the standard snacks used in most previous studies (22-24) is much less than that used in the present study which was 30g of carbohydrate for the standard snack.

In the present study, the only snack composition that was effective at all bedtime blood glucose levels at preventing nocturnal hypoglycemia, without significantly impacting on overall night time and morning glycemic control, especially at bedtime blood glucose concentrations of <7 mmol/L and 7-10 mmol/L was the standard snack. As the aim of this study was to ensure minimal disruption of participants' usual routines, no attempt was made to further modify the usual insulin dose regimens, including the bedtime insulin Further research is encouraged to determine the efficacy of meticulous titration of insulin dose, in the absence of a bedtime snack, on nocturnal glycemic control.

Although the sample size in this study limits generalizability of the findings, we feel confident, given that the results were both clinically and statistically significant, in making the following recommendations for the management of adults with type 1 diabetes treated with lispro insulin before meals, especially at supper and NPH insulin at bedtime: no bedtime snack appears to be necessary at bedtime (22h00) blood glucose concentrations >10 mmol/L. For bedtime blood glucose concentrations < 10 mmol/L, a bedtime snack is necessary. For a bedtime blood glucose concentration between 7-10 mmol/L, a standard, cornstarch or protein rich snack is beneficial. For bedtime blood glucose concentrations <7mmol/L, a standard or protein rich snack is beneficial. Although the addition of a small amount of protein to a bedtime snack has recently been questioned (29,38), the potential benefits for including protein far outweigh the risks of adding ~ 70 Calories. However, applied research, in an outpatient setting, is encouraged to elucidate the implications of these findings with respect to energy balance and body composition. Titration of the bedtime insulin dose may be necessary at all bedtime blood

glucose concentrations in order to minimize morning hyperglycemia; this would also require further research. Perhaps the ideal approach would be to aim for a bedtime blood glucose between 7-10 mmol/L with inclusion of a standard snack. The application of these findings to pediatric or other populations, such as type 2 diabetes, also warrants further research. Moreover, the application of these findings with the use of new insulin preparations such as glargine® and aspart® or continuous insulin infusion (CSII) also warrants further research to determine the efficacy of these recommendations under these conditions.

3.6 ACKNOWLEDGEMENTS

We would like to thank Bariatrix Inc. for supplying the protein drinks and the following nurses: France Bouchard, RN; Mary Shingler, RN and Chantal Legaré, RN for their invaluable assistance. We also thank Josianne Boudreau, Marie Lamarche, Madeleine Giroux and Ginette Sabourin for their technical expertise. We would also like to thank the American and Canadian Diabetes Associations for publishing parts of this study in their respective journals and the Canadian Diabetes Association for funding this study through an Applied Research Grant. Finally, we would like to thank the participants who made this study possible.

3.7 REFERENCES

1. Gale EAM, Tattersall RB: Unrecognized nocturnal hypoglycemia in insulin-treated diabetics. The Lancet May 19: 1049-1052, 1979.

2. Yale JF. Hypoglycemia. In: Evidenced-Based Diabetes Care. Gerstein HC, Haynes RB , editors. Hamilton/London: BC Decker Inc.; 2001. p. 380-395.

3. Bendtson I, Kverneland A, Parmming S and Binder C: Incidence of nocturnal hypoglycemia in insulin-dependent diabetic patients on intensive therapy. Acta Med Scand 223: 543-548, 1988.

4. Vervoort G, Goldschmidt HMG , Van Doorn LG: Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (≥4) daily insulin injection regimens. Diab Med 3: 794-799,1996.

5. Kalergis M, Aljaberi K, Schiffrin A, Meltzer S, Gougeon R, Yale JF: Frequency and duration of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management as determined by continuous glucose monitoring (abstract). Can J Diabetes Care 25: 156A, 2001.

6. The DCCT Research Group: The effect of intensive treatment of diabetes on the development of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329: 977-986, 1993.

7. The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90: 450-459, 1991.

8. The DCCT Research Group: Effect of intensive diabetes treatment in the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: diabetes control and complications trial. J of Ped 125 (2): 177-187, 1994.

9. Bolli GB, Fanelli CG, Perriello G, De Feo P: Nocturnal blood glucose control in type 1 diabetes mellitus. Diabetes Care 16 (1): 71-89, 1993.

10. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes (49): 2142-2148, 2000.

11. Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer P:Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes.Diabetes 47: 1920-1927,1998.

12. Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglcyemia in nondiabetic humans. Diabetes 40: 223-226, 1991.

13. Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a viscious cycle. Diabetes 40: 255-260, 1992.

14. Davis MR, Mellman M , Shamoon H: Further defects in counter-regulatory responses induced by recurrent hypoglycemia in IDDM. Diabetes 41: 1335-1340,1992.

15. Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UW, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. Diabetes 42: 610-618, 1993.

16. Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. N Engl J Med 338 (23): 1657-1662,1998.

17. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. Diabetes Care 12 (4): 239-244,1989.

18. Chen YT, Cornblath M, Sidbury J B: Cornstarch therapy in type I glycogen-storage disease. N Engl J Med 310 (3): 171-175, 1984.

19. Smit GPA, Berger R, Potasnick P, Moses SW, Fernandes J: The dietary treatment of children with type 1 glycogen storage disease with slow release carbohydrate. Ped Res 18(9): 879-881, 1984.

20. Wolfsdorf JI and Crigler JF: Cornstarch regimens for nocturnal treatment of young adults with type 1 glycogen storage disease. Am J Clin Nutr 65: 1507-1511, 1997.

21. Ververs MTC, Rouwe C, Smit GPA: Complex carbohydrates in the prevention of nocturnal hypoglycemia in diabetic children. Eur J Clin Nutr 47: 268-273,1993.

22. Kaufmann FR, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type I diabetes. J Diab Compl 10: 84-87,1996.

23. Kaufmann FR, Halvorson M, Kaufmann N: A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at diabetes camp. Diab Res and Clin Pract, 1996.

24. Kaufmann F, Halvorson M, Kaufmann N: A snack bar containing uncooked cornstarch to diminish hypoglycemia (abstract). Diabetes: 200A , 1996.

25. Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. J Int Med 245: 229-236, 1999.

26. Winiger G, Keller W, Laager R, Girard J, Berger W: Protein content of the evening meal and nocturnal plasma glucose regulation in type I diabetic subjects. Horm Res 44 (3): 101-104,1995.

27. Saleh, T and Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes 20 (8): 1231-1236, 1997.

28. Peters AL, Davidson MB. Protein and fat effects on glucose response and insulin requirements in subjects with insulin-dependent diabetes mellitus. Am J Clin Nutr 58: 555-560, 1993.

29. Hess A, Beebe CA. Glycemic effect of a small amount of protein added to an evening snack in type 1 diabetes (abstract). Diabetes Care 22 (Suppl 1): A306. 1999.

30. Anderson JH, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, DiMarchi R, Multicentre Insulin Lispro Study Group: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes 46: 265-270, 1997.

31. Koivisto VA: The human insulin analogue insulin lispro. Ann Int Med 30: 260-266,1998.

32. . Heller SR, Amiel S, Mansell P, UK Lispro study Group: Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 22 (10): 1607-1611, 1999.

33. Schiffrin A and Suissa S: Predicting nocturnal hypoglycemia in patients with type I diabetes treated with continuous subcutaneous insulin infusion. Am J Med 82: 1127-1132, 1987.

34. Pramming S, Thorsteinsson B, Bedtson I, Ram B, Binder C: Nocturnal hypoglycemia in patients receiving conventional treatment with insulin. BMJ 291: 376-379, 1985.

35. The DCCT Research Group: Nutrition interventions for intensive therapy in the diabetes control and complications trial. J Am Diet Assoc 93 (7): 768-772, 1993.

36. Esslinger K, Rochon G, Bonhomme S, Yale JF: Therapy of hypoglycemia by nurses on hospital wards: assessment of protocol knowledge. Can J Diabetes Care 25 (1): 14-21, 2001.

37. Sherwin, RS and Felig P. Effect of Glucagon on Amino Acid Metabolism and Gluconeogenesis In Glucagon: Physiology, Pathophysiology, Morphology of Pancreatic A-Cells, Elsevier, NY, 1981.

38. Franz, MJ: Protein controversies in diabetes. Diab Spect 13 (3): 132- 141, 2000.

Table 1: Bedtime Snack Compositions

Snack	Composition	CHO(g)	Pro(g)	Fat(g)	Kcal	*TAG(g)
Placebo	aspartame	0	0	0	0	0
Standard (control)	2 starch + 1 Pro	30	11	3	191	37
Cornstarch	1 starch + 14g CS + 1 Pro	29	11	3	187	36
Protein	1starch + 15g Pro + 1 Pro	15	24	3	192	30

*Tag (total available glucose) is based on the premise that 100% of the grams of carbohydrate; 60% of the grams of protein and 10% of the grams of fat are converted to glucose after digestion (35). Pro= 1 protein exchange; Placebo= aspartame containing orange drink. All 3snack conditions included the placebo drink. CS= cornstarch. CHO= carbohydrate; Pro= protein. One starch exchange of the standard snack was replaced by an equivalent amount of raw cornstarch in the cornstarch condition or an equivalent amount of protein in the protein snack.

Table 2: Baseline Participant Characteristics

N	9 men/ 6 women
Age (years)	41 ± 12 (23-65)
Duration of diabetes (years)	23 ± 11 (8-43)
HbA1c (%)	8.1 ± 1.2 (6.3 –10.3)
Body Mass Index (Kg/m^2)	25.6 ± 4.5 (18-35)
Evening basal insulin use	n=11: NPH at bedtime
	n=2: Ultralente at supper
	n=2: Ultralente at bedtime
Bedtime snack composition (compared to recommended standard snack†)	n=10: Less (n=5: no snack)
	n=3: Same
	n=2: More

Data are presented as means ± SD (range). HbA1c normal reference range at Royal Victoria Hospital= 4-6%. Standard snack according to our clinical practice: 20-30g carbohydrate and 1 protein exchange. Comparisons are based on amount of carbohydrate and/or protein, whereby *less; same; more* signifies a lower, similar or higher amount of carbohydrate and/or protein compared to that of the standard snack.

Table 3: Mean Nadir and Overnight Blood Glucose Concentrations by Bedtime Category Per Bedtime Snack Condition.

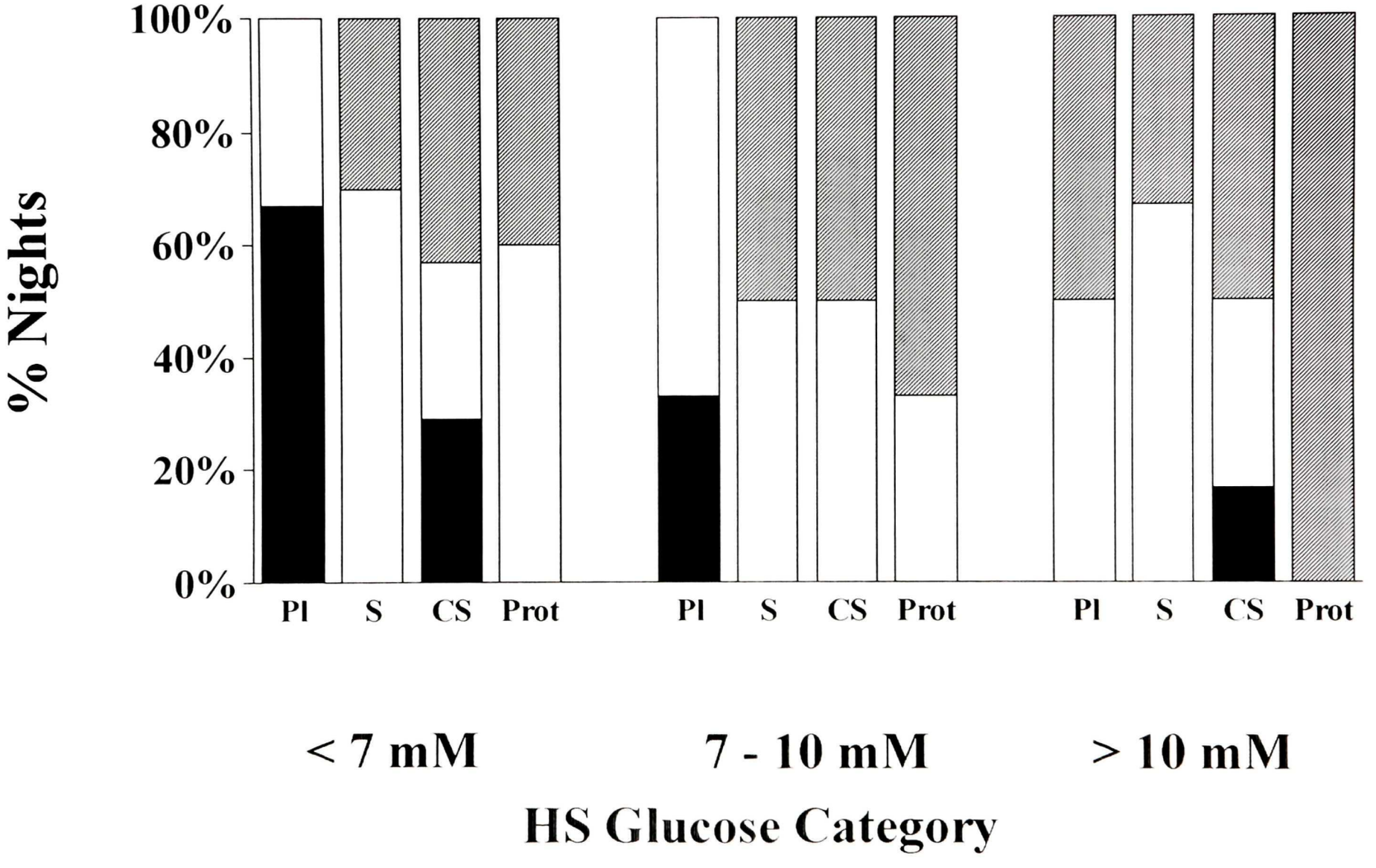
	< 7 mmol/L	7-10 mmol/L	>10 mmol/L
Nadir Glucose			
Placebo	3.2 ± 0.5a (2.6, 3.7)	4.6 ± 1.0 (3.1, 6.1)	8.0 ± 2.9 (3.5, 12.5)
Standard	6.8 ± 1.9b (5.0, 8.6)	9.4 ± 0.3 (6.9, 11.9)	9.7 ± 3.2 (6.3, 13.0)
Cornstarch	5.8 ± 2.5ab (3.2, 8.4)	8.2 ± 1.0 (-1.4, 17.7)	9.2 ± 5.2 (2.7, 16.0)
Protein	6.7 ± 2.8b (3.7, 9.7)	8.0 ± 2.9 (0.7, 15.0)	14.0 ±1.7 (11.2, 16.8)
	p 0.025	*P =0.048*	*p =0.13*
Overnight Glucose			
Placebo	5.8 ± 2.2a (5.2, 6.5)	6.3 ± 1.8a (5.5, 7.1)	10.4 ± 3.2a (8.6, 12.2)
Standard	9.7 ± 3.0b (8.8, 10.5)	10.5 ± 0.9b (9.9, 11.0)	11.1 ± 3.7a (10.0, 12.3)
Cornstarch	8.8 ± 3.9b (7.7, 9.9)	9.1 ± 1.2b (8.4, 9.8)	12.7 ± 4.8a (11.2, 14.2)
Protein	8.8 ± 3.2b (7.8, 8.6)	11.1 ± 3.9b (9.4, 12.8)	15.4 ± 2.4b (14.5, 16.2)
	p< 0.001	*p 0.001*	*p<0.001*

Data are presented as means ± SD (95% CI) for blood glucose values in mmol/L. Average overnight glucose: ab= p<0.001; Nadir glucose: ab= p<0.025. Within each bedtime glucose category, conditions which share the same letter are not statistically significant.

Figure Legends

Figure 1: Frequency of Nights with Hypoglycemia and Morning Hyperglycemia

White bars= no hypoglycemia and no morning hyperglycemia; black bars= hypoglycemia; hatched bars= morning hyperglycemia only. Pl= placebo; S= standard snack; CS= cornstarch snack; Prot= protein snack. Data represent the percentage of nights whereby there was nocturnal hypoglycemia, morning hyperglycemia (with no nocturnal hypoglycemia) and neither one with all 4 snack conditions according to 3 categories of HS glucose.


% Nights
100%
80%
60%
40%
20%
0%
Pl
S
CS
Prot
Pl
S
CS
Prot
Pl
S
CS
Prot
< 7 mM
7 - 10 mM
> 10 mM
HS Glucose Category

LINKAGE STATEMENT

In chapter 3, we demonstrated for the first time that the need for a bedtime snack and the most appropriate composition depend on the blood glucose level at bedtime. No bedtime snack appears to be necessary at bedtime blood glucose levels > 10 mmol/L. At bedtime blood glucose levels between 7-10 mmol/L, a standard snack or cornstarch-containing snack works best and at bedtime glycemic levels < 7 mmol/L, a standard snack and protein-rich snack are recommended. As we did not want to disrupt participants'usual routine, no further modification of the bedtime insulin dose was made during this study. We concluded that further research was thus needed to determine the efficacy of optimized titration of insulin dose, in the absence of a bedtime snack, on nocturnal glycemic control. The second study (chapter 4) was, therefore, designed to address this question. Specifically, we sought to answer whether it was possible to prevent nocturnal hypoglycemia, in free-living adults with type 1 diabetes, using optimized titration and delivery of bedtime insulin, including the use of continuous subcutaneous insulin infusion (CSII), in the absence of bedtime snacks.

CHAPTER 4

Impact of Optimized Titration and Delivery of Bedtime Insulin on Prevention of Nocturnal Hypoglycemia in Free-Living Adults with Type 1 Diabetes Undergoing Intensive Management: A Randomized, Controlled Trial Comparing Multiple Daily Injections of Insulin (with and without bedtime snacks) versus Continuous Subcutaneous Insulin Infusion

Maria Kalergis,[1,4] Alicia Schiffrin, [3] Réjeanne Gougeon, [1] Peter JH Jones, [4] and Jean-François Yale.[1,2]

[1] From the McGill Nutrition and Food Science Centre, Royal Victoria Hospital, McGill University Health Centre, Montreal QC

[2] From the Division of Endocrinology, Royal Victoria Hospital, McGill University Health Centre, Montreal, QC

[3] From the Division of Endocrinology, The Jewish General Hospital, Montreal, QC

[4] From the School of Dietetics and Human Nutrition, McGill University, Montreal, QC

Short Title: Impact of Optimized Titration and Delivery of Bedtime Insulin on Prevention of Nocturnal Hypoglycemia

Key words: Nocturnal Hypoglycemia; Intensive Management; Bedtime Snacks; Continuous Subcutaneous Insulin Infusion; CSII; Continuous Glucose Monitoring.

Journal

Diabetes Care (prepared for submission)

4.1 ABSTRACT

OBJECTIVE- To determine whether optimized titration and delivery of bedtime insulin with continuous subcutaneous insulin infusion (CSII) is superior to multiple daily injections of insulin or MDI (with and without bedtime snacks) in preventing nocturnal hypoglycemia in free-living adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS- Twenty nine adults participated in this 9 month randomized, controlled, crossover trial consisting of 3 strategies: Strategy 1 (MDI with a bedtime (HS) snack regimen tailored to the HS glycemic level); Strategy 2 (MDI with no HS snacks); Strategy 3: (CSII with no HS snacks). Titrations of insulin were based on 24-h glycemic profiles provided by the continuous glucose monitoring. System (CGMS). Glycemic profiles obtained at the end of each strategy, via the CGMS, were used to assess the incidence of nocturnal hypoglycemic episodes.

RESULTS- Ninety eight episodes occurred over 181 nights (54 episodes per 100 patient-nights) in 97% of patients. Twenty five episodes occurred with strategy 1; 39 with strategy 2 and 34 with strategy 3. In comparison to strategy 2, there was a 36% reduction in the number of episodes with strategy 1 and 13% reduction with strategy 3, $p=0.17$. There was significant difference in duration of hypoglycemia with strategy 1 (319 ± 36 min) versus strategies 2 and 3 (183 ± 27 min and 136 ± 28 min, $p<0.001$ respectively). The majority (64%) of episodes were asymptomatic and occurred primarily between 11pm and 2am. There was a 15% reduction ($p<0.001$), from baseline, in total daily insulin dose with strategy 3. There was no significant difference among the strategies with respect to metabolic control, body composition or quality of life.

CONCLUSIONS- The use of bedtime snacks, when appropriate, appears to significantly reduce the incidence of nocturnal hypoglycemia. Therefore, bedtime snacks, tailored to the bedtime glycemic level, should be encouraged in all adults with type 1 diabetes undergoing intensive management with MDI or CSII.

4.2 INTRODUCTION

Nocturnal hypoglycemia is a significant side effect of insulin replacement therapy with its occurrence having been described as early as 1928 (1). It is a significant problem in both children and adults (2-4) and with both conventional and intensive management regimens (5-7). The Diabetes Control and Complications Trial (DCCT) clearly demonstrated that attainment of normal glycemic control is necessary for prevention of long term complications associated with type 1 diabetes and this requires an intensive approach to management (6). However, intensive management is associated with a significant increase in the incidence of severe hypoglycemia, with approximately 40% of episodes occurring during the night, between midnight and 8 am (5, 8).

Nocturnal hypoglycemia is problematic as it has been suggested to lead to hypoglycemia unawareness (9, 10) and to deterioration in overall glycemic control (10), thus making the pursuit of normal glycemia more elusive. The etiology of nocturnal hypoglycemia is largely related to a mismatch of the pharmacokinetic profile of current insulin preparations with normal physiology, especially during the nocturnal period where insulin requirements often decrease at the same time that current basal insulin preparations (NPH or Ultralente) peak (10, 11). Furthermore, it has been well documented that there is a deterioration of the counterregulatory defense mechanisms to hypoglycemia over the natural course of type 1 diabetes (12, 13). This impairment of counterregulation may be the result of hypoglycemia itself (14-16), including nocturnal hypoglycemia (9, 10). This "vicious cycle" (16) whereby hypoglycemia begets hypoglycemia is believed to be a major cause of "hypoglycemia-associated autonomic failure" (16, 17). Moreover, it has recently been shown that sleep itself diminishes the

catecholamine response to hypoglycemia in type 1 diabetes (18). Therefore, prevention of nocturnal hypoglycemia is critical.

Strategies for prevention of nocturnal hypoglycemia, to date, include "relaxing" the glycemic targets associated with intensive management at the expense of metabolic control (19, 20) and the development of more physiologic insulin preparations such as insulin analogues (11) including insulin lispro (21, 22). Insulin replacement regimens such as multiple daily injections of insulin (MDI) with NPH insulin given at bedtime instead of supper (23) have also been employed in the hopes of preventing nocturnal hypoglycemia. Continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy, has been described as the "gold standard" for basal insulin replacement (11) especially for nocturnal control (10). However, no study to our knowledge, has specifically assessed the efficacy of CSII on prevention of nocturnal hypoglycemia. Several studies have also demonstrated the importance of bedtime snacks in the prevention of nocturnal hypoglycemia (3, 24) including specific bedtime snack compositions (25-30). In a recent study, we have demonstrated that the need for a bedtime snack and the most appropriate composition depends on the glycemic level at bedtime (30).

Despite the fact that nocturnal hypoglycemia continues to be a major obstacle in the pursuit of normal glycemia, little evidence exists as to the exact frequency of its occurrence, especially in free-living individuals. This is largely due to the fact that the majority of nocturnal hypoglycemic episodes are asymptomatic (1, 3, 31). Therefore, relying solely on self-reports, as in the case of all previous studies in free-living individuals is misleading. With the advent of the Continuous Glucose Monitoring System

in 1999 (CGMS, Medtronic/MiniMed Inc., Sylmar, CA) (32) it became possible, for the first time, to determine the frequency of nocturnal hypoglycemia in free-living individuals. Moreover, this technology has enabled the evaluation of an individual's entire 24-hour glycemic profile under free-living conditions, thus allowing for more precise titrations of insulin therapy. Its use has already been shown to lead to improved glycemic control in adults and children with type 1 diabetes (32-34).

Against this background, we undertook a randomized, controlled, crossover trial to test the hypothesis that optimized titration and delivery of bedtime insulin using CSII would result in less nocturnal hypoglycemia compared to MDI (with or without inclusion of bedtime snacks), without deterioration of metabolic control or quality of life in free-living adults with type 1 diabetes who were treated to optimal glycemic targets.

Primary objectives of our study were to determine the incidence of nocturnal hypoglycemia and long-term glycemic control between MDI and CSII.

Secondary objectives were to determine: 1) occurrence (timing) of nocturnal hypoglycemic episodes; 2) duration of nocturnal hypoglycemic episodes; 3) morning (fasting) glycemic control; 4) body weight and composition; 5) lipid profile and 5) psycho-social adaptation (quality of life, self-efficacy and fear of hypoglycemia) between MDI and CSII.

We also sought to elucidate potential correlates or predictors of nocturnal hypoglycemia including: baseline and most recent HbA_{1c}, bedtime and morning (fasting) blood glucose level.

4.3 RESEARCH DESIGN AND METHODS

4.3.1 Participants and Study Design

Adults between 18 and 65 years of age with endocrine diagnosis of type 1 diabetes were considered for inclusion in this 9 month randomized, controlled crossover trial if they had diabetes for more than 3 years duration and were able and willing to adhere with the treatment regimen. Individuals were excluded if they had evidence of significant hepatic or renal disease; active cancer; had abused alcohol or drugs; and / or were participating in another clinical trial or had taken an investigational drug in the past 4 weeks. Women who were pregnant or intended to become pregnant in the next year were also excluded from the study. Individuals were eligible for participation if they had been on intensive insulin therapy using multiple daily injections of insulin for at least 1 year prior and were willing to use lispro insulin before meals, especially at supper if they had not already been doing so. Individuals with all levels of glycemic control (HbA_{1c}) were considered eligible if they had experienced at least 1 episode of nocturnal hypoglycemia in the past year.

4.3.2 Description of Treatment Strategies

After a 2 week screening period which consisted of switching participants to lispro insulin if warranted, participants were randomized into a treatment sequence using a manually-derived randomization schedule. Participants were allocated to a particular order of treatment which consisted of 3 strategies. Strategy 1: MDI with a bedtime snack regimen, tailored to bedtime blood glucose levels, based on findings from our inpatient trial as described, in detail, elsewhere (30); Strategy 2: MDI with no bedtime snack and

Strategy 3: CSII with no bedtime snack. In Strategy 1, participants did not consume a bedtime snack if their blood glucose at bedtime was >10mmol/L. They consumed a standard snack, which was equivalent to 2 starch + 1 protein exchange, when their bedtime blood glucose was between 7-10 mmol/L and a protein-rich snack, which was equivalent to 1 starch + 3 protein exchanges when their bedtime blood glucose was <7 mmol/L, specifically between 4-6.9 mmol/L. Participants were thoroughly educated on snacks which conformed to the above criteria by a registered dietitian and were provided with a list of examples. Pure protein drink mixes, equivalent to 2 protein exchanges per 250mL, were made available to each participants courtesy of Bariatrix Inc. (Lachine, QC). A time-dependent switch or crossover point occurred at the end of each strategy, after 3 months (+/- 2 weeks) with the first month of each strategy considered as a run-in period. During the MDI strategies, participants were asked to use lispro insulin (Humalog ®; Eli Lilly, Indianapolis, IN) before meals, especially at supper with NPH insulin at bedtime (to be taken no later than 11:00pm) and to consume bedtime snacks, during strategy 1, within 1 hour of going to bed. Participants were provided with a study binder which contained their visit schedules, special instructions tailored to each strategy, insulin guides tailored to their needs as well as to each strategy and log sheets in which they recorded at least 4 capillary glucose readings per day (before meals, at bedtime and intermittently during the night, either at 2 or 4 am when warranted) either using the Precison Xtra® glucose meter which was made available to each participant, free of charge including free test strips for the entire duration of the study, courtesy of Medisense Inc. (Abbott Laboratories, Montreal, QC) or their own glucose meter, whichever they preferred. They also recorded insulin dose, the grams of carbohydrate

consumed per meal including a detailed description of any bedtime snack consumed, physical activity using a 5-point likert scale where 3 represented their "usual" level of activity; and any hypoglycemic reactions, defined as a capillary blood glucose<4 mmol/L with or without symptoms or symptoms leading to treatment. All patients received education on carbohydrate counting by a registered dietitian at baseline and every month as needed and were instructed on how to adjust their pre-meal insulin dose using individualized insulin to carbohydrate ratios as determined by the study endocrinologist Insulin guides were provided, which were individualized to each participant's needs and strategy, by the study endocrinologist, and consisted of insulin to carbohydrate ratios for the pre-meal insulin which was further adjusted according to a sliding scale for pre-meal blood glucose level and anticipated physical activity within 2 hours of each meal. As well, supplemental insulin was taken, as needed, in order to achieve target blood glucose levels consisting of fasting and pre-meal blood glucose targets of 4-7 mmol/L and 1-2 h post-meal targets between 5-10 mmol/L. Bedtime insulin was also adjusted according to a sliding scale for bedtime blood glucose level with avoidance of a "double correction" for blood glucose levels between 4-6.9 mmol/L for strategy 1 (ie- the appropriate bedtime snack was taken without down-titration of insulin dose as was done for strategies 2 and 3 at this blood glucose level). When bedtime blood glucose was <4mmol/L, participants were instructed to follow appropriate guidelines for the treatment of hypoglycemia (35) and to re-test and take appropriate action regarding bedtime snack and / or insulin dose once the blood glucose level was > 4 mmol/L in accordance to the strategy they were following. Participants received free insulin pumps and supplies for the entire duration of strategy 3, courtesy of Medtronic/Minimed Inc. (Sylmar, CA). Participants were

educated on the use of the MiniMed 507c insulin infusion pump by a certified insulin pump educator (MK) and were given detailed instructions for insulin replacement, by injection, in the case of pump failure and/or temporary insulin pump removal. They were also instructed on preventing potential complications associated with insulin pump therapy, namely reducing the risk of infection or contact dermatitis and diabetes ketoacidosis (36). In order to minimize the risk of infection, participants were asked to change their insulin infusion sets and reservoirs every 2-3 days. Participants wore the CGMS (Medtronic/MiniMed, Sylmar, CA) at the beginning (the first 3 days of the MDI strategies or within the second week of CSII) and at the end of each strategy (last 3 days) for a total of 6 times or 18 days, over a period of 9 months. The information from the CGMS was downloaded using the Com-Station® and the Solutions ® Software, version 2.0 (Medtronic/MiniMed , Sylmar, CA).

4.3.3 Description of Study Visits

Participants were scheduled for monthly clinic visits and were contacted on a weekly basis by the study coordinator either by telephone, fax or email. Participants also had 24-hour access to the study coordinator via pager and were asked to fax their log sheets at least once a week during the first 4 weeks of each strategy and at least every two weeks for the remainder of the strategy. Day to day adjustments of insulin dose were done by the participants according to their insulin guides and in consultation with the study endocrinologist if needed. Titrations of insulin therapy were done, at least every two weeks, by the study endocrinologist and were based on information provided by log sheets and when applicable by information obtained from glucose meters, which were

downloaded at each monthly clinic visit, and the 24-h glycemic profile obtained via the CGMS. Other information collected at each monthly clinic visit included weight (assessed on a digital scale with no shoes). Participants were also asked to complete a battery of validated questionnaires which consisted of two quality of life questionnaires: Medical Outcome Survey (37) and the Diabetes Quality of Life Questionnaire (38) and questionnaires assessing fear of hypoglycemia: Fear of Hypoglycemia Questionnaire (39); self-efficacy: The Insulin Management Self-Efficacy Scale (40) and perceived stress and complexity of treatment regimen: The Approach Questionnaire (41, 42) at baseline and in the beginning (within the first month) and at the end (within the last month) of each strategy. They also completed a descriptive questionnaire at baseline which consisted of information about their experience and management of hypoglycemia, particularly nocturnal hypoglycemia. At baseline and at the end of each strategy, participants received a physical examination by the study endocrinologist and had blood obtained after an 8h overnight fast for determination of HbA_{1c}; lipid profile (total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) and any other supplemental tests that were deemed necessary by the study endocrinologist. Body composition was assessed at baseline and at the end of each strategy every 3 months. Percent body fat was determined by bioelectrical impedance analysis (BIA) using the Tanita® Body Analyzer (Tanita Corporation, Tokyo, Japan), a method which has been validated and found to be highly correlated with results using dual-energy X-ray absorptiometry (43) and tetrapolar BIA (44). Waist circumference was assessed using a tape measure according to standard methodology as described elsewhere (45). Total daily insulin dose and insulin sensitivity were also assessed at baseline and at the end of each strategy by verifying patient log

sheets. Insulin sensitivity, expressed as the decrement in blood glucose per unit of lispro insulin was assessed by an insulin sensitivity index consisting of the calculation: 100 / total daily insulin dose (46). All tests were performed using routine automated methods at the biochemistry department of the Royal Victoria Hospital local laboratory. HbA_{1c} was determined using the Cobas Miras analyzer (Roche Canada Inc.) and total lipid profile was determined using the Bayer DAX 96 analyzer (Bayer Inc.), with LDL-cholesterol, determined using the Freidewald equation.

4.3.4 Efficacy Measures

Primary efficacy measures, on which sample size calculations were based, included incidence of nocturnal hypoglycemia defined as a blood glucose value of < 4 mmol/L occurring between 11pm and 7am, as determined via the CGMS, and long-term glycemic control as determined by HbA_{1c} every 3 months, at the end of each strategy. An episode of hypoglycemia was counted as distinct if it occurred at least 30 minutes after the end of the previous episode.

Secondary efficacy measures included: the nocturnal hypoglycemic level; the nadir nocturnal hypoglycemic level (the lowest level of hypoglycemia attained); timing and duration of hypoglycemia; morning (fasting) glycemic level; total lipid profile (total cholesterol, HDL, LDL, triglycerides); psycho-social adaptation (fear of hypoglycemia, quality of life, self-efficacy, perceived stress and complexity of treatment regimen); total insulin dose, insulin sensitivity and body composition (weight, BMI, % fat, waist circumference).

4.3.5 Statistical Analyses and Power Calculation

All statistical analyses were conducted using the Statistical Program for Social Sciences (SPSS, version 10.0, Chicago, IL) using all data collected since randomization. HbA_{1c}, the primary end point, and other continuous variables (total lipid profile, body composition, insulin dose, insulin sensitivity, nocturnal hypoglycemic level, duration of hypoglycemia) including psycho-social data were analyzed using a 2-way Analysis of Variance (ANOVA) with treatment and time as main effects and a time by treatment interaction as indicative of an "order" effect. Chi-square analyses were used to assess incidence and timing of nocturnal hypoglycemia and frequency of symptoms. Potential predictors of nocturnal hypoglycemia were assessed via a one-way ANOVA. A P value <0.05 was indicative of statistical significance with 95% CIs calculated for all continuous estimates where warranted.

The sample size projected for the study (n=20) was based on an 80% power of detecting a reduction of 50% in the incidence of nocturnal hypoglycemia and a difference of 1% in HbA_{1c} among the strategies, using the formula outlined in Jekel et al (47).

The study was approved by the Department of Medicine's Research Ethics Committee of the Royal Victoria Hospital and by the Institutional Review Board of McGill University.

4.4 RESULTS

A total of 32 adults were randomized into the study. Of these, 3 dropped out prior to the baseline visit for personal reasons which included: moving to another city; frequent business travel and a new job.

Twenty-nine adults (11 men and 18 women), aged 20 to 65, with type 1 diabetes ranging from 6 to 47 years participated in this 9 month randomized, controlled, crossover trial. The majority of participants (21/29=72%) completed all 3 strategies while 3 completed one strategy; 2 completed two strategies and 3 completed no strategy (only baseline). The size of the groups at the end of the study were as follows: Strategy 1 (n=22); Strategy 2 (n=24); Strategy 3 (n=24). There were no significant differences between full and partial completers in any parameter of importance. A detailed description of the baseline characteristics of participants is presented in Table 1. Participants were weight stable and had a mean body mass index of 26.2 kg/m^2 and a mean HbA_{1c} of 7.8% (reference: 4-6%) at baseline. The majority (n=25) took lispro insulin before meals and all used lispro insulin at supper. The majority of subjects (n=26) took NPH insulin at bedtime. Only 1 subject had used CSII with regular insulin prior to the study. However this subject also used MDI consisting of regular insulin before meals and NPH insulin at bedtime, at intermittent intervals, in the past year prior to the study. All but one subject used CSII for 24 hours per day over the entire duration of strategy 3. One subject, because of severe contact dermatitis, was able to use CSII only during the night. No subject used carbohydrate counting or carbohydrate to insulin ratios prior to the study.

All the subjects adjusted their bedtime insulin dose according to their bedtime blood glucose results using a sliding scale as recommended by their physician. The majority (62%) of participants consumed bedtime snacks either all of the time or most of the time while 38% consumed bedtime snacks some of the time. The majority (20/29) never adjusted the size or composition of their bedtime snack according to their bedtime blood glucose level and the majority of participants (20/29) consumed a bedtime snack that contained less carbohydrate and protein than the standard snack (2 starch +1 protein) which we found to be one of the most effective snack compositions at reducing the incidence of nocturnal hypoglycemia in a previous study (29).

4.4.1 Nocturnal Hypoglycemia

At the end of each strategy, a total of 181 nights were available for evaluation. Of these, 80 or 44% comprised at least one or more episodes of nocturnal hypoglycemia. In total, 98 episodes (54 per 100 patient-nights) occurred in 97% of patients. Of the 98 episodes, 25 episodes over 60 nights (42 per 100 patient-nights) occurred at the end of strategy 1; 39 episodes over 58 nights (67 per 100 patient-nights) occurred at the end of strategy 2 and 34 episodes over 63 nights (54 per 100 patient-nights) occurred at the end of strategy 3 (Fig 1). In comparison to strategy 2 which had the highest incidence of nocturnal hypoglycemia, there was a 36% reduction in the number of hypoglycemic episodes with strategy 1 and 13% reduction with strategy 3, p=0.17. Strategy 1 also resulted in a 26% reduction of nocturnal hypoglycemia compared to strategy 3, p=0.17.

There were no clinically or statistically significant differences among the strategies with respect to the mean initial level of hypoglycemia or the mean nadir level

of hypoglycemia attained, which reached <2.8 mmol/L for all strategies, as outlined in Table 2. However, there was a clinically and statistically significant difference in the mean ± SE duration of hypoglycemia, with the highest duration being with strategy 1 (319 ± 36 min) versus strategies 2 and 3 (183 ± 27 min and 136 ± 28 min, $p<0.001$ respectively) as outlined in Table 2.

More than half of episodes (52%) occurred between 11pm and 2 am; 32% occurred between 4am and 8am and only 18% occurred between 2am and 4 am. Also as illustrated in Figure 1, 48% of the episodes occurred between 11pm and 2am with a similar proportion between 2am-4am and 4am-8am (24 and 28% respectively) with strategy 1. With strategies 2 and 3, a very similar pattern indicated that more episodes occurred "early", between 11pm and 2am (51 and 52% respectively) with a significant proportion also occurring "late", between 4am and 8am (36 and 29% respectively) and relatively less episodes occurring midway, between 2am-4am (13 and 18% respectively).

Overall, 64% of the episodes were asymptomatic and the majority of participants (83%) experienced at least one or more episodes without any symptoms. The majority of episodes were asymptomatic for all 3 strategies, with strategy 2 consisting of the most asymptomatic episodes at 77% with an equivalent proportion (56%) for strategies 1 and 3, $p=0.11$.

4.4.2 Bedtime and Morning Glycemic Control

As depicted in Table 2, bedtime glycemic control, as determined via the CGMS, was not significantly different among the strategies, although it was slightly better with strategy 3 (8.5 ± 0.49 mmo/L) compared to strategies 1 and 2 (9.5 ± 0.54 and 9.9 ± 0.51 mmol/L respectively, $p=0.13$).

No significant differences with respect to morning (fasting) glycemic control were observed among the strategies.

4.4.3 HbA_{1c}

There were no clinically or statistically significant differences among the strategies or in comparison to baseline with respect to long term glycemic control, as outlined in Table 3.

The mean ± SE HbA_{1c} level at baseline was 7.8% ± 0.18 and remained fairly consistent throughout each strategy, only increasing slightly by as much as 0.2 with strategy 3 compared to the other strategies.

4.4.4 Lipid Profile

There were no clinically or statistically significant differences among the strategies or in comparison to baseline with respect to any of the lipid parameters as outlined in Table 3.

There was a slight improvement in all lipid parameters with all strategies in comparison to baseline. The mean ± SE LDL cholesterol level at baseline was: 2.6 ± 0.15 mmol/L and it decreased with each strategy, by as much as 0.3 mmol/L with strategy 3. The mean ± SE HDL cholesterol level at baseline was: 1.5 ± 0.10 mmol/L and it increased with each strategy, by as much as 0.2 mmol/L with all three strategies. The mean ± SE triglyceride level at baseline was: 0.98 ± 0.11 mmol/L and it decreased with each strategy, by much as 0.12 with strategy 1.

4.4.5 Body Weight and Composition

As outlined in Table 3, compared to baseline, there was a slight increase in weight with strategies 1 and 3, in the order of 1.2 and 1.6 kg respectively, and a slight decrease in weight with strategy 2 in the order of 0.6kg ($p= 0.91$). In completers ($n=21$), compared to baseline (75.9 ± 3.5 kg) only strategy 3 (76.4 ± 3.6) resulted in a slight increase in body weight of 0.5kg , whereas there was a slight decrease with both strategies 1(75.5 ± 3.6) and 2 (75.4 ± 3.8) in the order of 0.4 kg and 0.5 kg respectively ($p= 0.98$).

There were no clinically or statistically significant differences with respect to body composition (BMI, % fat, waist circumference) as compared to baseline or among the strategies.

4.4.6 Total Daily Insulin Dose and Insulin Sensitivity

There was a clinically and statistically significant ($p<0.001$) difference with respect to % change in total daily insulin dose, from baseline, by about 15 % with strategy 3. Strategies 1 and 2 resulted in slight increases in insulin dose compared to baseline (3% and 6% respectively). Total daily insulin dose, expressed as units/kg, was also lower with strategy 3 (0.60 ± 0.05) compared with strategies 1 and 2 (0.69 ± 0.1 and 0.76 ± 0.1 respectively, $p=0.10$). Insulin sensitivity, expressed as the decrement in blood glucose per unit of lispro insulin, tended to improve with strategy 3 compared with strategies 1 and 2 (2.5 ± 0.16 versus 2.1 ± 0.16 and 2.0 ± 0.16 mmol/L respectively, $p=0.08$). Furthermore, more individuals (79%) were able to decrease their total daily

insulin dose with strategy 3 compared with 45% of patients with strategy 1 and only 21% with strategy 2 ($p<0.001$).

4.4.7 Psycho-Social Adaptation

There were no clinically or statistically significant differences among the strategies for any of the psycho-social outcomes (fear of hypoglycemia, quality of life, self-efficacy, preceived stress and complexity).

With respect to fear of hypoglycemia, a moderate level of fear existed at baseline which did not improve or worsen with any strategy (Table 4).

Participants appeared to have a good general quality of life, as assessed using the Medical Outcome Survey (data not shown) and a good diabetes-specific quality of life, as assessed by the Diabetes Quality of Life questionnaire at baseline (Table 4) which did not deteriorate with any strategy.

Participants also had a good sense of self-efficacy with respect to all parameters of their diabetes management at baseline and did not appear to find their treatment regimen stressful or complex. These observations remained consistent throughout each strategy (Table 4).

4.4.8 Predictors of Nocturnal Hypoglycemia

Baseline and Recent Glycemic Control (HbA_{1c})

There was no significant relationship between baseline HbA_{1c} level and nocturnal hypoglycemia. The baseline HbA_{1c} level for the presence and absence of nocturnal hypoglycemic episodes was 7.6 ± 0.1 versus 7.8 ± 0.1 respectively, p=0.15. However, there was a significant relationship between category of glycemic control at baseline and the mean number of nocturnal hypoglycemic episodes, whereby a higher mean number of nocturnal hypoglycemic episodes occurred in individuals classified as having optimal glycemic control compared to those classified with suboptimal and inadequate glycemic control (2.3 ± 0.3 episodes vs. 1.1 ± 0.1 and 1.4 ± 0.4 episodes respectively, p=0.005).

There was a significant relationship between the HbA_{1c} level at the end of each strategy and nocturnal hypoglycemia, whereby the occurrence of nocturnal hypoglycemia was associated with a lower mean HbA_{1c} level compared to the absence of nocturnal hypoglycemia (7.8% ± 0.09 vs. 8.0% ± 0.08, $p<0.05$). Furthermore, participants classified as having optimal glycemic control, at the end of each strategy, had significantly more nocturnal hypoglycemic episodes, on average, compared to individuals classified as having either suboptimal or inadequate glycemic control (6.2 ± 0.6 episodes vs. 3.8 ± 0.3 and 3.0 ± 0.6 episodes respectively, p=0.001)

Bedtime and Morning (fasting) Blood Glucose

There was a significant relationship between bedtime and morning glycemic control and nocturnal hypoglycemia.

The mean bedtime glucose level was higher in the absence of nocturnal hypoglycemia compared to the occurrence of nocturnal hypoglycemia (10.2 ± 0.4 mmol/L vs. 8.5 ± 0.4 mmol/L respectively, $p<0.001$). With strategy 1, however, there was no significant difference between bedtime blood glucose and nocturnal hypoglycemia which was 9.9 ± 0.7 mmol/L in the absence of nocturnal hypoglycemia vs. 9.5 ± 1.0 mmol/L with occurrence of hypoglycemia ($p=0.71$).

The mean morning glucose level was higher in the absence of nocturnal hypoglycemia compared to the occurrence of nocturnal hypoglycemia (10.7 ± 0.36 vs. 5.5 ± 0.33 mmol/L respectively, $p< 0.001$).

4.5 CONCLUSIONS

In this study we assessed optimized titration and delivery of bedtime insulin, using continuous glucose monitoring technology, in 29 adults with type 1 diabetes undergoing intensive management with CSII and MDI (with and without bedtime snacks). To our knowledge, this is the first study of its kind to assess the efficacy of optimized titration and delivery of bedtime insulin, in the presence and absence of bedtime snacks, using continuous glucose monitoring technology as a decisional aid.

This study found that the incidence of nocturnal hypoglycemia, although not completely eliminated, is substantially reduced by inclusion of a bedtime snack regimen which is tailored to the bedtime glycemic level. Although we hoped to obtain a reduction of at least 50% in the incidence of nocturnal hypoglycemia, this level was not achieved indicating that nocturnal hypoglycemia remains a significant problem despite advances in insulin preparations, insulin delivery regimens and technology. However, reductions in the order of 36% and 26% in the incidence of nocturnal hypoglycemia were achieved with inclusion of bedtime snacks to an MDI regimen (strategy 1) compared to an MDI regimen without inclusion of bedtime snacks (strategy 2) or to CSII, which also did not include bedtime snacks (strategy 3). Despite the use of lispro insulin at supper and NPH at bedtime, two strategies which have proven to be efficacious in reducing the incidence of nocturnal hypoglycemia in adults with type 1 diabetes (20, 22, 23), our data indicate that bedtime snacks are necessary. Even the use of CSII, the "gold standard" of nocturnal insulin replacement (10, 11) failed to compensate for exclusion of bedtime snacks, even though the total daily insulin dose was significantly reduced with CSII. A reduction of insulin dose with CSII compared to MDI has also been demonstrated by some studies

(48, 49) but not others (50). Furthermore, the inclusion of bedtime snacks does not negatively impact on body composition or metabolic control in comparison with strategies which do not include bedtime snacks.

However, although the incidence of nocturnal hypoglycemia was lowest with strategy 1, there was a significant increase in the duration of the hypoglycemic episodes with this strategy compared to the other strategies indicating that recovery from hypoglycemia may be may be impaired. Perhaps substrate availability somehow alters glucose counterregulation to hypoglycemia. It has been shown that prior stimuli of glucose counterregulatory hormones, such as exercise and hypoglycemia, diminishes their efficacy to subsequent hypoglycemia possibly mediated through secretion of cortisol (17). Although no study has evaluated the stimulus of substrate or specific substrates on the efficacy of counterregulation to hypoglycemia. it has been shown that protein is a stimulant of the counterregulatory hormones glucagon and cortisol (51). Thus it is conceivable, that inclusion of a bedtime snack that contains protein, may diminish the efficacy of counterregulation to hypoglycemia thus prolonging the hypoglycemia. Future research is needed to address this hypothesis and clarify this finding. The shortest duration of hypoglycemia was with CSII indicating counterregulation may have been improved despite a higher incidence of nocturnal hypoglycemia compared to strategy 1. However, both CSII and strategy 1 resulted in a similar proportion of episodes which were asymptomatic indicating that awareness to hypoglycemia was similar for both strategies despite the longer duration of hypoglycemia with strategy 1. Conversely, strategy 2 resulted in the highest incidence of asymptomatic hypoglycemic episodes.

With respect to occurrence of hypoglycemic episodes, we found the highest frequency of nocturnal hypoglycemia was in the early part of the night between 11pm and 2am, in agreement with a previous inpatient study in adults with type 1 diabetes who were undergoing intensive management with human regular insulin before meals and NPH at bedtime (3). The increased frequency of nocturnal hypoglycemia in the early part of the night is likely due to the greater insulin sensitivity between midnight and 2am (9).

Consistent with the findings of previous studies of intensive management (6, 52) weight increased in our study albeit to a similar extent for all strategies. Despite this increase in weight there was no deterioration in metabolic control as assessed by HbA_{1c} and total lipid profile. In fact, the lipid profile appeared to improve with all strategies. Furthermore, the percentage of body fat and waist circumference did not change indicating that perhaps this increase in weight is due to gains in both lean tissue and fat mass (53). There was no deterioration in any psycho-social parameters including quality of life, indicating that intensive therapy with both MDI and CSII is well accepted as has been previously shown (6, 52). However, the moderate level of fear of hypoglycemia, at baseline, did not improve with any particular strategy indicating that perhaps adults living with type 1 diabetes always have a certain level of fear with regards to hypoglycemia. This fear may represent a barrier to optimal glycemic control, a concern that has been recently raised by some investigators (54, 55). Perhaps 3 months was not long enough to see an effect. Further research is therefore required to clarify this observation.

This study is the first to outline potential predictors of nocturnal hypoglycemia which include: baseline HbA_{1c} level (category of glycemic control only); recent HbA_{1c} (actual level and category of glycemic control); bedtime and morning (fasting) glycemic

level. A lower baseline and most recent HbA_{1c} level was associated with a higher incidence of nocturnal hypoglycemia. This finding is in partial agreement with the DCCT which found that a higher baseline HbA_{1c} level and a lower most recent HbA_{1c} level were the most pertinent predictors of severe hypoglycemia, which occurred primarily overnight (5,6). With respect to the bedtime blood glucose level, we found that a bedtime blood glucose level >10 mmol/L appeared to be protective against nocturnal hypoglycemia. This observation is in agreement with a previous inpatient study we conducted in adults with type 1 diabetes (30). Also in agreement with another inpatient study (3), we found that nocturnal hypoglycemia was followed by a lower blood glucose level in the morning (< 6 mmol/L). These findings may have implications regarding clinical practice guidelines for bedtime and fasting glycemic targets, especially in the context of intensive management.

This study clearly demonstrates that despite our best efforts and advances in insulin preparations, regimens and technology, nocturnal hypoglycemia continues to be a significant problem in free-living adults with type 1 diabetes undergoing intensive management, even in the context of sub-optimal glycemic control. Although metabolic control did not deteriorate in our study, as was the case in a recent study on avoidance of nocturnal hypoglycemia whereby glycemic targets were "relaxed" (20), we were not able to attain the "optimal" glycemic control we were pursuing, a finding which has been confirmed in all previous studies of intensive management in the context of a typical clinical setting (49, 50, 52).

Although CSII was superior to MDI with bedtime snacks on several important efficacy measures including: total daily insulin dose, insulin sensitivity and duration of hypoglycemia, it did not abolish the need for a bedtime snack, even in the context of insulin lispro which has been shown to be superior to regular insulin for use in CSII (47) Further research is therefore required to assess the efficacy of bedtime snacks in the context of CSII.

Therefore, given these findings, bedtime snacks tailored to the bedtime glycemic level should be used in all adults with type 1 diabetes undergoing intensive management with MDI or CSII, even with the use of insulin lispro. Further research is required to extend these findings to other populations such as children with type 1 diabetes or with the use of newer insulin preparations such as aspart ® or glargine ® which are gaining in popularity.

4.6 ACKNOWLEDGEMENTS

We would like to thank Medtronic/Minimed Inc. for providing insulin pumps and supplies and two CGMS® units. We would also like to thank Medisense Inc. for providing Precision Xtra ® glucose meters and test strips and Bariatrix Inc. for providing the protein drink mixes. We would also like to thank the Canadian Diabetes Association for providing funding for this study through an Applied Research Grant and for publishing parts of this study as abstracts in their journal. We would also like to extend our gratitude to the staff of the Metabolic Day Centre, particularly to the following endocrinologists who supported this study: Dr. Sara Meltzer, MD; Dr. David Morris, MD; Dr. Mark Sherman, MD; and Dr. Walter Gregory, MD. Finally we would like to thank all the participants.

4.7 REFERENCES

1. Gale EAM, Tattersal RB: Unrecognized Nocturnal Hypoglycemia In Insulin-Treated Diabetics. The Lancet May 19: 1049-1052, 1976

2. Bendtson I, Kverneland A, Pramming S, Binder C: Incidence of nocturnal hypoglucemia in insulin-dependent diabetic patients on intensive therapy. Acta Med Scand 223: 543-548, 1988

3. Vervoort G, Goldschmidt HMG, Van Doorn LG: Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple daily injection regimens. Diabetic Medicine 13: 794-799, 1996

4. Yale, JF: Hypoglycemia, In: Evidenced-Based Diabetes care, H. Gerstein, Haynes, RB, Editor. 2001, BC Decker Inc: Hamilton/London. p. 380-395.

5. The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90: 450-459, 1991

6. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 329: 977-986, 1993

7. The DCCT Research Group: Effect of intensive diabetes treatment in the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: diabetes control and complications trial. J of Ped 125: 177-187, 1994

8. The DCCT Research Group: Nutrition interventions for intensive therapy in the diabetes control and complications trial. J Am Diet Assoc 93(7): 768-772, 1993

9. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of Hypoglycemia Unawareness by Asymptomatic Nocturnal Hypoglycemia. Diabetes 42: 1233-1237, 1993

10. Bolli GB, Fanelli CG, Perriello G, De Feo P: Nocturnal blood glucose control in type 1 diabetes mellitus. Diabetes Care 16: 71-89, 1993

11. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A. Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 49: 2142-2148, 2000

12. Gerich, JE: Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37: 1608-1617, 1988

13. Cryer PE, Fisher JN, Shamoon H: Hypoglycemia: Technical Review. Diabetes Care 17(7): 734-755, 1994

14. Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 47: 223-226, 1991

15. Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UM, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. Diabetes 42: 610-618, 1993

16. Cryer, PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a viscious cycle. Diabetes 41: 1335-1340, 1992

17. Cryer, PE: Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 281: E1115-E1121, 2001

18. Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia in IDDM children. Diabetes Care 338: 1657-1662, 1998

19. Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P, Porcellati F, Scionti L, Santeusano F, Brunetti P, Bolli GB: Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most neuroendocrine responses to, smptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 42: 1683-1689, 1993

20. Fritsche A, Stefan N, Haring H, Gerich J, Stumvoll M: Avoidance of hypoglycemia awareness by increasing b-adrenergic sensitivity in type 1 diabetes. Ann Int Med 134(9): 729-736, 2001

21. Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB: Administration of neutral protamine hagedorn insulin at bedtime versus with dinner in type 1 diabeets mellitus to avoid nocturnal hypoglycemia and improve control. Ann Int Med 136(7): 504-514, 2002

22. Ahmed ABE, Home PD: The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. Diabetes Care 21: 32-37, 1998

23. Heller SR, Amiel S, Mansell P, UK Lispro Study group: Effect of the fast-acting insulin analog lispor on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 22(10): 1607-1611, 1999

24. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. Diabetes Care 4: 239-244, 1989

25. Ververs MTC, Rouwe C, Smit GPA: Complex carbohydrates in the prevention of nocturnal hypoglycemia in diabetic children. Eur J Clin Nutr 47: 268-273, 1993

26. Kaufmann F, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type 1 diabetes. J Diab Compl 10: 84-87, 1996

27. Kaufmann FR, Halvorson M, Kaufmann N: A snack bar containing uncooked cornstarch to diminish hypoglycemia (abstract). Diabetes 200A, 1996

28. Saleh T, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes 20(8): 1236-1236, 1997

29. Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. J Int Med 245: 229-236, 1999

30. Kalergis M, Schiffrin A, Gougeon R, Jones PJH, Yale JF: Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes mellitus undergoing intensive insulin management using lispro insulin ac meals: a randomized, placebo-controlled, crossover trial. Diabetes Care, In Press, 2002

31. Kalergis M, Aljaberi K, Schiffrin A, Meltzer S, Gougeon R, Yale JF: Frequency and duration of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management as determined by continuous glucose monitoring (abstract). Can J Diabetes Care 25: 156A, 2001

32. Koschinsky T, Heinemann L: Sensors for glucose monitoring: technical and clinical aspects. Diabetes Metab Res Rev 17: 113-123, 2001

33. Bode BW, Gross TM, Thornton KR, Mastrototaro JJ: Continuous glucose monitoring used to adjust diabeets therapy improves glycosylated hemoglobin: a pilot study. Diab Res Clin Pract 46: 183-190, 1999

34. Gross TM, Bode BW, Einthorn D, Kayne DM, Reed JH, White NH, Mastrototaro JJ: Performance evaluation of the minimed continuous glucose monitoring system during patient home use. Diab Technol Ther 2(1): 49-56, 2000

35. Esslinger K, Rochon G, Bonhomme S, Yale JF: Therapy of hypoglycemia by nurses on hospital wards: assessment of protocol knowledge. Can J Diabetes Care 25(1): 14-21, 2001

36. Lenhard MJ, Reeves GD: Continuous subcutaneous insulin infusion. Arch Int Med 161: 2293-2300, 2001

37. Stewart AL, Hays RD, Ware JE: The MOS short-form general health survey: reliability and validity in a patient population. Medical Care 26(7): 724-735, 1988

38. The DCCT Research Group: Reliability and validity of a diabetes quality of life measure for the diabetes control and complications trial (DCCT). Diabetes Care 11(9): 725-732, 1988

39. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 10(5): 617-621, 1987

40. Hurley AC, Shea CA: Self-efficacy: strategy for enhancing diabetes self-care. Diabetes Educator 18(2): 1-8, 1992

41. Kalergis, M: "The evaluation of three treatment strategies in subjects with type I diabetes mellitus undergoing intensive diabetes management: metabolic, psycho-social and educational implications." Diss. McGill U: Montreal, 1996.

42. Kalergis M, Pacud D, Strychar I, Meltzer S, Jones PJH, Yale JF: Optimizing insulin delivery: assessment of three strategies in intensive diabetes management. Diabetes, Obesity and Metabolism. 2: 299-305, 2000

43. Rubiano F, Nunez C, Heymsfeld SB: A comparison of body composition techniques. Annals of the New York Academy of Sciences. 904: 335-338, 2000

44. Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM: Evaluation of the novel tanita body-fat analyser to measure body composition by comparison with a four-compartment model. Brit J Nutr. 83: 115-122, 2000

45. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Déspres JP: A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. Am J Clin Nutr 64: 685-693, 1996

46. Davidson, PC: Bolus and supplemental insulin, In: The Insulin Pump Therapy Book, Frederickson L, Editor. 1995, MiniMed Technologies: Sylmar. p. 59-71.

47. Jekel JF, Elmore JG, Katz DL, Epidemiology, Biostatistics and Preventive Medicine. 1996: W.B. Saunders Company.

48. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. Diabetes Care. 19(4): 324-327, 1996

49. Hanaire-Broutin H, Melki V, Bessiere-Lacombe S, Tauber JP, The Study group For The Development of Pump Therapy in Diabetes: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using lispor in type 1 diabetic patients on intensifeid treatment. Diabetes Care 23(9): 1232-1235, 2000

50. Tsui E, Barnie A, Ross S, Parkes R, Zinman B: Intensive insulin therapy with insulin lispro: a randomized tial of continuous subcutaneous insulin infusion versus multiple daily injection. Diabetes Care 24(10): 1722-1727, 2001

51. Winiger G, Keller W, Laager R, Girard J, Berger W: Protein content of the evening meal and nocturnal plasma glucose regulation in type 1 diabetic subjects. Horm Res 44: 101-104, 1995

52. Haakens K, Dahl-Jorgenson K, Vaaler S, Aagenaes O, Mosand R, Hanssen KF: What happens in the long-term to the intensively treated IDDM pateinet?: a four year follow-up. Pract Diab Int 12(4): 178-181, 1995

53. The DCCT Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the diabetes control and complications trial. Diabetes Care 24 (10): 1711-1721.

54. Sumner J, Baber C, Williams V: What do patients with type 1 diabeets know about hypoglycemia? Pract Diab Int 17(6): 187-190, 2000

55. Rubin, RR: Hypoglycemia and quality of life. Can J Diabetes. 26(1): 60-63, 2002

Table 1: Baseline Participant Characteristics

N	29
Gender	11 men; 18 women
Age (years)	41± 12 (20 to 65)
Duration of diabetes (years)	23 ± 10 (6 to 47)
†HbA_{1c} (%)	7.8 % ± 1.07 (6.1 to 10.2)
††Category of Control	Sub-optimal
optimal (N)	N= 5
sub-optimal (N)	N= 17
inadequate (N)	N= 7
Body Mass Index (kg/m^2)	26.2 ± 4.55 (18.0 to 42.2)
Total Daily Insulin Dose (U/Kg)	0.70 ± 0.26 (0.30 to 2.33)

Data are presented as Means ± SD (range). † HbA_{1c} reference at Royal Victoria Hospital: 4-6%. †† Category of control according to Canadian Guidelines (57), whereby optimal= <115% of upper limit of normal (ULN); sub-optimal= 115%-140% of ULN; inadequate=>140% of ULN.

Table 2: Mean Bedtime Glucose, Nocturnal Hypoglycemia (initial level, nadir and duration) and Morning (fasting) Glucose According to Strategy.

	Strategy 1 (MDI with HS snacks)	**Strategy 2** (MDI with no HS snacks)	**Strategy 3** (CSII with no HS snacks)
Bedtime Glucose (mmol/L)	9.5 ± 0.54 (8.5 to 10.6)	9.9 ± 0.51 (8.9 to 10.9)	8.5± 0.49 (7.6 to 9.5)
Nocturnal Hypoglycemia (mmol/L)	3.6 ± 0.07 (3.5to 3.8)	3.7 ± 0.05 (3.6 to 3.8)	3.7± 0.05 (3.6 to 3.8)
nadir	2.4 ± 0.12 (2.1 to 2.6)	2.6 ± 0.09 (2.4 to 2.8)	2.6± 0.10 (2.5 to 2.8)
duration (min)	319 ± 36 (248 to 389)a	182 ± 27(129 to 235)b	136±28 (80 to 192)b
Morning Glucose (mmol/L)	8.7 ± 0.57 (7.5 to 9.8)	7.9 ± 0.53 (6.8 to 9.0)	7.9± 0.51 (6.9 to 8.9)

Data are presented as means ± SE (95% CI). All data are based on CGMS results. All data (except duration of hypoglycemia) are presented in mmol/L. ab, $p<0.001$ (strategy 1 vs. strategies 2 and 3).

Table 3: Metabolic Control, Body Composition and Insulin Sensitivity According to Strategy.

	Baseline	**Strategy 1** (MDI with HS snacks)	**Strategy 2** (MDI with no HS snacks)	**Strategy 3** (CSII with no HS snacks
HBA_{1c} (%)	7.8 ± 0.18 (7.5 to 8.2)	7.9 ± 0.21 (7.5 to 8.3)	8.0 ± 0.19 (7.6 to 8.3)	8.1 ± 0.19 (7.7 to 8.4)
Total-C (mmol/L)	4.56 ± 0.18 (4.20 to 4.91)	4.56 ± 0.21 (4.14 to 4.98)	4.66 ± 0.19 (4.29 to 5.03)	4.55 ± 0.19 (4.17 to 4.93)
LDL-C (mmol/L)	2.61 ± 0.15 (2.31 to 2.91)	2.53 ± 0.18 (2.18 to2.89)	2.60 ± 0.16 (2.29 to 2.92)	2.32 ± 0.16 (2.00 to 2.94)
HDL-C (mmol/L)	1.50 ± 0.10 (1.31 to 1.70)	1.63 ± 0.12 (1.40 to 1.87)	1.66 ± 0.13 (1.45 to 1.86)	1.59 ± 0.11 (1.38 to 1.80)
Triglycerides (mmol/L)	0.98 ± 0.11 (0.78 to 1.2)	0.86 ± 0.12 (0.62 to 1.1)	0.87 ± 0.11 (0.65 to 1.1)	0.99 ± 0.11 (0.77 to 1.2)
Weight (kg)	73.8 ± 3.2 (67.6 to 80.1)	75.0 ± 3.7 (67.7 to 82.3)	73.2 ± 3.8 (65.8 to 80.7)	75.4 ± 3.5 (68.4 to 82.3)
BMI (kg/m^2)	26.6 ± 0.96 (24.7 to 28.5)	26.1 ± 1.10 (23.9 to 28.4)	25.1± 1.10 (22.8 to27.4)	26.3± 1.10 (24.2 to 28.4)
Body Fat (%)	28.8 ± 1.58 (25.6 to 31.9)	27.8 ± 1.84 (24.3 to 31.5)	29.1 ± 1.87 (25.3 to 32.8)	29.3 ± 1.73 (25.9 to 32.8)
Waist (cm)	84.3 ± 2.89 (78.5 to 90.0)	86.4 ± 3.36 (79.7 to 93.0)	85.0 ± 3.41 (78.2 to 91.8)	86.6 ± 3.17 (80.3 to 92.9)
†Insulin Dose *% change*	N/A	2.6 ± 3.7 (-4.8 to 10.1)a	6.0 ± 3.6 (-1.3 to 13.3)a	-14.8 ± 3.5 (-21.8 to 7.7)b
units/kg	0.70 ± 0.05 (0.65 to 0.84)	0.69 ± 0.06 (0.58 to 0.80)	0.76 ± 0.06 (0.65 to 0.88)	0.59 ± 0.05 (0.49 to 0.70)
‡Insulin Sensitivity Factor	2.18 ± 0.17 (1.86 to 2.51)	2.16 ± 0.19 (1.77 to 2.53)	2.20 ± 0.19 (1.83 to 2.58)	2.51 ± 0.18 (2.15 to 2.87)

Data are presented as Means ± SE (95% CIs). † % change of insulin dose from baseline. ‡ Insulin sensitivity factor is the decrement in blood glucose per unit of lispro insulin. ab. $p<0.001$ (strategy 3 vs. strategies 1 and 2) .

Table 4 : Psycho-Social Outcomes According to Strategy

	Baseline	**Strategy 1** (MDI with HS Snacks)	**Strategy 2** (MDI with no HS Snacks)	**Strategy 3** (CSII with no HS Snacks)
Fear of Hypoglycemia	2.6 ± 0.11 (2.4 to 2.8)	2.5 ± 0.13 (2.2 to 2.7)	2.5 ± 0.12 (2.3 to 2.7)	2.4 ± 0.12 (2.1 to 2.6)
Diabetes Quality of Life (DQOL)	2.4 ± 0.11 (2.1 to 2.6)	2.3 ± 0.13 (2.0 to 2.50	2.2 ± 0.12 (2.0 to 2.4)	2.4 ± 0.12 (2.1 to 2.6)
Self-Efficacy	2.8 ± 0.07 (2.7 to 2.9)	2.8 ± 0.08 (2.6 to 2.9)	2.8 ± 0.08 (2.7 to 3.0)	2.9 ± 0.09 (2.7 to 3.1)
Perceived Stress and Complexity	2.4 ± 0.16 (2.1 to 2.8)	2.5 ± 0.19 (2.1 to 2.8)	2.1 ± 0.17 (1.7 to 2.4)	2.3 ± 0.18 (1.9 to 2.6)

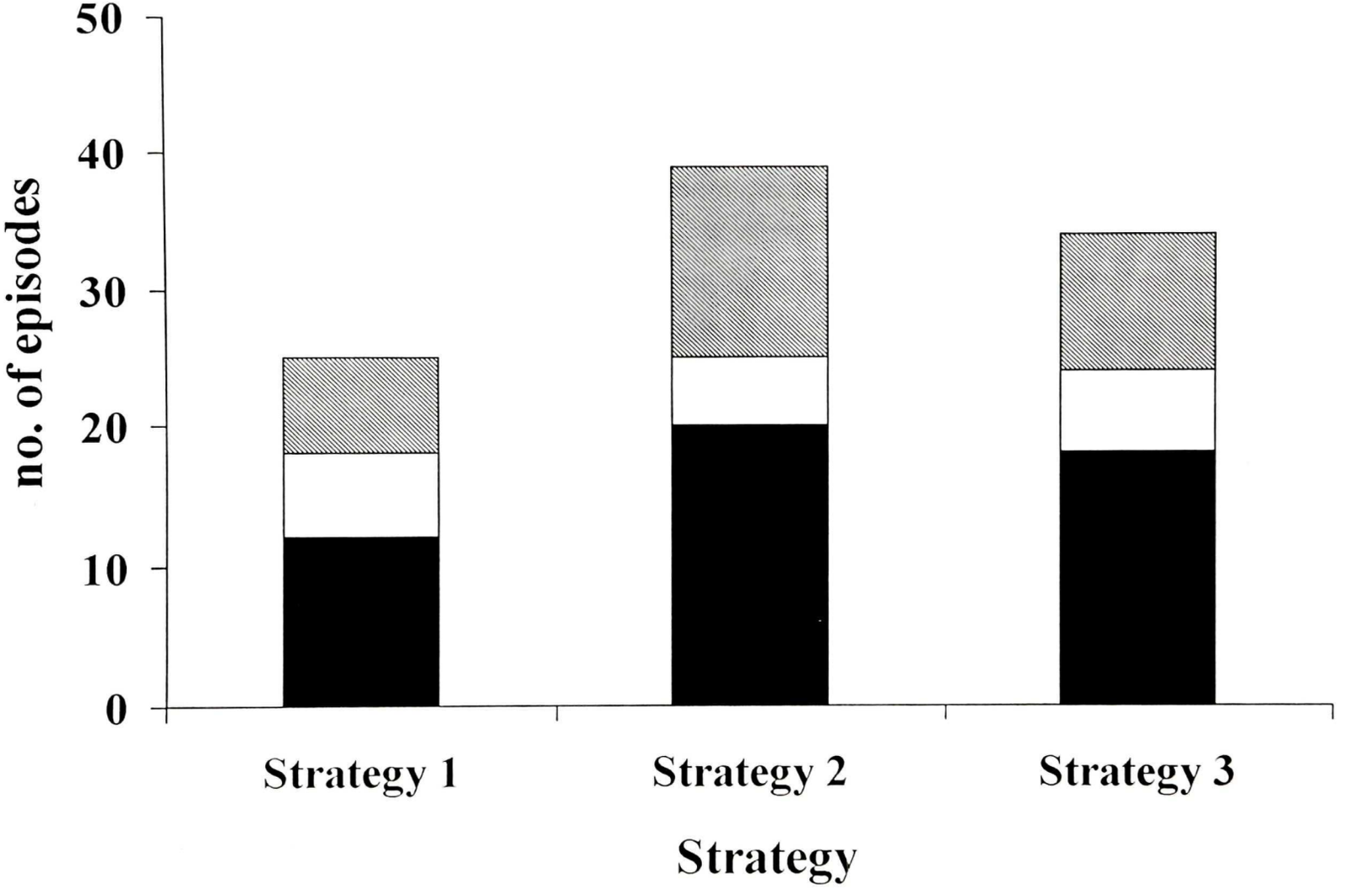
Data are presented as Means ± SE (95% CIs) for total scale scores. Scores are ranked on a scale of 1-5, where a higher score implies more fear, worse quality of life, worse sense of self-efficacy and an increased level of perceived stress and complexity.

Figure Legends

Figure 1. Incidence and Timing of Nocturnal Hypoglycemic Episodes by Strategy

black bar= 11pm-2am; white bar= 2am-4am; hatched bar= 4am-7am.

NS, p= 0.17.


50
40
30
20
10
0
no. of episodes
Strategy 1
Strategy 2
Strategy 3
Strategy

LINKAGE STATEMENT

In chapter 4, we explored whether it was possible to prevent nocturnal hypoglycemia, in the absence of bedtime snacks, by optimized titration and delivery of bedtime insulin. Optimized delivery of bedtime insulin included the use of continuous subcutaneous insulin infusion or CSII.

Part of the rationale regarding the importance of prevention of nocturnal hypoglycemia pertains to the fact that hypoglycemia, including nocturnal hypoglycemia, can compromise the defenses to subsequent hypoglycemia. As CSII therapy is considered the "gold standard" of nocturnal insulin replacement, we sought to determine what the impact of 3 months of CSII therapy would be on catecholamine response and symptom awareness to a standardized stimulus of hypoglycemia. We sought to answer this question in chapter 5. In order to provide a standardized stimulus of hypoglycemia, we utilized the one-step hypoglycemic clamp technique, an experimental model of clinical hypoglycemia.

CHAPTER 5

Catecholamine Response and Symptom Awareness to Hypoglycemia in Adults with Type 1 Diabetes Undergoing Intensive Management with Optimized Titration and Delivery of Bedtime Insulin Using Continuous Subcutaneous Insulin Infusion.

Maria Kalergis, [1,2] Réjeanne Gougeon, [1] Alicia Schiffrin, [3] Peter JH Jones [2] and Jean-François Yale [1,4]

[1] From the McGill Nutrition and Food Science Centre, Royal Victoria Hospital, McGill University Health Centre, Montreal, QC

[2] From the School of Dietetics and Human Nutrition, McGill University, Montreal, QC

[3] From the Division of Endocrinology, Jewish General Hospital, Montreal, QC

[4] From the Division of Endocrinology, Royal Victoria Hospital, McGill University Health Centre, Montreal, QC

Short Title: Catecholamine Response and Symptom Awareness to Hypoglycemia with Optimized Titration and Delivery of Bedtime Insulin Using CSII

Key words: Nocturnal Hypoglycemia; Intensive Management; Counterregulation; Continuous Subcutaneous Insulin Infusion; CSII; Bedtime Insulin; Hypoglycemic Clamp

Journal

Diabetes Care (prepared for submission)

5.1 ABSTRACT

OBJECTIVE- To determine catecholamine response and symptom awareness during a hypoglycemic clamp before and 3 months after continuous subcutaneous insulin infusion (CSII) in a subgroup of adults with type 1 diabetes randomized to a trial assessing the efficacy of CSII on prevention of nocturnal hypoglycemia.

RESEARCH DESIGN AND METHODS- 10 adults (5 men, 5 women) with a mean ± SD age of 36 ± 10 years and type 1 diabetes for a mean ± SD duration of 20.8 ± 9.4 years (6 to 40 years) participated in this study of experimentally-induced hypoglycemia, using a one-step hypoglycemic clamp technique, prior to and 3 months after undergoing intensive management using CSII. After an overnight fast, indwelling catheters were inserted for continuous infusion of insulin and variable infusion of glucose. Catecholamine response, symptom awareness and cognitive function were assessed during euglycemia, hypoglycemia and recovery.

RESULTS- There was a significant ($p<0.001$) increase in catecholamines and in autonomic and neuroglycopenic symptoms with hypoglycemia prior to CSII therapy which did not change with CSII. Cognitive function significantly ($p<0.001$) deteriorated with hypoglycemia but improved immediately upon recovery. CSII therapy did not affect cognitive function responses. Three levels of awareness were identified during hypoglycemia: unaware, partially aware and fully aware. Individuals classified as unaware had significantly ($p<0.05$) diminished catecholamine responses compared to those classified as fully aware, with intermediate responses for those classified as partially aware.

CONCLUSIONS- This study demonstrates that 3 months of CSII therapy does not deteriorate catecholamine response, symptom awareness and cognitive function in response to experimentally-induced hypoglycemia.

5.2 INTRODUCTION

Hypoglycemia has been described as the main obstacle to the attainment of optimal glycemic control, which is required to prevent the long-term complications associated with type 1 diabetes (1). In type 1 diabetes, hypoglycemia is largely the result of both limitations in the pharmacokinetics of current therapeutic agents and compromised glucose counterregulatory defenses against hypoglycemia (2). Individuals with type 1 diabetes, of greater than 5 years duration, have impaired hormonal responses and symptom awareness during hypoglycemia (2). Within 1-5 years after diagnosis, the glucagon response to hypoglycemia becomes impaired or absent (3) for reasons that are not well understood but may be related to insulin deficiency (2). Therefore, individuals with type 1 diabetes become largely dependent on sympathoadrenal responses, especially epinephrine secretion and action, for appropriate counterregulation to hypoglycemia (2, 4). However, after several years, even the epinephrine response becomes attenuated (2). This attenuation is believed to be largely the result of antecedent hypoglycemia (2) as has been demonstrated in several studies (5-7) including nocturnal hypoglycemia (8). The absent glucagon response, coupled with an attenuated epinephrine, response leads to the syndrome of hypoglycemia unawareness or impaired awareness of hypoglycemia (2). Individuals with impaired awareness of hypoglycemia, estimated to be as many as half of those with long-standing diabetes, have a 5-fold increased risk of developing severe hypoglycemia (9), which appears to occur largely overnight (10). Some reasons as to why a disproportionate amount of severe hypoglycemic episodes occur overnight may be related to further diminution of counterregulatory hormonal response secondary to sleep itself (11). As well, the nocturnal period is associated with a large proportion of

asymptomatic hypoglycemic episodes (12, 13) and thus decreased detection. Futhermore, limitations in the pharmacokinetics of current basal insulin preparations such as NPH and Ultralente are such that circulating levels often peak at the same time insulin requirements are at their nadir. However, improvement of defective catecholamine response and symptom awareness is possible and may be accomplished through avoidance of hypoglycemia (14, 15).

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy has been described as the "gold standard" for basal insulin replacement (16), especially for nocturnal control (3). Furthermore, the advent of the Continuous Glucose Monitoring System (CGMS) in 1999 as described elsewhere (17), has allowed not only for detection of nocturnal hypoglycemia, under free-living conditions, but also for the possibility of more precise titrations of insulin therapy thus optimization of insulin delivery, particularly during the nocturnal period.

Therefore, this study was undertaken in order to determine the impact of optimized titration and delivery of bedtime insulin via CSII, using continuous glucose monitoring technology as a decisional aid, on catecholamine response to and symptom awareness of hypoglycemia in a subgroup of subjects randomized to a crossover trial comparing the efficacy of CSII on prevention of nocturnal hypoglycemia, as reported elsewhere (18).

5.3 RESEARCH DESIGN AND METHODS

5.3.1 Participants and Methods

A subgroup of twenty nine individuals with type 1 diabetes who were participating in a study assessing the efficacy of CSII on prevention of nocturnal hypoglycemia (18) were approached to participate in this study. In addition to the eligibility criteria established for inclusion in the main randomized, controlled clinical trial (18), potential subjects for this sub-study were required to have had no past medical history of MI, stroke, or epilepsy. Eligibility for the main study consisted of the following: endocrine diagnosis of type 1 diabetes for more than 3 years duration, no significant hepatic or renal disease; active cancer; abuse of alcohol or drugs; and / or concurrent participation in another study or use of an investigational drug in the past 4 weeks. Women who were pregnant or intended to become pregnant in the next year were also excluded. Furthermore, potential participants for the sub-study were required to read and sign a separate informed consent form.

The goal of the main clinical trial was to assess the efficacy of 3 strategies on prevention of nocturnal hypoglycemia (18). Two of the strategies utilized MDI therapy consisting of lispro insulin before meals, specifically at supper and NPH insulin at bedtime. One of these strategies did not include bedtime snacks while the other consisted of a bedtime snack regimen which was tailored to the bedtime glycemic level (19). The third strategy used CSII with lispro insulin, which has been shown to be superior to regular insulin, for use with CSII in terms of improved glycemic control and reduction of self-reported hypoglycemic episodes, without negatively impacting on the counterregulatory hormone response to hypoglycemia (20). Participants were

randomized to a specific sequence of treatment strategies via a manually-derived randomization schedule. A time-dependent crossover point occurred at 3 months (+/- 2 weeks). Participants received frequent contact (at least every 2 weeks) including monthly clinic visits to titrate and optimize insulin therapy using information provided by daily log sheets, memory-equipped glucose meters and the 24-hour glycemic profiles obtained over 3 days, from the CGMS at the beginning and end of each strategy. The goal of the study was to titrate and optimize insulin therapy so as to reduce the incidence of nocturnal hypoglycemia without compromising on the pursuit of optimal glycemic control which consisted of fasting and pre-meal targets of 4-7 mmol/L, and 1-2 h post meal targets of 5-10 mmol/L. The incidence of nocturnal hypoglycemia, was defined as a reading of < 4 mmol/L occurring between 11pm and 7am as assessed via the CGMS (Medtronic/MiniMed, Sylmar, CA), at the end of each strategy.

Prior to, and after 3 months of CSII therapy, each participant's response to hypoglycemia was formally tested using a one-step hypoglycemic clamp technique with human regular insulin, based on similar methodology as described elsewhere (11, 21). All participants had to wear the CGMS at least 1 day prior to the study. As we did not want to influence the true frequency of nocturnal hypoglycemia attained during each strategy, participants were only carefully instructed to avoid nocturnal hypoglycemia the night prior to the study by maintaining nocturnal glycemic levels >7 mmol/L. To accomplish this, participants were required to measure their blood glucose at midnight and at 2-3 am, in addition to bedtime and morning. Furthermore, participants were required to check their blood glucose at 10pm and consume a snack if their blood glucose was between 4-10 mmol/L. They were required to take a "standard snack" consisting of 2

starch + 1 protein exchange if their glycemic level at 10pm was between 7-10 mmol/L or a protein-enriched snack consisting of 1 starch + 3 protein exchanges if their blood glucose was between 4-6.9mmol/L. Their bedtime insulin was also decreased by 25% of their usual dose and taken at the same time as the snack. In addition, if the blood glucose level was <7 mmol/L during the night, participants were required to consume 250mL of orange juice. They were required to contact the study coordinator in the morning (by 6am) to report if any nocturnal hypoglycemia had occurred, at which time the study was cancelled and re-scheduled for the subsequent week. All subjects were studied in the post-absorptive state after an overnight fast. Each clamp was started at 8:00 am at the Crabtree Laboratories at the McGill Nutrition and Food Science Centre (Royal Victoria Hospital, McGill University Health Centre). An indwelling catheter was inserted in an antecubital vein for administration of insulin and glucose and into the dorsal hand vein for blood sampling. The hand was placed in a heated box at 65°C to arterialize the venous blood. A priming dose ($80mU.m^{-2}.min^{-1}$) of regular human insulin (Humulin R, Eli Lilly, Indianapolis, IN) was infused for the first 10 min, followed by a continuous infusion of 40 $mU.m^{-2}.min^{-1}$ for the rest of the study. A 20% glucose solution (Abbott Laboratories, Montreal, Canada) was infused at variable rates to maintain the target glucose levels based on plasma glucose determinations at 5 minute intervals (2 minute intervals during hypoglycemia). After a 1 hour euglycemic clamp (target glucose of 100mg/dL or 5.5 mmol/L), the glucose level was lowered to 50 mg/dL (2.8 mmol/L) for 40 minutes. The change from euglycemia to the hypoglycemic target occurred within a mean ± SE time of 24 ± 1.9 minutes. Blood samples for the determination of the level of catecholamines (epinephrine and norepinephrine) were drawn at baseline (pre-

euglycemic target), at 20-minute intervals during euglycemia, at the hypoglycemic target and at 20-minute intervals during hypoglycemia and at 5 and 20 minutes during the recovery period (20 minutes duration, target blood glucose ≥ 5.5 mmol/L). All subjects were blinded to the level of glycemia during the three periods of the study.

Awareness of hypoglycemic symptoms was assessed with a validated questionnaire (8, 22) at baseline and at the same intervals when blood was drawn for assessment of catecholamines. Symptoms were ranked on a linear analog scale from 0 (none) to 5 (severe). Symptom scores were calculated for autonomic (anxiety, palpitations, hunger, tremor, sweating, nausea, irritability), neuroglycopenic (dizziness, tingling, blurred vision, difficulty concentrating, weakness, headache, fatigue, sleepiness) and the global scale scores (autonomic + neuroglycopenic). Scores were converted to percentages. Awareness was also assessed using a qualitative questionnaire in which participants were asked to report how they were feeling and to estimate their blood glucose level. Participants were considered to be aware of their hypoglycemia if they reported to "not feeling well" or "feeling low" and if they estimated their blood glucose level to be < 4 mmol/L. This assessment was also conducted at the same intervals as the other measures. Cognitive function was also assessed using a validated test of attention and information processing: subtraction of serial 7's (23) at the same intervals. This test consisted of a standardized, random assignment of numbers starting from 96-104, from which participants were asked to subtract 7 and continue doing so from the answer obtained, for 60 seconds. The percentage of correct responses and the response time within 60 seconds formed the two components of the cognitive function assessment.

The respiratory quotient (RQ), indicative of substrate utilization (24), was determined using indirect calorimetry via the use of the DeltaTrac ® metabolic monitor (SensorMedics Corp, Annaheim, CA) at baseline (pre-euglycemic target) and after 20 minutes of euglycemia and hypoglycemia. The baseline assessment was not used in the analysis as this was only performed in order to help accustom participants to the technique (24) which involves breathing under a transparent canopy for 20 minutes The respiratory quotient represents the amount of carbon dioxide exhaled per quantity of oxygen consumed (24). At the end of each study, participants were provided with a meal and 2 potassium tablets of 1500 mg (one taken immediately with their meal and one consumed at home with their dinner). Blood glucose levels were monitored to ensure euglycemia (≥ 5.5 mmol/L) had been established prior to allowing the subjects to leave.

Plasma glucose concentrations were analyzed by the glucose oxidase method using the Beckman Glucose Analyzer II (Beckman Coulter Inc., Fullerton, CA). Blood for the determination of the catecholamines (epinephrine and norepinephrine) was collected in GSH-EGTA tubes, centrifuged at 4°C at 2000g for 15 minutes and the plasma frozen at –70°C until assay which was done with a radioenzymatic technique (sensitivity <50pmol/L) as described elsewhere (25).

5.3.2 Statistical Analyses

All statistical analyses were conducted using the Statistical Program for Social Sciences (SPSS, version 10.0, Chicago, IL). One-way repeated measures analyses of variance (ANOVA) with Bonferroni assessment for main effects of study and time, and for study by time interaction were used to assess catecholamine response, symptom awareness and cognitive function before and after CSII therapy at 3 periods (9 time points): euglycemia (target, 20, 40 and 60 minutes); hypoglycemia (target, 20 and 40 minutes) and recovery (5 and 20 minutes). HbA_{1c}, bedtime and morning glycemia and the mean, nadir and duration of nocturnal hypoglycemia were analyzed using a one way ANOVA with Tukey's Honestly Significant Difference (HSD) for post- hoc analyses. The number and awareness of nocturnal hypoglycemic episodes at the end (last 3 days) of the strategy prior to CSII and at the end (last 3 days) of the CSII period were assessed with chi-square analysis. Subjects were also categorized, post-priori, according to their level of subjective qualitative awareness during the 3 time points of experimentally-induced hypoglycemia into 3 categories: unaware (no awareness at any of the time points); partially aware (aware at some but not all the time points) and fully aware (aware at all time points). Catecholamine response, symptom awareness (autonomic and neuroglycopenic) and cognitive function were assessed according to the 3 categories of awareness by a one way ANOVA with Tukey's HSD for post-hoc analyses. Descriptive data are presented as means ± SD and experimental data are expressed as means ± SE. A P value <0.05 is indicative of statistical significance.

The study was approved by the Royal Victoria Hospital's Research Ethics Committee and the Institutional Review Board of McGill University.

5.4 RESULTS

5.4.1 Participant Characteristics

Ten adults met inclusion criteria for the hypoglycemic clamp study and participated in both clamp studies: one prior to and the second after 3 months of CSII therapy.

As outlined in Table 1, participants consisted of an equal proportion of men and women, with a mean age of 36 years and with type 1 diabetes for a mean duration of 20.8 years. Participants were weight stable with a mean body mass index (BMI) of 27.2 kg/m^2 and a mean HbA_{1c} at baseline of 7.5%. All were using MDI therapy for more than one year, with NPH insulin at bedtime and lispro insulin before meals, specifically at supper. Three individuals had peripheral neuropathy and no one had documented autonomic neuropathy.

5.4.2 Clinical Period

As outlined in Table 2, in this group of individuals, there was no significant difference in the mean HbA_{1c} (%) level at the end of CSII in comparison to pre CSII (7.6 ± 0.2 vs. 7.9 ± 0.3, respectively, p=0.45). As well, bedtime and morning glycemic control were also not significantly different prior to and at the end of CSII. Although there appeared to be a lower duration of nocturnal hypoglycemia at the end of CSII compared to pre CSII, this finding was not statistically significant (114 min ± 29 versus 163 min ± 63 respectively, p=0.44). There was no significant difference in the number of nocturnal hypoglycemic episodes pre CSII and at the end of CSII (p=0.32). The same proportion of subjects (6/10) had at least one episode of nocturnal hypoglycemia pre CSII and at the end of CSII over 26 nights per group. Overall, 5 subjects either stayed the same (n=2) or

improved (n=3) while 5 worsened with CSII therapy, with respect to the number of nocturnal hypoglycemic episodes. However, an equivalent proportion (50%) of nocturnal hypoglycemic episodes were symptomatic pre and at the end of CSII and the proportion of participants who had symptoms with respect to nocturnal hypoglycemic episodes at the end of CSII compared to pre CSII was not statistically significant (40% versus 30% respectively, NS).

5.4.3 Clamp Studies

Blood Glucose Profiles

Figure 1 illustrates the blood glucose profiles during the two experiments. There was no significant difference between any of the corresponding mean plasma glucose levels for the two clamp studies at any time point. In particular, there was no significant difference with the plasma glucose nadirs during the hypoglycemic periods.

The glucose infusion rates, expressed as mg/kg/min, were not significantly different between the 2 studies (4.87 ± 0.42mg/kg/min versus 5.33 ± 0.51mg/kg/min respectively, p=0.50). The Coefficient of Variation (CV) for the glucose infusion rates for the two studies was < 10% (study 1= 7.14% and study 2= 9.81%).

Catecholamine Response

Figure 2 and Table 3 illustrates the mean plasma epinephrine before and after CSII therapy during 3 periods: euglycemia, hypoglycemia, and recovery. There was a significant increase ($p<0.001$) in the mean epinephrine response during hypoglycemia in comparison to euglycemia. Plasma epinephrine remained higher than during euglycemia at 5 min recovery but not at 20 minutes. During the hypoglycemic period, there was significantly ($p<0.001$) more epinephrine at 20 and 40 minutes of hypoglycemia compared with hypoglycemia at time 0 (target). There was no significant difference in the epinephrine response between the two groups at any time point.

Norepinephrine was also significantly higher during hypoglycemia compared to euglycemia ($p<0.001$) as depicted in Figure 3 and Table 3. However, the change of the norepinephrine during hypoglycemia from euglycemia, was less pronounced than that of the epinephrine response.

Symptom Awareness

As illustrated in Figure 4 and Table 3, there was a significant ($p<0.001$) increase in autonomic symptom responses during hypoglycemia in comparison to euglycemia. There was no statistically significant difference between the groups at any time point.

Similar findings were also obtained for the neuroglycopenic symptom response (Figure 5 and Table 3), indicating that there was a significant ($p<0.001$) increase in the neuroglycopenic response with hypoglycemia compared to euglycemia but no difference in the magnitude of this response between the groups at any time point. The total

symptom score (data not shown) also increased significantly ($p<0.001$) during hypoglycemia compared to euglycemia but was similar in both groups.

Cognitive Function

The mean score or percentage of correct responses (Figure 6 and Table 3) was equally high for both groups at euglycemia and there was no deterioration or significant difference during hypoglycemia between groups.

However, there was a significant ($p=0.001$) deterioration with respect to the response time (Figure 7 and Table 3) during hypoglycemia compared to euglycemia which appeared to improve immediately upon recovery (at 5 minutes). There was no difference between the groups in this regard.

Subjective Awareness

Subjects were categorized into 3 levels of awareness during the 3 time points of hypoglycemia (target, 20min, 40min). The categories were as follows: unaware (no awareness at any of the time points during hypoglycemia); partially aware (awareness at some, but not all time points); fully aware (aware at all time points).

There was a significant difference in epinephrine response (Table 4) among subjects classified as unaware vs. those classified as either partially and fully aware at 40 minutes of hypoglycemia ($p<0.05$). Similar findings were obtained for the norepinephrine response (Table 4) with a statistically significant difference at 40 minutes of hypoglycemia ($p<0.05$) between those who were classified as unaware versus those classified as fully unaware.

With respect to autonomic symptoms, participants who were fully aware appeared to have the highest response, those who were unaware had the lowest response and those with partial awareness had an intermediate response (NS, p=0.09 at time 0). No significant differences were identified for neuroglycopenic symptoms (Table 4).

Differences were noted for cognitive function (Table 4), as represented by the % of correct responses attained, with a significant difference at 40 minutes of hypoglycemia (p=0.005) between subjects with full awareness compared to those without awareness. No statistically significant differences were noted with respect to response time. However, subjects with full awareness had the fastest response and those with no awareness had the slowest response, while those with partial awareness achieved an intermediate response (NS, p=0.07 at 40 minutes).

An equal number of subjects (3/10) were unaware before and at the end of CSII. There was no significant difference in the proportion of subjects who were fully or partially aware at the end of CSII compared to pre CSII : fully aware 60% vs. 40% respectively, p=0.50 and partially aware : 10% vs. 30% respectively, p=0.50.

Respiratory Quotient

The mean RQ was significantly higher during euglycemia compared to hypoglycemia (0.90 ± 0.02 versus 0.86 ± 0.02 respectively, p=0.008). No significant differences were noted prior to and at the end of CSII (0.86 ± 0.02 vs. 0.88 ± 0.02, p=0.60).

5.5 CONCLUSIONS

In this study we examined the effect of 3 months of optimized titration and delivery of bedtime insulin via continuous insulin infusion (CSII) on catecholamine response and symptom awareness to experimentally-induced hypoglycemia in adults with type 1 diabetes of greater than 5 years duration.

Our results indicate that despite the relatively long duration of type 1 diabetes in this group of individuals, the catecholamine response to hypoglycemia appeared to be adequate prior to CSII therapy and similar to that reported in individuals without diabetes (21). Furthermore, the catecholamine response to hypoglycemia remained unchanged following 3 months of CSII therapy. This finding is in agreement with a previous study (26) and contrary to an earlier study which showed deterioration in catecholamine response following a similar duration of CSII therapy (21). In a recent study by Kanc and colleagues (26), in which CSII was substituted only at night for NPH insulin, in 14 adults with type 1 diabetes, there was no change in the catecholamine response after 2 months of CSII therapy. However, the catecholamine response was much lower than in healthy control subjects prior to CSII therapy (26). Although the catecholamine response did not change, CSII therapy was able to increase the glycemic level at which autonomic symptoms first appeared (26). The authors attributed this improvement, with respect to the glycemic threshold for autonomic symptoms, to a significant reduction in the frequency of self-reported daytime hypoglycemic episodes and likely to a reduction in nocturnal hypoglycemic episodes. However, the latter could not be assessed due to a lack of available data (26). In contrast to the study by Kanc and colleagues and the present study, an earlier study be Simonson and colleagues (21)

demonstrated a significant deterioration in catecholamine response following 4 to 8 months of CSII therapy. The discrepancy between the studies may be partially due to the different durations of diabetes in the subjects involved. A long duration of diabetes (>15 years) has been identified as a significant risk factor in the etiology of hypoglycemia unawareness (27,28) and impaired counterregulatory hormone response (3). The mean duration of diabetes in the study by Kanc et al was 12.5 years with a range of 7-20 years (26) and in the earlier study by Simonson et al, the mean duration was 32 years with a range of 23 to 45 years. In the present study, the mean duration of diabetes was 20.8 years (6 to 40 years). However, despite the very long duration of diabetes in the study by Simonson et al, catecholamine response was similar to that of control subjects, without diabetes, prior to CSII therapy (21). However, in contrast to the present study, the catecholamine response to hypoglycemia deteriorated with CSII therapy (21).

In the present study, the norepinephrine response to hypoglycemia also increased to a similar extent prior to and at the end of CSII. However, the change in mean plasma levels with hypoglycemia from euglycemia was lower in comparison to that of epinephrine, in agreement with previous studies (3, 8, 15, 26).

Symptom awareness, as assessed via a validated questionnaire quantifying both autonomic and neuroglycopenic symptoms, also significantly increased during hypoglycemia to a similar extent before and after CSII therapy. This is contrary to the study of Kanc et al (26) which found improved awareness with CSII therapy. Although there were more nocturnal hypoglycemic episodes with CSII therapy, symptomatic awareness did not deteriorate. Furthermore, this is the first study to report different levels of awareness to hypoglycemia that could only be identified by the qualitative assessment.

Despite the very limited sample size upon categorizing our subjects, post priori, according to 3 levels of awareness during experimentally-induced hypoglycemia (unaware, partially aware, fully aware), we found that this classification was able to identify significant differences with respect to catecholamine response and cognitive function, particularly between individuals classified as unaware and fully aware. However, further research, based on these classifications a priori and with larger samples, is needed to clarify this observation.

With respect to cognitive function, although a similar percentage of correct responses were attained during hypoglycemia compared with euglycemia, the response time was significantly longer during hypoglycemia compared to euglycemia. An improvement in response time occurred immediately upon recovery. This immediate improvement of cognitive function upon recovery is in contrast to data reported in a recent study, which found that cognitive function lagged behind the restoration of glucose levels in 8 healthy males (29). However, the tests used between the two studies are not the same. Also, in contrast to a recent study in adults with type 1 diabetes (26), we did not find a deterioration in cognitive function with CSII therapy. Again, this may be due to the differences in the tests used.

This is the first study, to our knowledge, to assess recovery from hypoglycemia in the context of diabetes with respect to catecholamine response, symptom awareness and cognitive function. In this regard, we found that the catecholamine response (epinephrine and norepinephrine) was decreased immediately upon recovery (within 5 minutes) but remained significantly different from euglycemic levels until 20 minutes into recovery.

This study demonstrates that 3 months of CSII therapy in adults with long-term type 1 diabetes does not deteriorate catecholamine response, symptom awareness and cognitive function in response to experimentally-induced hypoglycemia.

5.6 ACKNOWLEDGEMENTS

We would like to thank Medtronic/MinMed Inc. for the loan of insulin pumps and supplies and two CGMS units. We would also like to thank the following individuals: Dr. Stéphanie Chevalier for her role during the clamp studies and for critical review of the manuscript, Dr. Kansuda Thongthai for assistance with some of the data analyses, Dr. Khaled Aljaberi and Dr. Abdulla Alfutaisi for providing medical care to the participants, Mary Shingler, RN, Chantal Legaré, RN and France Bouchard, RN for nursing assistance during the clamp studies, Marie Lamarche, Madeleine Giroux, Ginette Sabourin and Connie Nardollilo for technical support, Dr. Jeffrey Halter for analysis of catecholamines and Dr. Errol B. Marliss for invaluable advice and critical review of the manuscript. Finally, we would like to thank the volunteers who participated in this study and the Canadian Diabetes Association for providing funding.

5.7 REFERENCES

1. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 329: 977-986, 1993

2. Cryer P: Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 281: E1115-E1121, 2001

3. Bolli G, De Feo P, Comagnucci P, Cartechni MG, Angeletti G, Santeusano F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. Diabetes 32: 71-89, 1983

4. Yale JF: Hypoglycemia. In Evidence-Based Diabetes Care, Gerstein HC, Haynes RB, editors. 2001, BC Decker Inc: Hamilton/London. p. 380-395.

5. Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 47: 223-226, 1991

6. Davis MR, Mellman M., Shamoon H: Further defects in counter-regulatory responses induced by recurrent hypoglycemia in IDDM. Diabetes 41: 1335-1340, 1992

7. Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UM, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. Diabetes 42: 610-618, 1993

8. Veneman T, Mitrakou A., Mokan M, Cryer P, Gerich J: Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. Diabetes 42: 1233-1237, 1993

9. Cryer P: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a vicious cycle. Diabetes 41: 1335-1340, 1992

10. The DCCT Research Group: Nutrition interventions for intensive therapy in the diabetes control and complications trial. J Am Diet Assoc 93(7): 768-772. 1993

11. Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia in IDDM children. Diabetes Care 338: 1657-1662, 1998

12. Vervoort G, Goldschmidt HMG, Van Doorn LG: Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple daily injection regimens. Diabetic Medicine 13: 794-799, 1996

13. Kalergis M, Aljaberi K, Schiffrin A, Meltzer S, Gougeon R, Yale JF: Frequency and duration of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management as determined by continuous glucose monitoring (abstract). Can J Diabetes Care 25: 156A, 2001

14. Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P, Porcellati F, Scionti L, Santeusano F, Brunetti P, Bolli GB: Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 42: 1683-1689, 1993

15. Fritsche A, Norbert S, Haring H, Gerich J, Stumvoll M: Avoidance of hypoglycemia awareness by increasing ß-adrenergic sensitivity in type 1 diabetes. Ann Int Med 134 (9): 729-736, 2001

16. Lepore M, Pampanelli S., Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 49: 2142-2148, 2000

17. Koschinsky T, Heinemann L: Sensors for glucose monitoring: technical and clinical aspects. Diabetes Metab Res Rev 17: 113-123, 2001

18. Kalergis M, Schiffrin A, Gougeon R, Meltzer S, Jones PJH, Yale JF. " Impact of optimized titration and delivery of bedtime insulin on prevention of nocturnal hypoglycemia in free-living adults with type 1 diabetes undergoing intensive management: a randomized, controlled trial comparing MDI (with and without bedtime snacks) versus CSII", Chapter 3. Diss. McGill U: Montreal, 2002.

19. Kalergis M, Schiffrin A, Gougeon R, Jones PJH, Yale JF: Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes mellitus undergoing intensive insulin management using lispro insulin ac meals: a randomized, placebo-controlled, crossover trial. Diabetes Care, In Press, 2002

20. Tsui EYL, Chiasson JL, Tildesley H, Barnie A, Simkins S, Strack T, Zinman B: Counterregulatory hormone responses after long-term continuous subcutaneous insulin infusion with lispro insulin. Diabetes Care 21(1): 93-96, 1998

21. Simonson DC, Tamborlane W., DeFronzo RA, Sherwin RS: Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type 1 diabetes. Ann Int Med 103: 184-190, 1985

22. Hepburn DA, Deary IJ, Frier BM, Patrick AW, Quinn JD, Fisher BM: Symptoms of acute insulin-induced hypoglycemia in human with and without IDDM. Diabetes Care 14 (11): 949-957 , 1991

23. Folstein MF, Folstein SE, McHugh PR: Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975. 12: 189-198, 1975

24. Simonson DC, De Fronzo R, Indirect calorimetry: methodological and interpretative problem, editorial review. The American Physiological Society. E399-E413, 1990

25. Evans MI, Halter JB, Porte D: Comparison of double and single isotope enzymatic derivative methods for measuring catecholamines in plasma. Clin Chem 28: 764-770, 1978

26. Kanc K, Janssen .MMJ, Keulen ETP, Jacobs MAJM, Popp-Snijders C, Snoek FJ, Heine RJ: Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counterregulatory hormonal responses and warning symptoms of hypoglycemia in IDDM. Diabetologia 41: 322-329, 1998

27. Amiel SA, Sherwin R, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 37: 901-907, 1988

28. Cryer PE, Fisher J, Shamoon H, Hypoglycemia: technical review. Diabetes Care 17(7): 734-755, 1994

29. Evans ML, Pernet A, Lomas J, Jones J, Amiel SA: Delay in onset of awareness of acute hypoglycemia and of restoration of cognitive performance during recovery. Diabetes Care 23(7): 893-897, 2000

Table 1: Baseline Participant Characterstics

N: Gender	10: 5 men; 5 women
Age (y)	36 ± 10 (22 to 50)
Duration of Diabetes (y)	20.8 ± 9.4 (6 to 40)
†HbA_{1c} (%)	7.5 ± 1.0 (6.1 to 9.7)
BMI (kg/m^2)	27.2 ± 4.0 (22.9 to 36.5)
Total Daily Insulin Dose (U/kg)	0.9 ± 0.5 (0.5 to 2.3)

Data are presented as means ± SD (range). †HbA_{1c} normal reference range at Royal Victoria Hospital= +-6%.

Table 2: Glycemic Control and Incidence and Duration of Nocturnal Hypoglycemia Before and After 3 Months of CSII Therapy.

	Pre CSII (MDI)	End of CSII
HbA_{1c} (%)	7.6 ± 0.2	7.9 ± 0.3
Bedtime Glucose (mmol/L)	9.6 ± 0.8	9.1 ± 0.9
Morning Glucose (mmol/L)	9.4 ± 0.8	8.8 ± 0.8
Nocturnal Hypoglycemia # episodes/ # nights	8 / 26	12 / 26
nadir (mmol/L)	2.6 ± 0.2	2.6 ± 0.7
duration (min)	163 ± 63	114 ± 29

Data are presented as means ± SE (except for no. of nocturnal hypoglycemic episodes which are presented as totals). All data (except HbA_{1c}) are based on information obtained from the CGMS. No significant differences between the groups.

Table 3: Catecholamine Response, Symptom Awareness and Cognitive Function Before and After CSII

		Euglycemia (min)	Hypoglycemia (min)			Recovery (min)		P value
		60	0	20	40	5	20	Time
Epinephrine (nmol/L)	Pre-CSII	0.25 (0.03)a	0.64 (0.21)a	1.46 (0.33)b	1.91 (0.31)b	1.22 (0.23)b	0.50 (0.09)a	<0.001
	Post-CSII	0.24 (0.03)a	0.72 (0.21)a	1.38 (0.33)b	1.66 (0.31)b	0.74 (0.23)b	0.41 (0.09)a	<0.001
Norepinephrine (nmol/L)	Pre-CSII	1.91 (0.20)a	1.86 (0.18)a	2.29 (0.21)b	2.50 (0.24)b	2.22 (0.21)b	2.13 (0.21)b	<0.001
	Post-CSII	1.68 (0.20)a	1.91 (0.18)a	2.28 (0.21)b	2.58 (0.24)b	2.28 (0.21)b	2.14 (0.21)b	<0.001
Autonomic Symptoms (%)	Pre-CSII	9.3 (2.7)	12.0 (4.6)	17.3 (6.1)	20.1 (7.4)	11.3 (4.1)	10.9 (3.2)	<0.001
	Post-CSII	8.0 (2.7)	15.4 (4.6)	21.3 (6.1)	19.9 (7.4)	13.1(4.1)	7.6 (3.2)	<0.001
Neuroglycopenic Symptoms (%)	Pre-CSII	13.8 (2.9)	20.8 (5.0)	22.5 (5.5)	24.8 (6.4)	18.3 (5.0)	13.5 (3.7)	<0.001
	Post-CSII	9.9 (2.9)	18.1 (5.0)	22.8 (5.5)	20.4 (6.4)	17.3 (5.0)	7.6 (3.7)	<0.001
Cognitive Function								
score (%)	Pre-CSII	76.0 (10.7)	74.0 (9.3)	78.0 (9.9)	74.0 (11.2)	82.0 (11.1)	84.0 (6.6)	0.65
	Post-CSII	66.0 (10.7)	82.0 (9.3)	78.0 (9.9)	86.0 (11.2)	74.0 (11.1)	94.0 (6.6)	0.65
response time (s)	Pre-CSII	16.4 (2.9)	16.9 (2.0)	20.3 (4.4)	20.8 (5.3)	16.4 (2.8)	13.4 (2.3)	0.001
	Post-CSII	15.6 (2.9)	16.0 (2.0)	17.7 (4.4)	26.6 (5.3)	15.8 (2.8)	15.1 (2.3)	0.001

Data are presented as means (SE). P values are presented for time only.Time points which share the same letter are not signifcantly different.

Table 4: Catecholamine Response, Symptom Awareness and Cognitive Function During Hypoglycemia According to 3 Categories of Subjective Awareness

	Time (min)	Unaware (n= 6)	Partially Aware (n= 4)	Fully Aware (n= 10)	P value
Epinephrine (nmol/L)	0	0.42 ± 0.26	0.90 ± 0.14	0.74 ± 0.13	0.50
	20	0.67 ± 0.25	1.59 ± 0.23	1.78 ± 0.31	0.10
	40	0.93 ± 0.28	1.88 ± 0.70	2.24 ± 0.18 *	0.02
Norepinephrine (nmol/L)	0	0.25 ± 0.25	0.65 ± 0.64	0.55 ± 0.14	0.62
	20	0.52 ± 0.23	1.40 ± 110.8	1.70 ± 0.04	0.10
	40	0.81± 0.27	1.72 ± 0.75	2.19 ± 0.61*	0.02
Autonomic Sx score (%)	0	6.2 ± 2.0	7.9 ± 4.1	20.6 ± 5.3	0.09
	20	15.0 ± 6.0	6.8 ± 4.1	26.9 ± 6.9	0.17
	40	6.7 ± 1.1	17.9 ±16.0	28.9± 7.3	0.17
Neuroglycopenic Sx score (%)	0	14.2 ± 5.2	18.8± 13.0	22.9± 4.0	0.58
	20	19.8 ± 7.8	13.1± 7.6	28.1 ± 5.0	0.31
	40	12.9 ± 6.2	18.1 ± 14.0	30.1 ± 5.5	0.22
Cognitive Function score (%)	0	76.7 ± 10.9	65.0 ± 23.6	84.0 ± 7.2	0.56
	20	66.7 ± 15.2	80.0 ± 14.1	84.0 ± 8.8	0.56
	40	46.7 ± 19.1	80.0 ± 11.5	100.0 ± 0.00*	0.005
Cognitive Function response time (s)	0	18.9 ± 3.9	16.0 ± 1.7	15.2 ± 1.3	0.53
	20	27.0 ± 9.3	16.8 ± 4.4	15.1 ± 1.5	0.23
	40	34.3 ± 10.3	27.8 ± 6.1	15.7 ± 1.5	0.07

Data are presented as means ± SE. P values for ANOVA. * Significantly ($p<0.05$) different vs. unaware.

Figure Legends

Figure 1. Plasma Glucose Levels Before and After CSII therapy.

Diamonds with broken lines represent the plasma glucose levels prior to CSII and squares with solid lines represent the plasma glucose levels at the end of CSII. $p<0.001$ for overall trend (repeated measures ANOVA). No significant differences between the groups at any time point.

Figure 2. Epinephrine Response Before and After CSII therapy.

Diamonds with broken lines represent the epinephrine response prior to CSII and squares with solid represent the epinephrine response at the end of CSII. Time points which share the same letter are not statistically significant. $p<0.001$ for overall trend (repeated measures ANOVA); ab $p<0.001$.

Figure 3. Norepinephrine Response Before and After CSII Therapy.

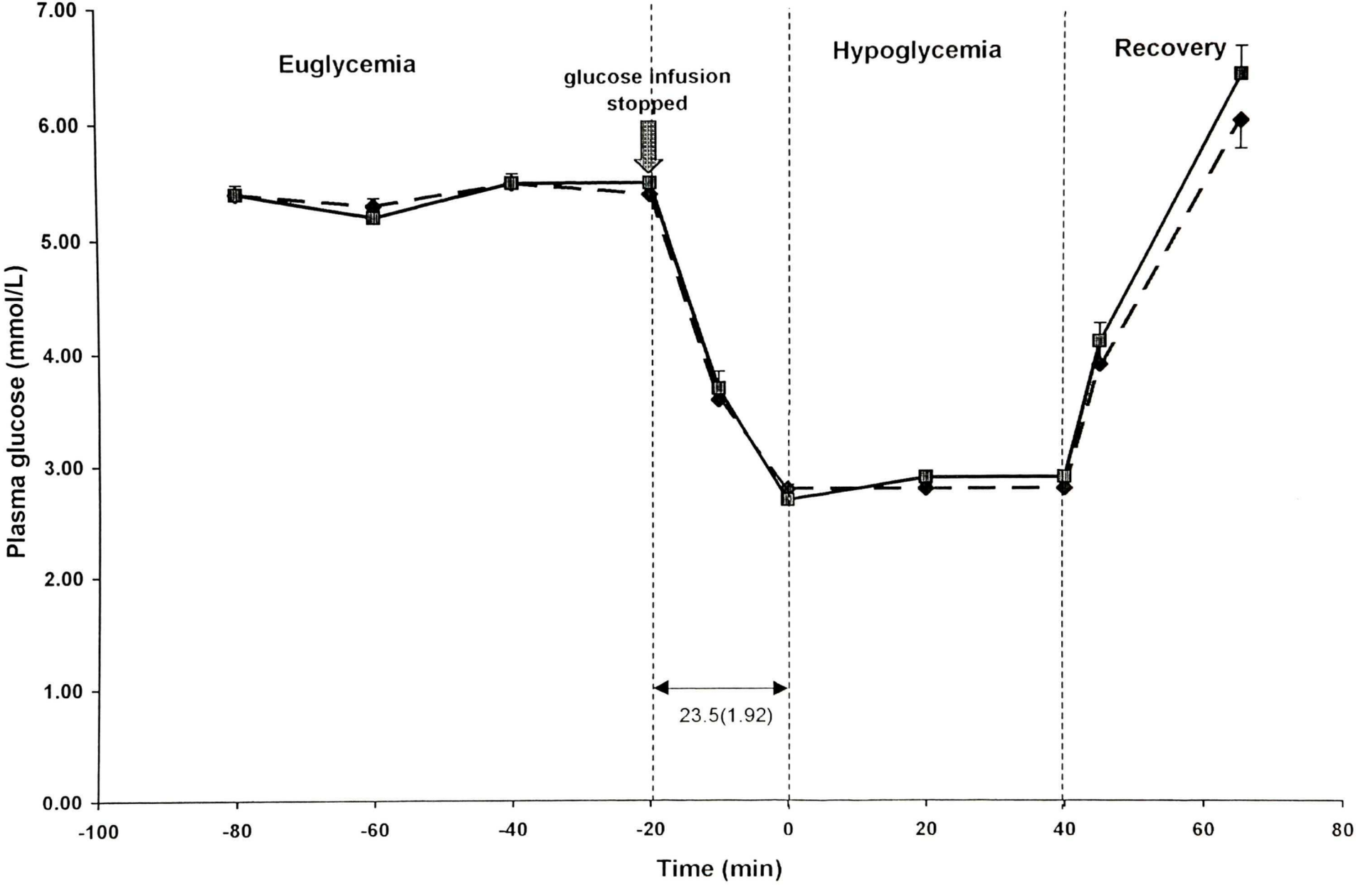
Diamonds with broken lines represent the norepinephrine response prior to CSII and squares with solid lines represent the norepinephrine response at the end of CSII. Time points which share the same letter are not statistically significant. $p<0.001$ for overall trend (repeated measures ANOVA); ab $p<0.001$.

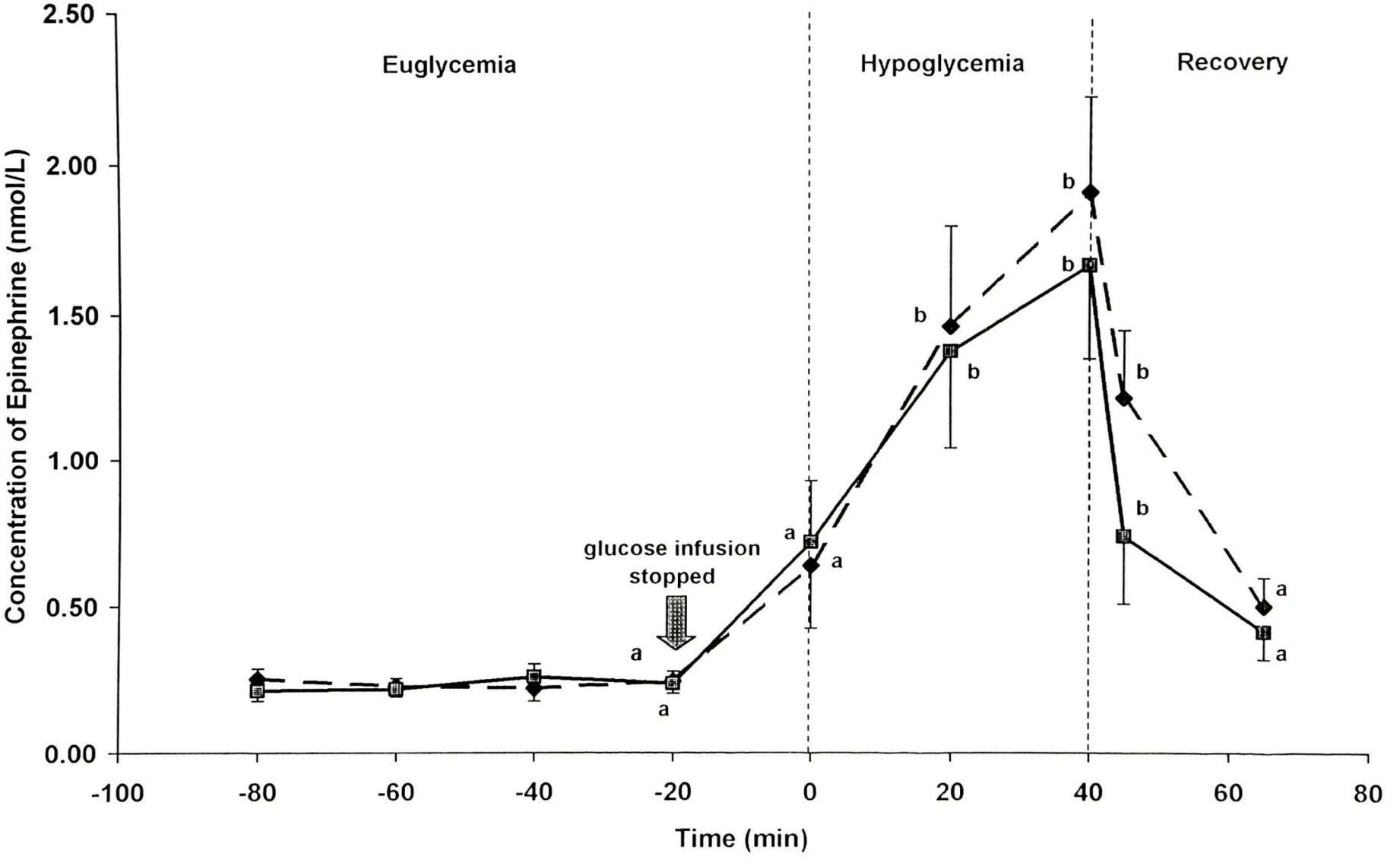
Figure 4. Autonomic Symptom Response Before and After CSII Therapy.
Diamonds with broken lines represent the autonomic symptom response prior to CSII and squares with solid lines represent the autonomic symptom response at the end of CSII. $p<0.001$ for overall trend (repeated measures ANOVA).

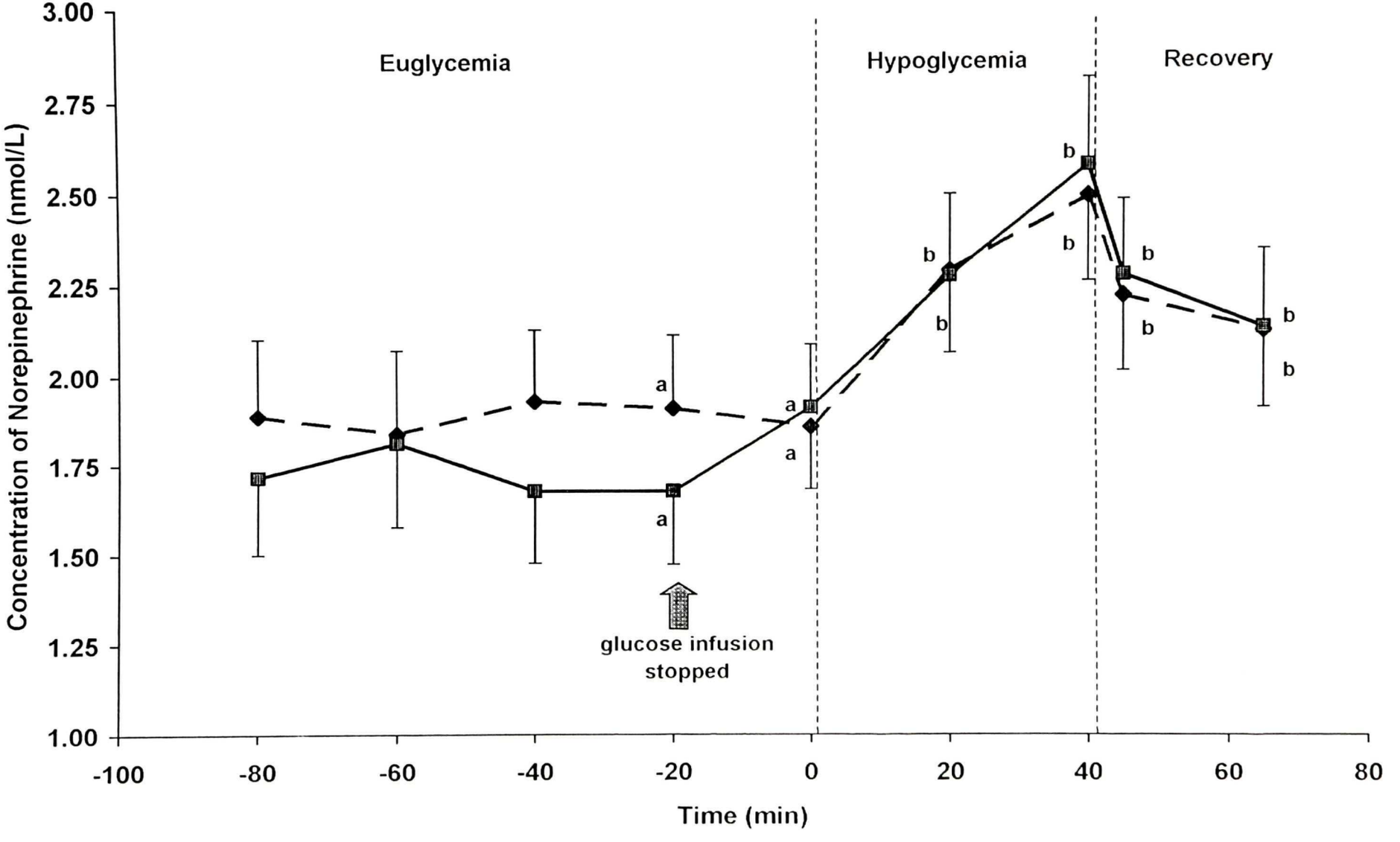
Figure 5. Neuroglycopenic Symptom Response Before and After CSII Therapy
Diamonds with broken lines represent the neuroglycopenic symptom response prior to CSII and squares with solid lines represent the neuroglycopenic symptom response at the end CSII. $p<0.001$ for overall trend (repeated measures ANOVA).

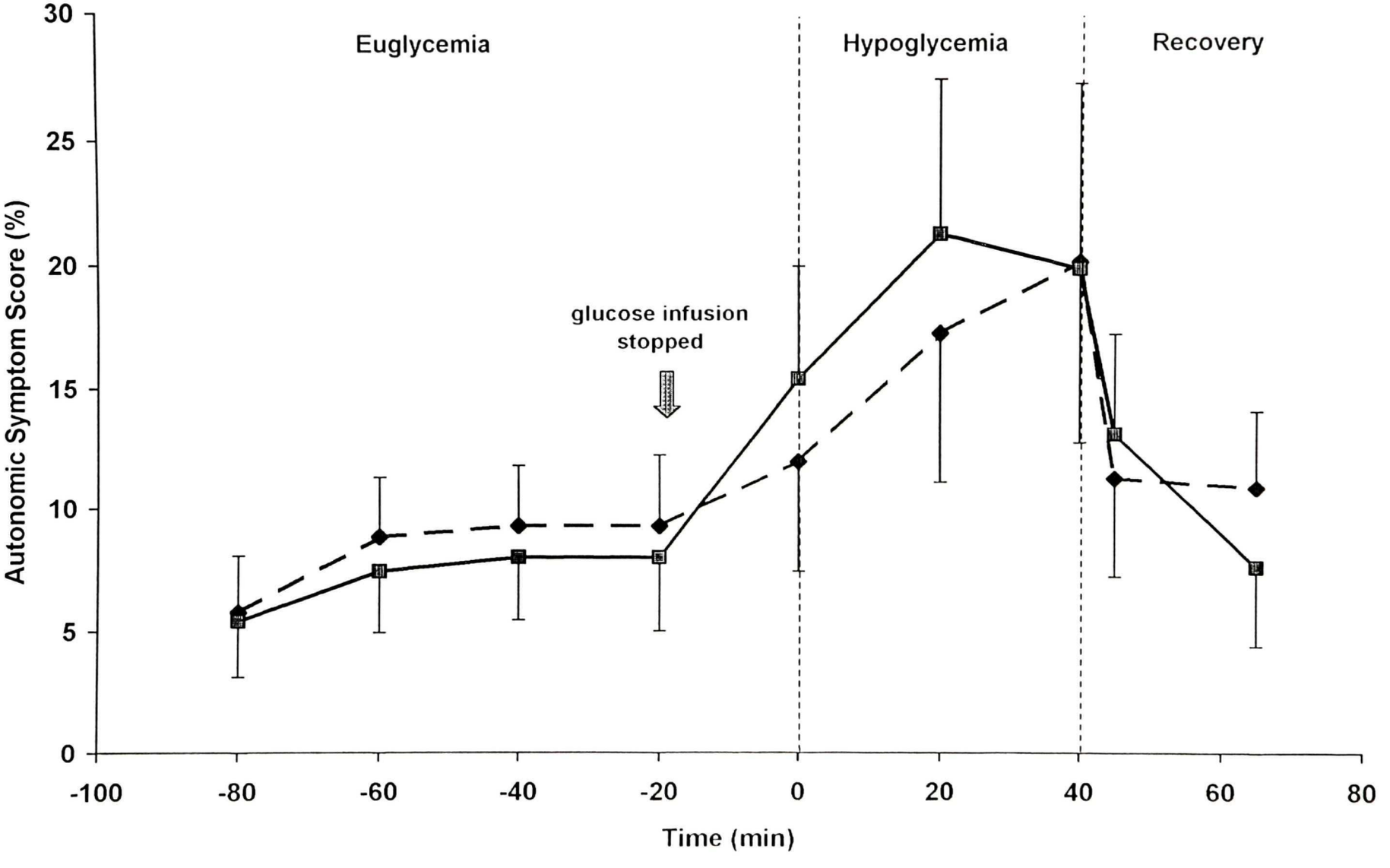
Figure 6. Cognitive Function (Score) Before and After CSII Therapy.
Diamonds with broken lines represent cognitive function (score) prior to CSII and squares represent cognitive function (score) at the end of CSII. NS, $p>0.05$

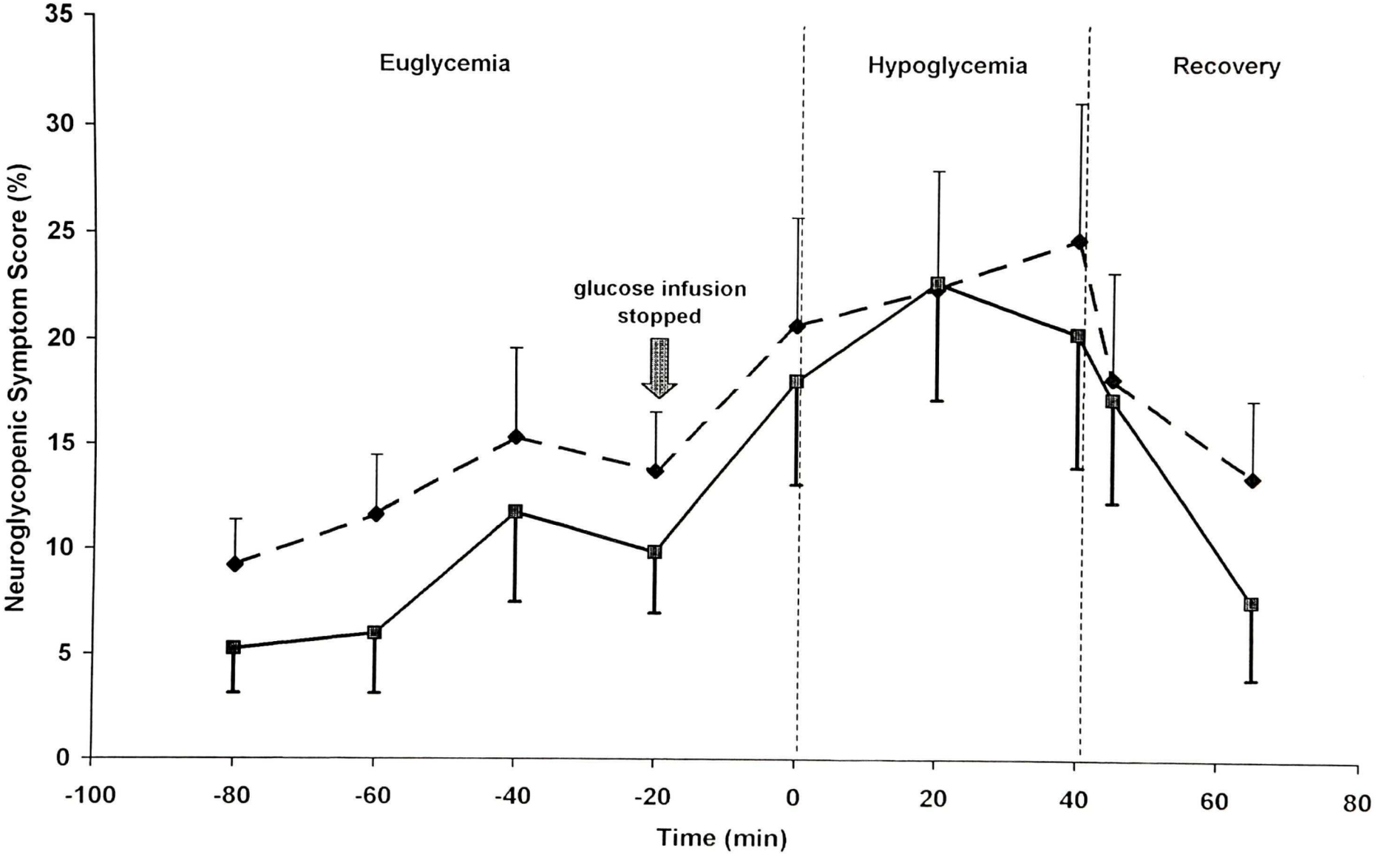
Figure 7. Cognitive Function (Response Time) Before and After CSII Therapy.
Diamonds with broken lines represent cognitive function (score) prior to CSII and squares with solid lines represent cognitive function (score) after CSII. $p=0.001$ for overall trend (repeated measures ANOVA).

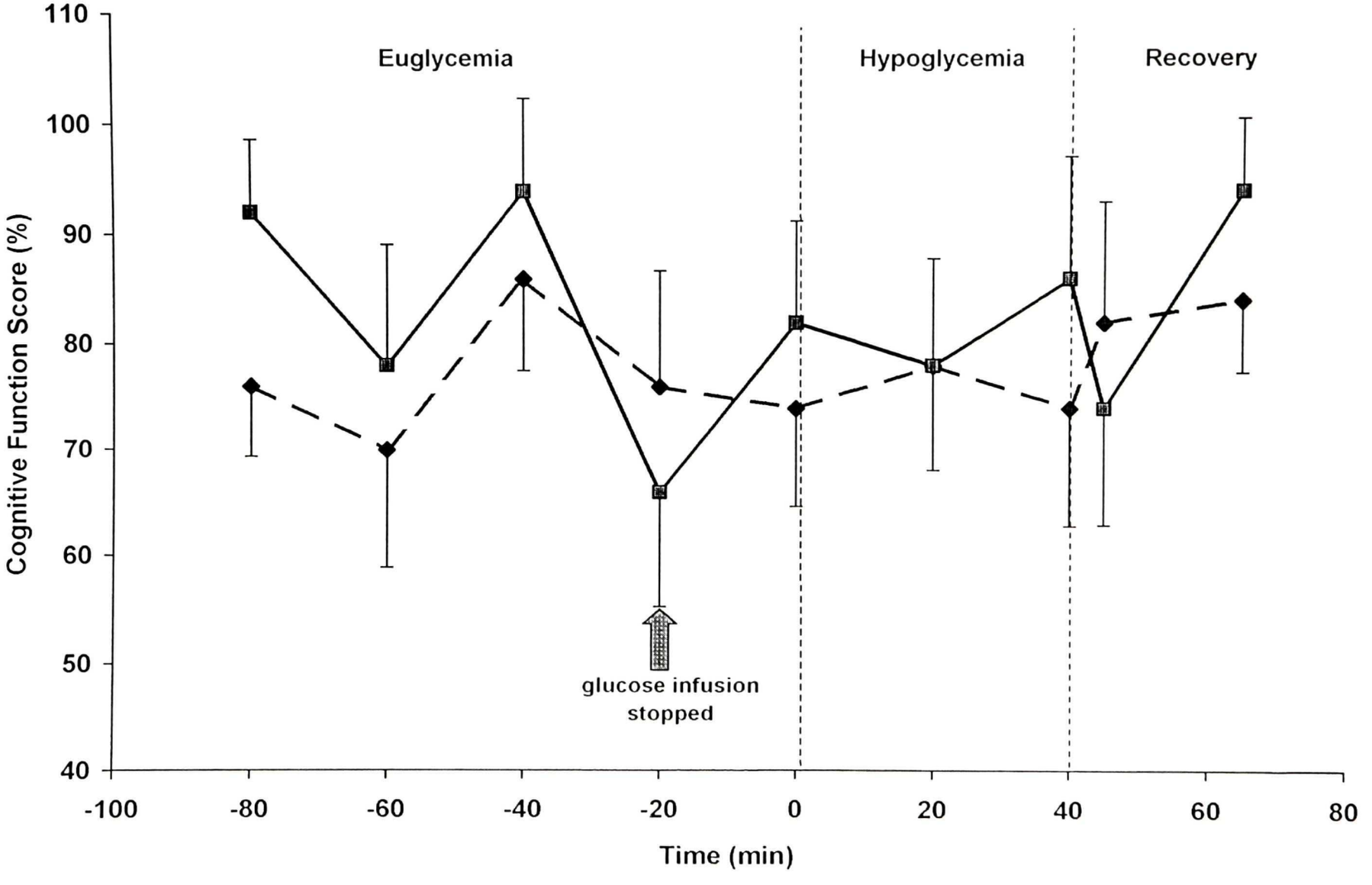

Euglycemia
glucose infusion stopped
Hypoglycemia
Recovery
Plasma glucose (mmol/L)
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
-100
-80
-60
-40
-20
0
20
40
60
80
Time (min)
23.5(1.92)

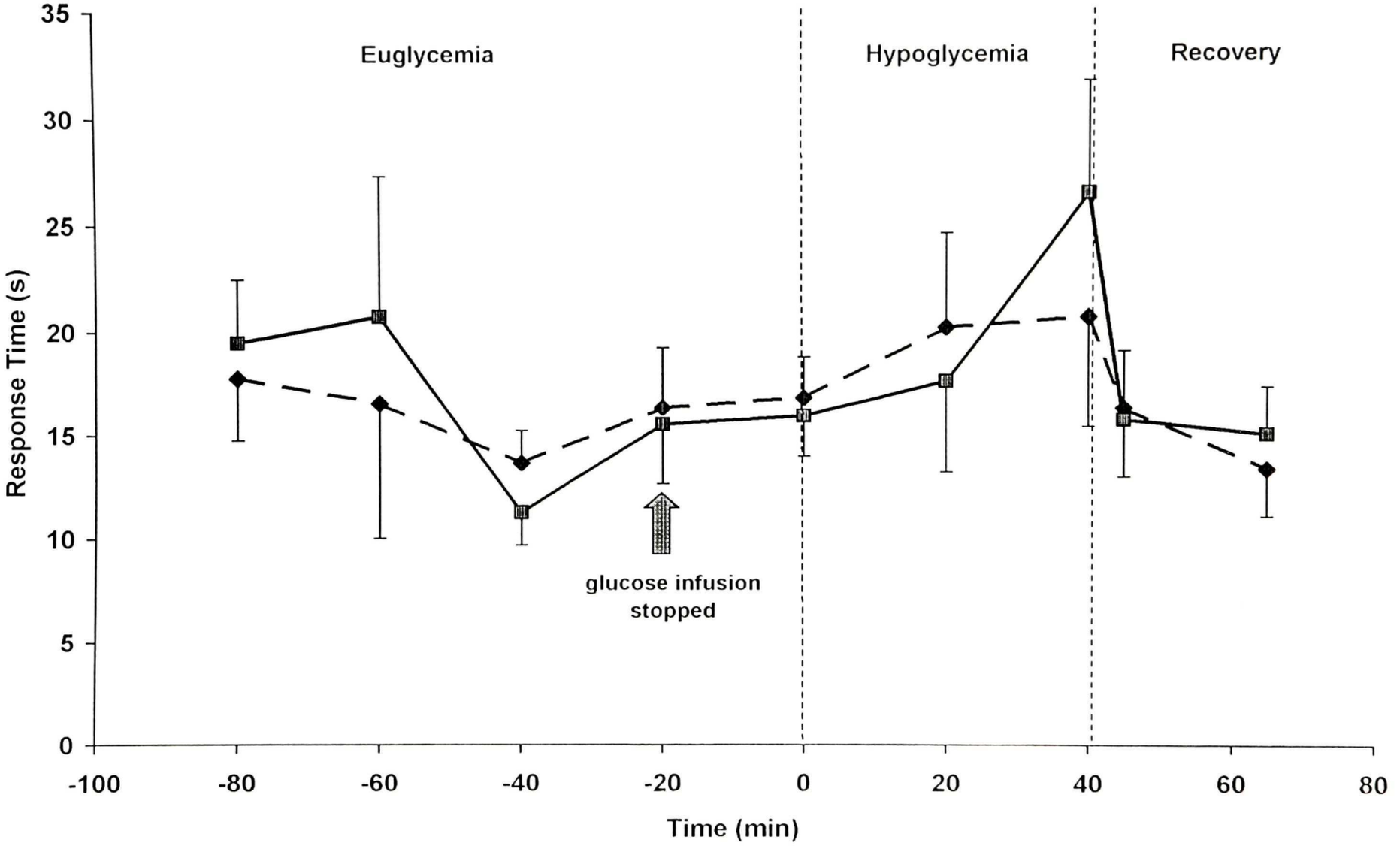

Euglycemia
Hypoglycemia
Recovery
glucose infusion stopped
Concentration of Epinephrine (nmol/L)
Time (min)
2.50
2.00
1.50
1.00
0.50
0.00
-100
-80
-60
-40
-20
0
20
40
60
80
a
b


Euglycemia
Hypoglycemia
Recovery
Concentration of Norepinephrine (nmol/L)
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
-100
-80
-60
-40
-20
0
20
40
60
80
Time (min)
glucose infusion stopped
a
b


Euglycemia
Hypoglycemia
Recovery
glucose infusion stopped
Autonomic Symptom Score (%)
Time (min)
30
25
20
15
10
5
0
-100
-80
-60
-40
-20
0
20
40
60
80


Euglycemia
Hypoglycemia
Recovery
glucose infusion stopped
Neuroglycopenic Symptom Score (%)
Time (min)
35
30
25
20
15
10
5
0
-100
-80
-60
-40
-20
0
20
40
60
80


Euglycemia
Hypoglycemia
Recovery
Cognitive Function Score (%)
110
100
90
80
70
60
50
40
-100
-80
-60
-40
-20
0
20
40
60
80
Time (min)
glucose infusion
stopped


Euglycemia
Hypoglycemia
Recovery
glucose infusion stopped
Response Time (s)
Time (min)
35
30
25
20
15
10
5
0
-100
-80
-60
-40
-20
0
20
40
60
80

CHAPTER 6

SUMMARY AND CONCLUSION

The rationale behind the undertaking of this doctoral research was the high priority given to the need for prevention of nocturnal hypoglycemia in type 1 diabetes, especially in the context of intensive management (The DCCT Research Group 1991; The DCCT Research Group 1993). This doctoral research addressed the paucity of data in the area of prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management.

The first study of this thesis was undertaken to compare the impact of 3 bedtime snack compositions and no snack (placebo) on prevention of nocturnal hypoglycemia using a randomized, placebo-controlled, crossover, inpatient study design. Results of this study indicated, for the first time, that the need for and composition of a bedtime snack are dependent on the bedtime glycemic level, whereby no snack is necessary at a bedtime glycemic level > 10 mmol/L. At bedtime glycemic levels < 10 mmol/L, a bedtime snack is warranted. At glycemic levels between 7-10 mmol/L, a standard or cornstarch-containing snack works best and at levels < 7mmol/L, a standard or protein-rich snack is recommended. Unlike previous studies (Ververs et al 1993; Kaufman and Devgan 1996; Kaufman et al 1996; Axelsen et al 1999), we did not find that the use of raw cornstarch was superior in the prevention of nocturnal hypoglycemia compared to the other snack compositions, especially at bedtime glucose concentrations < 7 mmol/L. In this study we found that the only snack composition that was effective at all bedtime blood glucose levels at preventing nocturnal hypoglycemia, without significantly impacting on overall night time and morning glycemic control, especially at bedtime glycemic levels < 7

mmol/L and 7-10 mmol/L was the standard snack. Our findings with regard to the role of protein, in addition to those of previous studies (Saleh and Cryer 1997; Hess and Beebe 1999), clearly demonstrate that protein is an appropriate alternative in the bedtime snack of individuals with type 1 diabetes since for an equivalent amount of calories and less carbohydrate, the protein rich snack was equally effective as the standard snack in preventing nocturnal hypoglycemia. This is a very important finding since there is current controversy regarding the impact and need for protein in the bedtime snack composition of people with type 1 diabetes (Franz 2000).

In the second study, a 9 month, randomized, controlled outpatient trial was employed to elucidate the efficacy of optimized titration and delivery of bedtime insulin, in the presence and absence of bedtime snacks, on prevention of nocturnal hypoglycemia in free-living adults with type 1 diabetes undergoing intensive management. The results of this study included an estimate of the incidence of nocturnal hypoglycemia in free-living adults with type 1 diabetes undergoing intensive management for the first time We found that at the end of each strategy, in a total of 181 nights, there were 98 episodes of nocturnal hypoglycemia (54 episodes per 100 patient-nights) in 97% of individuals This is likely an underestimation of the true frequency of nocturnal hypoglycemia, in this population, as this estimate was derived in the context of a program aiming for prevention of nocturnal hypoglycemia. This study found that the incidence of nocturnal hypoglycemia, although not completely eliminated, is substantially reduced by inclusion of a bedtime snack regimen which is tailored to the bedtime glycemic level. Despite the use of lispro insulin at supper and NPH insulin at bedtime, two strategies which have been shown to be efficacious in the prevention of nocturnal hypoglycemia (Ahmed et al

1998; Heller et al 1999; Fanelli et al 2002), our data indicate that bedtime snacks are necessary. Even the use of CSII, the "gold standard" of nocturnal insulin replacement (Bolli et al 1993; Lepore et al 2000) failed to compensate for exclusion of bedtime snacks. Moreover, this study provided important information regarding potential predictors of nocturnal hypoglycemia which included: a lower baseline and most recent HbA_{1c} level, a bedtime glycemic level < 10mmol/L and a morning glycemic level < 6 mmol/L.

The final study was a sub-study of the outpatient trial assessing the efficacy of three months of CSII therapy on catecholamine and symptom responses to a standardized stimulus of hypoglycemia (2.8 mmol/L) using an experimental model of clinical hypoglycemia: the one-step hypoglycemic clamp technique. In this study, participants underwent the hypoglycemic clamp experiment two times (prior to and 3 months after CSII therapy). The results of this study indicate that despite the relatively long duration of diabetes in our group of participants (mean of 20.8 years), the catecholamine response to hypoglycemia appeared to be adequate prior to CSII therapy and similar to that reported in individuals without diabetes (Simonson et al 1985). Furthermore, the catecholamine response remained unchanged following 3 months of CSII therapy in contrast to a previous study (Simonson et al 1985). Three levels of awareness during hypoglycemia were identified, for the first time, in this study. Individuals were classified as being fully aware (aware at all time points during hypoglycemia); partially aware (aware at some but not all time points) and unaware (no awareness at any time point). Important observations were made between these 3 levels of awareness and catecholamine response, symptom awareness and cognitive function, some of which

reached statistically significance. Also, this is the first study, to our knowledge, to assess recovery from hypoglycemia in the context of diabetes with respect to catecholamine response, symptom awareness and cognitive function. In this regard, we found that the catecholamine response was decreased immediately upon recovery (within 5 minutes) but remained significantly different from euglycemic levels until 20 minutes into recovery.

Although the aforementioned studies were performed separately, the results are interrelated. The first study clearly demonstrated that the need for a bedtime snack is dependent on the bedtime glycemic level. When this strategy was then employed in a "real life" setting it was again shown that inclusion of a bedtime snack when necessary (when the bedtime blood glucose level is < 10mmol/L) works better than just relying on titration of insulin dose without regard to bedtime snacks. Taken together these two studies clearly indicate that bedtime snacks should be recommended to all adults undergoing intensive management with MDI and CSII. As there is no mention regarding the need and appropriate bedtime snack composition in the most recent clinical practice guidelines (American Diabetes Association 2002; Meltzer et al 1998), these two studies will greatly influence clinical practice as they provide Level 2 evidence for the inclusion of bedtime snacks when the bedtime glycemic level is below 10 mmol/L. The cut-off level of 10 mmol/L is also very important to consider as current guidelines (American Diabetes Association 2002; Meltzer et al 1998) consider this level to be inappropriate According to the current American guidelines (American Diabetes Association 2002), the bedtime glycemic level is targeted at between 6-8 mmol/L (American Diabetes Association 2002). The Canadian guidelines do not currently include a bedtime target (Meltzer et al 1998). The first two studies performed, therefore provide Level 2 evidence

for either considering a bedtime target of above 10 mmol/L (without inclusion of a bedtime snack) or maintaining the target at bedtime between 4-10 mmol/L with the inclusion of an appropriate bedtime snack composition as per our findings. Also the second study showed that a morning glycemic level of < 6 mmol/L may be indicative of nocturnal hypoglycemia. This is a very important finding in two regards. The first regard is with respect to a long held belief that nocturnal hypoglycemia is followed by "rebound hyperglycemia" which is known as the Somogyi effect (Somogyi 1938). However, our study, in addition to other studies (Gale and Tattersall 1979; Bendtson et al 1988; Vervoort et al 1996), provides proof that nocturnal hypoglycemia is often followed by a lower and not a higher morning glycemic level. This is a very crucial finding as current clinical practice guidelines aim for morning (fasting) glycemia between 4-7 mmol/L (American Diabetes Association 2002; Meltzer et al 1998). Our study provides Level 2 evidence for the need to increase the morning glycemic target to above 6 mmol/L and / or to verify the presence of nocturnal hypoglycemia when the morning glycemic level is < 6 mmol/L. The final study of this doctoral research was designed on the premise that CSII therapy (without inclusion of bedtime snacks) would be the best strategy at preventing nocturnal hypoglycemia. As this was not the case, further research is needed to determine whether or not inclusion of bedtime snacks (in the context of MDI and CSII) can improve catecholamine and symptom responses to hypoglycemia.

In conclusion, this research has made significant contributions to the existing literature in the areas of prevention of nocturnal hypoglycemia, intensive management and counterregulation to hypoglycemia. Despite the use of continuous glucose monitoring, more physiological insulin preparations and regimens, our research indicates that nocturnal hypoglycemia remains an unresolved obstacle in the intensive management of type 1 diabetes. However, the use of bedtime snacks, when appropriate (ie- at bedtime glycemic levels < 10 mmol/L) will substantially reduce the frequency of nocturnal hypoglycemia. Our findings also confirm that CSII therapy is a viable option in the intensive management of adults with type 1 diabetes as it does not deteriorate the catecholamine and symptom responses to hypoglycemia. As CSII therapy did not include bedtime snacks, further research is warranted with respect to the role of bedtime snacks in the context of CSII therapy. Further research is needed to extend these findings in other contexts including in children with type 1 diabetes who also face a high risk of nocturnal hypoglycemia and in whom nocturnal hypoglycemia may have more serious consequences. The role of bedtime snacks with the use of newer insulin preparations such as insulin aspart® and glargine® also warrants further research.

6.1 References

Ahmed ABE, Home PD: The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. Diabetes Care 21: 32-37, 1998

American Diabetes Association: Clinical practice recommendations 2002. Diabetes Care 25 (suppl 1): s1-s147, 2002

Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. J Int Med 245: 229-236, 1999

Bendtson I, Kverneland A, Pramming S, Binder C: Incidence of nocturnal hypoglucemia in insulin-dependent diabetic patients on intensive therapy. Acta Med Scand 223: 543-548, 1988

Bolli G, De Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. Diabetes 32: 134-141, 1983

Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB: Administration of neutral protamine hagedorn insulin at bedtime versus with dinner in type 1 diabeets mellitus to avoid nocturnal hypoglycemia and improve control. Ann Int Med 136 (7): 504-514, 2002

Franz M: Protein Controversies in Diabetes. Diab Spect 13 (3): 132-141, 2000

Heller SR, Amiel S, Mansell P, UK Lispro Study group: Effect of the fast-acting insulin analog lispor on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 22 (10): 1607-1611, 1999

Gale EAM, Tattersal RB: Unrecognized Nocturnal Hypoglycemia In Insulin-Treated Diabetics. The Lancet May 19: 1049-1052, 1976

Hess A, Beebe CA: Glycemic effect of a small amount of protein added to an evening snack in type 1 diabetes (abstract). Diabetes Care 22 (suppl 1): 306A. 1999

Kaufman FR, Halvorson M, Kaufman ND: A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at Diabetes Camp. Diab Res Clin Pract 1: 1-5, 1996

Kaufmann F, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type 1 diabetes. J Diab Compl 10: 84-87, 1996

Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 49 (12): 2142-8, 2000

Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D: 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ 159 (suppl 8): s1-s29, 1998

Saleh T, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes 20 (8): 1236-1236, 1997

Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS: Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type 1 diabetes. Ann Int Med 103: 184-190, 1985

Somogyi M: Insulin as a cause of extreme hyperglycemia and instability. Wkly Bull St Louis Med Soc 32: 498-500, 1938

The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90: 450-459, 1991

The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 329: 977-986, 1993

Ververs MTC, Rouwe C, Smit GPA: Complex carbohydrates in the prevention of nocturnal hypoglycemia in diabetic children. Eur J Clin Nutr 47: 268-273, 1993

APPENDIX

Ethics Approval Certificates

ETHICAL ACCEPTABILITY OF RESEARCH INVOLVING HUMAN SUBJECTS REPORT OF THE ANIMAL CARE COMMITTEE

Required for all Applications Proposing Research Involving Human Subjects

Funds from the Canadien Diabetes Association may not be used for research involving animals unless the research proposed **has been found acceptable by a Research Ethics Board appointed and operating in accord with the MRC Guidelines on Research Involving Human Subjects (1987) and/or the MRC Guidelines for Research on Somatic Cell Gene Therapy in Humans (1990).**

(The completed form must be received by CDA not later than sixty (60) days after the deadline date for receipt of the application. If the required form is not available within this time frame, the application will not be considered.)

CONFORMITÉ À L'ÉTHIQUE EN MATIÈRE DE RECHERCHE SUR DES ÊTRES HUMAINS RAPPORT DU COMITÉ D'ÉTHIQUE POUR LA RECHERCHE

Obligatoire pour toutes les demandes concernant des recherches sur des êtres humains

Les fonds que l'Association canadienne du diabète a accordés ne pourront servir à des recherches sur des animaux à moins que le **Comité d'éthique pour la recherche, établi et dirigé conformément aux Lignes directrices du CRM concernant la recherche sur des sujets humains (1987) ou aux Lignes directrices du CRM concernant la recherche et la thérapie génique somatique chez les humains (1990), n'ait convenu que la recherche proposée répond aux normes d'éthique.**

(Le formulaire dûment rempli doit être reçu par l'ACD au plus tard soixante (60) jours après la date limite de réception de la demande. Si le formulaire n'est pas fourni à l'expiration de ce délai, la candidature ne sera pas étudiée.)

STATEMENT FROM THE INSTITUTION* IN WHICH THE RESEARCH WILL BE PERFORMED

The Research Ethics Board established by

Royal Victoria Hospital

(Institution* in which the research will be performed)
(Etablissement* où se déroulera la recherche)

as examined the protocol for the research funds entitled:

Prevention of Nocturnal Hypoglycemia in Type 1 Diabetes

(Use the same title as on the application submitted to CDA)
(Utiliser le titre qui paraît sur la demande présentée à l'ACD)

submitted by

Jean-François Yale

(Name(s) of applicant(s) as appearing on the application to CDA)
(Nom(s) du(des) candidat(s) apparaissant sur la demande présentée à l'ACD)

and found the proposed protocol involving human subjects to be ethically acceptable.

Date: April 4, 1995

Signatures:

Jean-François Yale
(Signature)

Applicant(s) / Candidat(s)

* Institution includes universities, hospitals, research institutes or companies.

DÉCLARATION DE L'ÉTABLISSEMENT* OÙ SE DÉROULERA LA RECHERCHE

Le Comité d'éthique pour la recherche établi par

a étudié la demande de financement de la recherche intitulée :

présentée par

et a convenu que la recherche proposée sur des humains est conforme à l'éthique.

L.A. Marcos

(Print name of Institution's* Representative for **Research Involving Human Subjects**) / (Nom en lettres moulées du délégué de l'établissement* **en matière de recherche sur les humains**)

May 6 1995
Date

* Par établissement, on entend les universités, les hôpitaux, les instituts de recherche ou les compagnies.

Faculty of Medicine
3655 Drummond Street
Montreal, QC H3G 1Y6
Fax: (514) 398-3595

Faculté de médecine
3655, rue Drummond
Montréal, QC, H3G 1Y6
Télécopieur: (514) 398-3595

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board consisting of:

LAWRENCE HUTCHISON, MD

SHARI BAUM, PHD — PATRICIA DOBKIN, PHD

HAROLD FRANK, MD — NEIL MACDONALD, MD

NANCY MAYO, PHD — WILSON MILLER, MD

LUCILLE PANET-RAYMOND, BA — HARVEY SIGMAN, MD

has examined the research project **A05-M27-00** entitled "**Prevention of Nocturnal Hypoglycemia in Adults with Type I Diabetes Mellitus**"

as proposed by: Dr. Jean-François Yale (Applicant) to _____ (Granting Agency, if any)

and consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

May 9, 2000
Date

Chair, IRB

Dean of Faculty

Institutional Review Board Assurance Number: M-1458