Low-Carbohydrate and Ketogenic Diets in Adults with Type 1 and Type 2 Diabetes

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ABSTRACT

Low-carbohydrate diets (LCDs) have increasingly gained interest in the diabetes community over the last two decades. The ketogenic diet (KD) is a variation of a LCD which is very-low in carbohydrates (CHO) and high in fat. These diets continue to intrigue individuals despite the lack of strong, long-term evidence.

The first part of this thesis aims to better understand the experience of adults with diabetes with following the KD, such as reasons to start the diet, motivators, support systems, sources of information, and challenges. **Methods:** In this qualitative study, adults living with type 1 (T1D) or type 2 (T2D) diabetes and following the KD for ≥3 months were recruited. 14 semistructured interviews were conducted in-person, audio-recorded, and transcribed. Thematic analysis by concept mapping was conducted. **Results:** Participants were 54.5±10.1 years old and followed the KD for 6 to 19 (median 5) months; 43% were male and 79% had type 2 diabetes. The main motivation to start the KD was to improve glycemic control or to reduce/stop taking diabetes medications. Social disapproval and lack of support from a health-care professional were the main challenges, which were prevailed by self-reported benefits such as improved glycemic control, weight loss, and increased satiety. **Conclusion:** A wide range of self-reported benefits strongly motivated individuals to follow the KD despite the lack of safety information and/or support.

Furthermore, there is a particular concern of the safety of LCDs, particularly the KD, in individuals with T1D where injected insulin doses need to match CHO intake for proper glycemic control. In addition, higher fat intake, as in LCDs and KDs, may aggravate blood lipids in individuals with T1D, who already have an increased risk of cardiovascular (CV) events. Manuscript 2 aims to evaluate the relationship of LCD, assessed using a LCD score, with glycemic control and CV risk

factors in adults with T1D. **Methods:** This cross-sectional study used data collected in a T1D registry in Québec, including self-reported or measured anthropometric data, history of moderate and severe hypoglycemic episodes, impaired awareness of hypoglycemia (Clarke score ≥4), and biochemical data (hemoglobin A1c (HbA1c), LDL-cholesterol, and non-HDL-cholesterol). 24-hour dietary recalls were collected and ranked by each macronutrient in order to calculate the LCD score. Participants were divided into quartiles (Q) based on LCD scores. **Results:** 285 adults (aged 48.2±15.0 years; T1D duration of 25.9±16.2 years) were included. Overall, participants reported low carbohydrate and fiber intakes and high fat intake compared to recommendations. Mean carbohydrate intake ranged from 31.2±6.9% (Q1) to 56.5±6.8% of total energy (Q4). Compared to Q4, more people in Q1 reported HbA1c ≤7% (Q1: 53.4% vs Q4: 29.4%; *P*=0.011). Compared to Q3, more people in Q1 reported no history of severe hypoglycemia (Q1: 60.0% vs Q3: 31.0%; *P*=0.004). There were no differences between quartiles for frequency of moderate hypoglycemia events (*P*=0.784), impaired awareness of hypoglycemia (*P*=0.269) and lipid profile: LDL-cholesterol (*P*=0.290) and non-HDL-cholesterol (*P*=0.118). **Conclusions:** Low carbohydrate intake is associated with a higher probability of reaching HbA1c target and lower frequency of history of severe hypoglycemia, but not with moderate hypoglycemia frequency, impaired hypoglycemia awareness, nor CV risk factors.

LCDs appear to have benefits on glycemic control in adults with both T1D and T2D. As LCDs continue to gain interest in the diabetes community, it is important to acknowledge possible adverse effects on glycemic control as well as lifestyle and social challenges when following these diets. Further long-term studies of the effect of LCDs in T1D and T2D are needed to help HCPs establish clinical recommendations for individuals wishing to follow these diets.

RÉSUMÉ

Les personnes vivant avec le diabète ont démontré un intérêt grandissant envers les diètes faibles en glucides (DFG). Le régime cétogène (RC), une diète très faible en glucides et élevé en lipides, attire les personnes vivant avec le diabète, malgré le manque de preuves scientifiques solides et sur le long terme.

La première partie de cette thèse vise à comprendre le point de vue des adultes vivant avec le diabète par rapport au RC. **Méthodes:** Auprès d'adultes vivant avec le diabète de type 1 (DT1) ou de type 2 (DT2) qui suivaient le RC depuis au moins 3 mois, nous avons mené des entrevues semi-structurées. Nous avons analysé les thèmes au moyen de la cartographie conceptuelle. **Résultats:** Les participants avaient 54,5 ± 10,1 ans et avaient suivi le RC durant 6 à 19 (médiane 5) mois; 43 % étaient des hommes et 79 % avaient le DT2. La principale motivation à commencer le régime était l'amélioration du contrôle glycémique, ou la réduction ou l'arrêt des médicaments. La désapprobation sociale et le manque de soutien de la part des professionnels de la santé étaient les principaux défis, mais ceux-ci étaient mineur en comparaison aux bénéfices tel que l'amélioration des glycémies, la perte de poids et la sensation de satiété. **Conclusion:** Les avantages rapportés, escomptés ou nouveaux, a fortement motivé les individus à suivre le RC en dépit du manque d'information sur la sécurité et/ou de soutien.

De plus, il existe une réelle préoccupation concernant la sécurité des DFG, incluant le RC, chez les individus vivant avec le DT1 qui doivent ajuster l'insuline selon les glucides consommées. Une diète avec un apport plus élevé en lipides peut aussi augmenter les lipides sanguins des individus vivant avec le DT1. La seconde étude évalue la relation entre les DFG, évaluées par un score, le contrôle glycémique et les marqueurs cardiométaboliques chez les adultes avec le DT1.

Méthodes: Cette étude transversale a utilisé des données d'un registre du DT1 au Québec, notamment des rappels alimentaires de 24 heures, des données anthropométriques autodéclarées, les antécédents d'hypoglycémie modérée et sévère, la capacité à percevoir les hypoglycémies et des marqueurs biochimiques (hémoglobine glyquée (HbA1c), cholestérol LDL, cholestérol non-HDL). Les participants ont été divisés en quartiles (Q) en fonction des scores DFG. **Résultats:** 285 adultes (âge: 48,2 ± 15,0 ans ; durée du DT1: 25,9 ± 16,2 ans) ont été inclus. Les participants ont rapporté des apports faibles en fibres et élevé en lipides. L'apport moyen en glucides variait de 31,2 ± 6,9 % (Q1) à 56,5 ± 6,8 % (Q4) de l'énergie totale. Par rapport au Q4, plus de personnes au Q1 ont rapporté une HbA1c ≤ 7 % (Q1: 53,4 % vs Q4: 29,4 %; *P*=0,011). Par rapport au Q3, plus de personnes au Q1 ont rapporté une fréquence plus faible d'hypoglycémie sévère (Q1: 60.0% vs Q3: 31.0%; *P*=0.004). Il n'y avait aucune différence entre les quartiles pour la fréquence des épisodes hypoglycémiques modérés, ainsi que la perception des hypoglycémies (*P*=0,269) et les marqueurs de risque CV: cholestérol-LDL (*P*=0,290) et cholestérol non-HDL (*P*=0,118). **Conclusion:** Un faible apport en glucides est associé à une probabilité plus élevée d'atteindre les cibles de HbA1c et à une fréquence plus faible d'hypoglycémie sévère, mais pas avec la fréquence d'épisodes d'hypoglycémie modérée, avec l'altération de la perception de l'hypoglycémie, ou à des marqueurs de risque CV.

Les diètes faibles en glucides semblent améliorer le contrôle glycémique chez les adultes atteints de DT1 et de DT2. Étant donné que ces diètes suscitent de l'intérêt dans la communauté diabétique, il est important de reconnaître les risques possibles ainsi que les défis liés au mode de vie et la vie sociale lors du suivi de tels régimes. D'autres études à plus long terme sont nécessaires

afin d'informer les professionnels de la santé pour leur permettre de guider et de soutenir les patients qui décident d'adhérer à ces diètes.

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CONTRIBUTION OF AUTHORS

In the following thesis, the two manuscripts presented were accomplished through collaborative efforts among authors.

In the first study, I was responsible for participant recruitment, data collection and transcription, data analysis, and redaction of the manuscript. In the second study, I was involved in the conception and study design, data collection, statistical analysis and interpretation, and redaction of the manuscript.

Dr. Anne-Sophie Brazeau was the principal investigator for both studies and contributed to all aspects of this research, from conception to the critical revision of manuscripts.

In the first study, Marie Raffray contributed to data collection, data analysis, and drafting of the manuscript. Amélie Roy-Fleming contributed to the data collection and critical revision of the manuscript. Sarah Blunden assisted in the recruitment of participants and revision of the manuscript.

In the second study, Élisabeth Nguyen contributed to data collection, statistical analysis and interpretation, and redaction of the manuscript. Dr. Rémi Rabasa-Lhoret was involved in data interpretation and the critical revision of the manuscript.

LIST OF ABBREVIATIONS

Abbreviation	*Description*
A1c	Glycated hemoglobin A_{1C}
AGE	Advanced glycation end products
ADA	American Diabetes Association
BG	Blood glucose
BMI	Body mass index
CFG	Canada's Food Guide
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CSII	Continuous subcutaneous insulin infusion, i.e. insulin pump
CV	Cardiovascular
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
GV	Glycemic variability
HCP	Health care professional/provider
HDL-c	High-density lipoprotein cholesterol
IAH	Impaired awareness of hypoglycemia
kcal	Kilocalories
KD	Ketogenic diet
LADA	Latent autoimmune diabetes in adults
LCD	Low-carbohydrate diet
LDL-c	Low-density lipoprotein cholesterol
MDI	Multiple daily injections
MUFA	Monounsaturated fatty acids
NO	Nitric oxide
OHA	Oral hyperglycemic agent
PUFA	Polyunsaturated fatty acids
PWT1D	People with type 1 diabetes
R24H	24-hour recall
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SFA	Saturated fatty acids
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TE	Total energy
TG	Triglycerides
TIR	Time-in-range
USDA	United States Department of Agriculture
WC	Waist circumference

CHAPTER 1
Introduction

1.1 TYPE 1 AND TYPE 2 DIABETES

1.1.1 Definition, Classification and Prevalence

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to insufficient insulin production, defective insulin action, or both [1]. Insulin is an anabolic hormone synthesized by β-cells of the pancreas which helps regulate blood glucose and plays a key role in energy metabolism. The pancreas maintains blood glucose levels at a narrow range of 4.0 to 6.0 mmol/L by the opposing hormonal functions of insulin and glucagon. Insulin acts to decrease blood glucose after a meal, whereas glucagon (secreted by α-cells of the pancreas) acts to increase blood glucose when plasma glucose is low, such as in between meals, and during sleep or exercise [2].

Diabetes can be classified into 2 main types: type 1 and type 2. Type 1 diabetes (T1D) is an autoimmune disorder characterized by the idiopathic destruction of the β-cells of the pancreas, resulting in insulin deficiency. Its cause remains unknown, however environmental factors and genetic predisposition are proposed to play a role [3]. Furthermore, type 2 diabetes (T2D) is characterized by insulin resistance with or without impairment in insulin production, in which cells are unable to respond to insulin. The pathogenesis of T2D is multifactorial, though it is proposed that environmental factors, such as overeating and sedentary lifestyle, play a larger role than aging and genetics [4].

In 2019, the International Federation of Diabetes estimated that 463 million people globally were living with diabetes, which is expected to rise by 25% by 2030 [5]. In Canada, it was

estimated that 3.88 million people (10% of the population) were living with diagnosed diabetes (T1D and T2D) in 2021; 5 to 10% of whom (194 000 to 388 800 people) had T1D [6]. A recent meta-analysis estimated that T1D affects 9.5% of the world's population and an incidence of 15 per 100 000 people [7].

Diabetes is associated with increased health risks and comorbidities. Chronic hyperglycemia can cause detrimental damage to the body, particularly to macrovascular and microvascular organ systems. Macrovascular complications include coronary artery disease, peripheral arterial disease and stroke, and microvascular complications include diabetic nephropathy, neuropathy, and retinopathy [8].

1.1.2 Blood Glucose Monitoring and Glycemic Targets

Diabetes management is primarily assessed by a hemoglobin A1c (HbA1c or A1c) blood test, which measures the average blood glucose concentration over the last 2 to 3 months. Therapeutic targets for A1c are ≤7.0% for most adults with T1D or T2D. Stringent glycemic control of A1c ≤6.5% may be recommended in adults with T2D with a low risk of hypoglycemia in order to further reduce the risk of microvascular complications. On the contrary, A1c targets are broadened to 7.1% to 8.5% in certain conditions such as frailty, functional dependence, or a history of recurrent severe hypoglycemia or hypoglycemia unawareness [9].

Blood glucose can be self-measured by a capillary finger prick test using a blood glucose meter. Regular blood glucose monitoring is encouraged and to be measured at various points of the day, such as fasted, before and after meals, and at bedtime, especially in individuals taking insulin as hypoglycemia is more common [10, 11]. Recent technology has allowed for more

convenient, less invasive testing of blood glucose, where continuous glucose monitoring (CGM) systems replace the need for multiple finger prick tests. CGM involves a subcutaneously-inserted sensor applied to the arm or abdomen which continuously monitors interstitial glucose concentrations transmitted and recorded by a portable display unit [10].

1.1.3 Hypoglycemia

Blood glucose monitoring is a main component of diabetes care, especially in T1D. This is primarily due to the increased risk of hypoglycemia associated with insulin use, though this is also a concern, however less frequent, in individuals with T2D who use insulin or insulin-secreting medications, called insulin secretagogues. Hypoglycemia is characterized by the development of autonomic and/or neuroglycopenic symptoms, such as sweating, palpitations, trembling, difficulty concentrating, confusion, weakness, and vision changes. Hypoglycemia can be further classified into 3 types according to severity, also known as level 1 to 3 by the American Diabetes Association (ADA) described in **Table 1** below [12].

Table 1 – Hypoglycemia Classification [12]

Level	Description
Level 1	3.0 mmol/L (54 mg/dL) ≤ BG < 3.9 mmol/L (<70 mg/dL)
Level 2	BG <3.0 mmol/L (<54 mg/dL)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

Hypoglycemia awareness is a syndrome that may complicate strict glycemic control in individuals with T1D or severely insulin-deficient T2D [12]. Impaired awareness of hypoglycemia (IAH) is characterized by the deficient counterregulatory hormone release and diminished autonomic response, resulting in attenuated warning symptoms that previously allowed an individual to recognize early signs of hypoglycemia [12, 13]. Prevention of hypoglycemia is critical, as a history of IAH has an impact on physiological defences against subsequent hypoglycemic episodes, which can lead to a vicious cycle of recurrent hypoglycemia [13].

1.1.4 Pharmacological Treatment

There is no cure for T1D, and prior to the discovery of insulin, T1D was considered a fatal disease. Lifelong insulin therapy is required for T1D management, which can be achieved by conventional or intensive insulin therapy [14]. Conventional therapy involves 1 to 2 fixed-dose insulin injections by pen or syringe administered at set times of the day. The dosage of insulin is dependent on the individual's diet regimen, where meal times and carbohydrate (CHO) intake must be consistent from day to day. Intensive therapy involves multiple daily injections (MDI, also known as basal-bolus insulin therapy) of insulin by pen or syringe, or by continuous subcutaneous insulin infusion (CSII) via an external insulin pump [11]. Intensive therapy allows for more flexibility as insulin doses are calculated and injected to cover estimated CHO intake. As demonstrated by the landmark Diabetes Control and Complications Trial (DCCT) in 1993, intensive insulin therapy is associated with improved glycemic control and can significantly reduce and delay the onset of long-term cardiovascular (CV) and microvascular complications in people living with T1D [15]. In the DCCT, A1c was significantly reduced however weight gain and frequency of hypoglycemia was

significantly higher with intensive insulin therapy compared to conventional insulin therapy [16]. This landmark study is largely responsible for the widespread use of intensive insulin therapy today.

Pharmacological treatment of T2D is variable; it can be managed by diet alone or in conjunction with oral hyperglycemic agents (OHAs) and if needed, insulin therapy. In individuals with newly diagnosed T2D, nutrition therapy is the first line of treatment. If nutrition therapy is unsuccessful at reaching glycemic targets (A1c ≤7.0%), an OHA will be added. If A1c remains ≥1.5% above target, additional OHAs are considered. Insulin therapy is added only when symptomatic hyperglycemic and/or metabolic decompensation is present [17]. Pharmacotherapy in T2D can be subject to change; in fact through healthy behaviour interventions and weight loss, OHAs can be withdrawn and in some cases, T2D remission can be achieved [18].

1.1.5 Nutrition Therapy

In addition to pharmacological treatment, diabetes management requires important dietary considerations. Nutrition therapy can have a profound effect on diabetes management; in fact it can effectively improve glycemic control by reducing A1c by 1.0% to 2.0% [19]. According to Diabetes Canada's 2018 Clinical Practice Guidelines, it is recommended that individuals with diabetes consume 45 to 65% of energy from CHO, 15 to 20% as protein, and 20 to 35% as fat. These guidelines also encourage individuals to follow *Eating Well with Canada's Food Guide*, and emphasize the consumption of a variety of food groups, adequate fibre intake from whole grains and low glycemic-index (GI) CHO sources, adequate unsaturated fat intake (monounsaturated fatty acids, MUFAs, and polyunsaturated fatty acids, PUFAs), limited saturated fatty acid (SFA)

intake (<9% of total energy), and avoidance of trans fats. In individuals with overweight or obesity, weight loss is encouraged to achieve a healthy body weight in order to improve glycemic control, reduce CV risk, and prevent long-term diabetes complications [19].

More recently, Diabetes Canada released a position statement on low-CHO diets (LCDs) as LCDs increased in popularity in the diabetes community [20]. The position statement acknowledged the many limitations in current literature and the inability to recommend LCDs to all people living with diabetes at this time. Moreover, Diabetes Canada recommended health care professionals (HCPs) to support their patients in whichever dietary pattern they choose, including LCDs and KDs. People living with diabetes are encouraged to consult their HCP to discuss how to safely initiate the diet to achieve desired goals and avoid adverse effects. The current position statement takes a conservative stance on LCDs and KDs in the context of diabetes with emphasis on supporting patients to choose their dietary pattern based on their goals, values, and preferences. Similar recommendations have been reported in recent years in position statements by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [21], Diabetes Australia [22], and Diabetes UK [23].

1.1.6 Cardiovascular Disease

Pathophysiology

People living with diabetes have an increased risk of premature mortality and morbidity, much of which is attributable to cardiovascular disease (CVD). In a recent meta-analysis, the standardized mortality ratio attributable to CVD was estimated to be 5.7 for men and 11.3 for women with T1D [24]. While the correlation between diabetes and CVD is well established, the

mechanisms by which poor glycemic control predisposes people to vascular disease is complex and not fully understood. Hyperglycemia and insulin resistance play a large role in the development of atherosclerosis by causing endothelial and smooth muscle cell dysfunction. Endothelial cells are responsible for regulating vascular function and structure. Endothelial cells produce nitric oxide (NO), a key marker of vascular health, which causes vasodilation and protects blood vessels from injury, such as atherosclerosis [25].

Hyperglycemia induces endothelial dysfunction by the reduction of NO bioavailability and excess production of reactive oxygen species (ROS) [26]. In brief, ROS accumulation triggers several biochemical pathways which further cascade the production of ROS and highly oxidant compounds called advanced glycation end products (AGEs), leading to an increase in oxidative stress and subsequent reduction of NO bioavailability [16, 27, 28]. In addition, this cascade of biochemical reactions provokes vasoconstriction, platelet aggregation, and upregulation of pro-inflammatory genes. Altogether, these events ultimately lead to the formation of macrophage foam cells, precursors of atherosclerotic plaque, which characterizes the initiation of atherosclerosis [25]. Atherosclerosis is an inflammatory disorder of the arterial wall which can lead to myocardial infarction, stroke, disability, and death [29, 30].

Cardiovascular Risk Factors

While diabetes confers an independent risk for CVD, many studies show that CVD can be prevented or slowed in people with diabetes by controlling for individual CVD risk factors [31]. The large international case-control INTERHEART study, including people from 52 countries, identified 9 modifiable risk factors of CVD, which include smoking, dyslipidemia, hypertension, diabetes,

abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity. These risk factors accounted for over 90% of the population-attributable risk of a first myocardial infarction [32].

The DCCT and its follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated that glycemic control was protective against CVD in people living with T1D. Over a mean follow-up of 28 years, improved glycemic control (mean A1c 7.0%) with intensive insulin therapy was associated with a 30% reduction in any CVD event compared to conventional insulin therapy (mean A1c 9.0%) [33]. While lower A1c appears to be protective, hypoglycemia also confers independent CVD risk, particularly in individuals with underlying CVD or high CV risk [34]. This is due to autonomic physiological responses to hypoglycemia, which cause transient cardiac stress by increasing blood flow to the brain, myocardium, and splanchnic circulation, in order to maintain glucose supply to the brain and to promote hepatic glucose production. Consequently, heart rate, peripheral blood pressure, myocardial contractility, and stroke volume are increased, resulting in an increased workload on the myocardium [35, 36]. In individuals with underlying CVD or a longer duration of diabetes, this may cause myocardial ischemia, as arteries are less elastic and effective at recovering from transient increases of central arterial pressure caused by hypoglycemia [37].

In T2D, the importance of glycemic control on lowering the risk of microvascular disease is well documented [38-45], however its benefit on macrovascular disease has not been demonstrated.

1.2 LOW-CARBOHYDRATE AND KETOGENIC DIETS

To date, there is no consensus on the macronutrient composition that defines a LCD or KD, however literature suggests that a low-CHO diet comprises of <26% to <30% of total energy (TE) as CHO (<150 g of CHO on a 2000 kcal diet), and a KD consists of 21-70 g of CHO or <10% TE and is characterized by a higher-fat composition (75% TE) [46]. The KD is named after its proposed mechanism where, in a hypocaloric or severe CHO-deficient diet, ketosis is induced. Ketosis is the metabolic formation of ketones by the liver which occurs when the body switches its primary fuel source from CHO to fatty acids in response to a scarce supply of glucose [47]. Due to this proposed "fat-burning" principle, the KD has gained media attention as a weight loss diet.

LCDs and KDs restrict or exclude multiple food groups, such as fruits, legumes, grain products, and some dairy products. This translates into excluding or restricting most fruits (with exception to berries), starchy vegetables (e.g. potatoes, corn), and grain products (e.g. rice, pasta, bread, etc.). The KD comprises of plenty of vegetables, meat, poultry, fish, eggs, and full-fat dairy products. Due to these food restrictions, LCDs and KDs may cause nutrient-deficiencies in fibre, B-vitamins, and vitamin A, C, D, and E, and in minerals including calcium, sodium, potassium, and magnesium [46, 48].

Furthermore, there is concern for adverse effects associated with LCDs, particularly with KDs. Upon starting the diet, the most commonly reported side effects include constipation, dizziness, headaches, muscle cramps, and fatigue. These side effects are referred to as the "keto flu" and typically resolve after a few days as the body shifts CHO to ketone bodies for energy [48, 49]. Other acute side effects include nausea, diarrhea, weakness, and dehydration. The long-term effects of the KD remain inconclusive, however caution is advised to individuals with lipid

disorders, CVD, a history of heart failure, kidney disease, and liver disease, or using medications for diabetes (OHA and/or insulin), hypertension, and anticoagulation, due to the high dietary fat composition of the KD [48].

1.3 THESIS OBJECTIVES AND HYPOTHESES

Objective 1

To understand the perspective of adults with diabetes when following a ketogenic diet, with regard to reasons for starting the diet, motivators, support systems, sources of information, and challenges in adhering with the diet.

Objective 2

To evaluate associations between the low-carbohydrate-diet (LCD) score, glycemic control, and cardiovascular risk factors in adults with type 1 diabetes. Hypothesis: Adults classified in the lower LCD score quartile, indicative of lower carbohydrate intake and higher fat and protein intake, will have improved glycemic control and attenuated cardiovascular risk factors compared to those in the highest LCD score quartile.

CHAPTER 2
Literature Review

2.1 LOW-CARBOHYDRATE DIETS IN TYPE 1 DIABETES

2.1.1 Glycemic Control

One of the concerns of following LCDs, notably KDs, is the increased risk of hypoglycemia in individuals with T1D or T2D taking insulin, where insulin doses need to be carefully adjusted to match CHO intake. A particular concern in T1D when following a KD is the diet's effect on delaying and diminishing hypoglycemia awareness, due to the inhibitory effects of ketones on counter-regulatory cerebral hormones, such as adrenaline, growth hormone, and cortisol [50]. In addition, hypoglycemia treatment with glucagon may be less effective due to low hepatic glycogen stores resulting from dietary CHO restriction as shown in a recent study [51].

Three experimental studies have investigated the effect of LCDs or KDs on glycemic control in adults with T1D. These randomized trials evaluated the short-term effect of a LCD on glycemic control in adults with T1D, where one study assessed very short-term outcomes at 1 week [52] and 2 studies assessed outcomes at 12 weeks [53, 54]. In the earlier pilot RCT by Kreb *et al.* [53], a 12-week intervention of a LCD (50-75 g CHO/day) with CHO-counting education showed a significant reduction in A1c (7.9% to 7.2%, $p<0.05$) in adults with T1D ($n=5$ per arm). However, when compared to the 12-week CHO-counting intervention group, 12-week measures of A1c were not significantly different between the groups (standard CHO counting 7.4% vs. LCD 7.2%). Notably, the impact on hypoglycemia was not assessed in this study. Similarly, Schmidt *et al.* [54] recently conducted a randomized cross-over trial comparing a 12-week LCD (<100 g CHO/day) to a 12-week high-CHO diet (HCD; >250 g CHO/day) in 10 adults with T1D. CGM showed that while

differences in mean glucose (LCD 8.8 mmol/L vs. HCD 8.9 mmol/L) and time-in-range (TIR; time spent in euglycemia at 3.9 to 10.0 mmol/L) were minor between interventions, the LCD showed significantly less time spent in hypoglycemia ≤3.9 mmol/L (1.9% TIR vs 3.6% TIR, $p<0.001$) and reduced glycemic variability (GV; 2.9 mmol/L vs. 3.3 mmol/L, $p=0.004$). These findings align with results of their previous cross-over study by Ranjan *et al.* [52] comparing the effects of a 1-week KD (<50 g CHO/day) to a 1-week HCD (>250 g CHO/day) in 10 adults with T1D. Similarly, the KD resulted in less time in hypoglycemia ≤3.9 mmol/L (2.2% vs 8.0% TIR, $p=0.03$) and reduced GV (1.9 vs 2.6 mmol/L, $p=0.02$). While there were no differences in mean glucose levels measured by CGM (7.3 vs 7.4 mmol/L, $p=0.99$), the KD resulted in more TIR (3.9 to 10.0 mmol/L; 83% vs 72%, $p=0.02$) than the HCD. Across these 3 randomized trials, A1c or mean glucose was not considered significantly different between a LCD or KD compared to a HCD or control diet, with inconclusive findings on TIR, GV, and hypoglycemia.

Three observational studies provided insight on the long-term outcomes of following a KD in T1D [55-58]. In a 1-year observational study, Nielsen *et al.* [58] aimed to evaluate the impact of an educational program and a LCD (20% CHO; 70-90 g/day) on glycemic control in 22 adults with T1D. The 2-month educational program covered principles of CHO-counting, insulin dosing, and blood glucose measurements in aims to reduce glucose fluctuations and A1c in individuals who reported poor glycemic control. Their findings showed that a LCD implemented after an educational program was able to achieve a significant reduction in A1c (7.4 ± 0.9% to 6.4 ± 0.7%, $p<0.001$) at 3 months, which was maintained at 12 months. In addition, hypoglycemia frequency was significantly reduced at both 3-month and 12-month follow-ups, averaging 0.5 ± 0.4 episodes per week at 12-months ($p=0.004$). In a subsequent analysis 7 years later, Nielsen *et al.* [57]

conducted a retrospective audit on participants who attended the educational program (*n*=48). The audit revealed a high rate of non-compliance with the LCD, where 52% (*n*=25) of participants stopped the diet after 2 years. Consequently, A1c reverted from 6.5 ± 0.8% at 3 months to 7.4 ± 0.9% at 4 years in these participants. In the subsample of participants who reported partial or excellent adherence (*n*=23, 48%), A1c improvements achieved at 3 months were maintained over 4 years. Mean change in A1c from baseline was considered significant ($p<0.001$) at -0.7 ± 0.4%, resulting in a mean A1c of 6.9 ± 0.8%.

Furthermore, Lennerz *et al.* [55] conducted an online survey including 316 people (*n*=131; 42% children) with T1D. Adult respondents (*n*=185) reported following a KD for a mean duration of 2.7 ± 3.6 years with a mean reported daily CHO target of 36 ± 16 g. Of the 127 respondents who reported changes in A1c pre- and post-KD, a significant mean change of -1.45 ± 1.05% was reported ($p<0.001$). The mean reported A1c was 5.64 ± 0.66% (*n*=176) and GV was 1.4 ± 0.7 mmol/L (*n*=64) among adult participants who provided this data. Out of 176 adult respondents, 12 (7%) reported having a hypoglycemic event requiring help from others in the past year, which was significantly reduced compared to pre-diet (23 (13%) adults per year, $p<0.001$).

Lastly, Leow *et al.*'s observational study [56] investigated the effect of a KD (<55 g CHO/day) in 11 adults with T1D who followed the diet for a mean duration of 2.6 ± 3.3 years. 7-day food journals revealed a mean intake of 6 ± 3% energy from CHO, 65 ± 10% from fat, and 24 ± 8% from protein. Mean A1c was 5.3 ± 0.4%, and mean daily GV was minimal at 1.5 ± 0.7 mmol/L, measured by blinded CGM over 7 days. Participants self-reported a mean and median of 0.4 ± 0.7 and 0 (range 0-2) episodes of level-2-hypoglycemia (see Table 1 for definition) per week, however blinded CGM revealed higher frequencies at 6.3 episodes per week (median 0.9 (0.0-2.0) per day).

The large discrepancy between self-reported and measured hypoglycemic episodes may be explained by IAH.

Of the 4 observational studies discussed, 2 studies [55, 56] revealed excellent mean A1c meeting targets in participants who followed a KD longer than 2 years on average. The other 2 studies [57, 58] revealed that almost half of participants met A1c targets, which were those who reported partial or complete adherence to an LCD. Furthermore, randomized trials investigating LCDs in T1D are limited to 3 studies of short-term dietary intervention. Of the 3 studies, all reported a non-significant difference in A1c when comparing a LCD (*n*=2) or KD (*n*=1) to a control diet or HCD. Lastly, hypoglycemia-related outcomes were measured in 5 of the 7 studies, however were difficult to compare due to differences in unit measurements and definitions of hypoglycemia used. Two of the studies [52, 54] revealed that a LCD or KD reduced time spent in level-1-hypoglycemia (BG <3.9 mmol/L) when compared to a HCD or control diet, while Leow *et al.* [56] found greater time spent in level-2-hypoglycemia (BG <3.0 mmol/L). The other 2 observational studies assessed rate or incidence of hypoglycemia, where participants reported a lower frequency of non-specified hypoglycemia [58] and incidence of level-3-hypoglycemia [55].

2.1.2 Lipid Profile

The consequences of following LCDs on lipid profiles in individuals with T1D remains controversial. Five studies (2 observational, 2 cross-over, 1 RCT) have investigated the effects of a LCD (*n*=2) or KD (*n*=3) on lipid profile in adults with T1D. In Kreb *et al.*'s pilot RCT [53], a 12-week intervention of a LCD (50-75 g CHO/day) with carbohydrate-counting education in adults with T1D (*n*=5 per arm) showed no significant differences in lipid profile (total-cholesterol, LDL, HDL, TG)

compared to those who took the same course without dietary intervention. Furthermore, Ranjan *et al.* [52] also assessed lipid profiles in their very short-term cross-over study. When comparing a 1-week KD (<50 g CHO/day) to a 1-week high-CHO-diet (HCD; >250 g CHO/day) in adults with T1D (*n*=5 per arm), lipid profile (total-cholesterol, LDL, VLDL, HDL, TG) was non-significantly different between interventions likely due to the short follow-up duration. Their most recent randomized open-label crossover trial [54] also assessed lipid profiles in adults with T1D. Comparing a 12-week LCD (<100 g/day CHO) and a 12-week HCD (>250 g/day CHO), there were no significant differences in TG, LDL, and total-cholesterol. Differences in HDL were minor within-groups, however the between-group difference was significantly higher in favour of the LCD intervention (p=0.005). A limitation to note among these studies is the relatively small sample size and short-term dietary intervention (≤3 months) which may fail to demonstrate impact on CV factors such as lipid profile, which take longer to develop.

Two recent observational studies, as previously mentioned, provide some insight on the long-term impact of a KD on lipid profiles in people with T1D. In the online survey conducted by Lennerz *et al.* [55], adult patient-reported data revealed mixed lipid profiles; with low TG, high HDL, high total-cholesterol, and high LDL-c, with 66% (*n*=45) of respondents having dyslipidemia (defined as TG >1.47 mmol/L, LDL >3.36 mmol/L, or HDL <0.91 mmol/L). Moreover, Leow *et al.* [56] found that in 11 participants following a KD for a mean duration of 2.6 ± 3.3 years, fasting lipid profiles revealed elevated total-cholesterol and TG in most participants (*n*=9; 82%), elevated LDL-c in some participants (*n*=3; 27%), however normal HDL-c levels in all participants.

Among the 5 studies aforementioned, the effect of a LCD or KD appears to increase HDL-c, however there are conflicting findings on the effect on TG, total-cholesterol, and LDL-c. The

paucity of RCTs in this population makes it difficult to rigorously assess the CV safety of LCDs and KDs. In addition, these studies have important limitations as consideration for fat distribution (% of total energy) and dietary quality of CHO and fat sources are not accounted for or described. Sources of CHO (e.g. refined CHO vs. whole grains) and fatty acids (e.g. SFA vs. MUFA and PUFA) and intake of fibre and trans fat all play a role in modifying CVD risk [19, 59].

2.1.3 Weight Loss/Management

Historically, individuals with T1D were lean with a low body mass index (BMI). Nowadays, as intensive insulin therapy prevails as the main treatment for T1D, individuals may struggle with weight gain as a potential side effect [60]. As demonstrated through the DCCT and subsequent EDIC study, intensive therapy was associated with a 33% increase in mean-adjusted risk of becoming overweight [61]. Today, studies estimate that the prevalence of overweight and obesity in the T1D population to be equal to that of the general population [62, 63]. As rates of overweight and obesity increase, people with T1D may face insulin resistance and further risk of developing CVD [54]. Achieving a healthy body weight is thus essential in reducing such complications.

Four studies (2 observational, 1 randomized cross-over study, 1 RCT) evaluated weight as a secondary outcome of interest in adults with T1D following a LCD [53, 54, 57, 64]. In a retrospective observational study of 30 adults with diabetes (10 T1D, 20 T2D), chart review revealed that the adherence of a KD of <30 g/day for 21.4 ± 22.3 months (range 2-79 months) resulted in significant weight loss (mean change -5.5 ± 9.7 kg) in the sample, where 18 subjects were on insulin therapy [64]. BMI data was not collected, thus the prevalence of overweight and obesity was not described in this sample. Moreover, Nielsen *et al.* [57] conducted a retrospective

audit on participants who attended an educational program in their earlier 2005 study (*n*=48). While weight loss was significant at 3 months of following a LCD (mean -2.5 kg), weight loss became insignificant after 4 years. This may be largely due to the high rate of non-compliance at 52% (*n*=25), where A1c reverted (6.5 ± 0.8% (3 months) to 7.4 ± 0.9% (4 years)) after 2 years of following the diet. The mean BMI of the sample at 4 years post-intervention was 25.7 ± 3.8 kg/m^2.

Weight was also assessed in the randomized trials by Kreb *et al.* [53] and Schmidt *et al*. [54]. Kreb *et al.* found no significant weight changes between the LCD group and standard CHO-counting group, however Schmidt *et al.* found a significant weight loss when individuals were on a LCD compared to a HCD. In the RCT by Kreb *et al.*, participants had a mean weight change of -1.9 kg on a LCD and +2.7 kg on a HCD at 3 months. While mean weight loss of 5 kg was considered non-significant, mean BMI was reduced from 27.5 ± 2.2 kg/m^2 to 25.8 ± 1.0 kg/m^2 in the LCD group, while the mean BMI of the control group remained relatively stable at 27.6 ± 6.1 kg/m^2 (mean change -0.1 kg) after 3 months. In Schmidt *et al.*'s cross-over study, the mean baseline BMI of the sample was 25.0 kg/m^2, however they did not report BMI post-intervention. Notably, inclusion criteria of the study limited participants to those with a BMI of 20 to 27 kg/m^2 which limits the generalizability of their findings to non-obese individuals.

Across the 4 studies, the effect of LCDs and KDs on long-term weight loss in adults with T1D remains inconclusive, thus the need for longer-term intervention studies. In addition, measuring dietary compliance may be an important consideration for future studies as poor compliance may skew results, as shown by Nielsen *et al.* [57] and Kreb *et al.* [53]. Lastly, in 3 of the 4 studies that reported BMI, these studies confirm that adult T1D populations appear to be

overweight, thus further emphasizing the need for weight loss interventions in managing diabetes and preventing long-term complications.

2.2 LOW-CARBOHYDRATE DIETS IN TYPE 2 DIABETES

The literature investigating LCDs in T2D is considerably more extensive and rigorous than it is for T1D. There is a paucity of RCTs in T1D, whereas several RCTs exist in T2D which assess various degrees of CHO-restricted dietary interventions and allow for meta-analyses to be conducted [65-67]. The most recent meta-analyses were conducted in 2021 by Goldenberg *et al.* [65], and in 2018 by McArdle *et al.* [66] and Sainsbury *et al.* [67].

Goldenberg *et al.* conducted a systematic review and meta-analysis evaluating the efficacy and safety of LCDs and KDs for T2D remission [65]. Further, McArdle *et al.* conducted a systematic review and meta-analysis which assessed KDs (20-50 g/day) and LCDs (<130 g/day) in comparison to moderate-CHO (130-225 g/day) or high-CHO (>225 g/day) diets in T2D [66]. Sainsbury *et al.* conducted a similar meta-analysis, however with emphasis on classifying dietary interventions by short-term (3 and 6 months) and long-term (12 and 24 months) durations [67].

2.2.1 Glycemic Control

Recent meta-analyses have concluded that there is no significant effect of CHO restriction on A1c. CHO-restricted dietary interventions (LCDs and KDs) ranged from 3 months to 2 years; with few studies evaluating outcomes beyond 1 year [68-70]. In a sub-analysis by McArdle *et al.* [66], the weighted mean difference (WMD) of A1c was clinically significant at -0.49% in 5 RCTs (*n*=229) assessing LCDs of 50 to 130 g/day CHO with a duration ≤6 months or outcome measurements at 6 months, with similar findings observed by Sainsbury *et al.* [67]. Whether these reductions can be maintained or not remains uncertain, as earlier reviews demonstrate improvements in A1c at 3 or 6 months which reverted after 12 months [67, 71-73]. Furthermore,

a major limitation observed in the RCTs was poor dietary compliance to prescribed CHO quantities in LCDs or KDs. In addition, the lack of isocaloric study arms, differences in baseline A1c, and adjustments to diabetes medications (OHAs) may also confound changes observed in A1c [66].

2.2.2 Lipid Profile

Several recent meta-analyses have assessed lipid profile as a secondary outcome [65-67, 72, 74, 75]. Analyses were limited due to incomplete blood lipid data provided by some RCTs. Overall, CHO-restricted diet groups were observed to significantly augment HDL-c [66, 67, 72, 74] and lower TG [65, 72, 74] compared to moderate-CHO or low-fat diet groups. Conversely, the findings on LDL-c are inconsistent among these meta-analyses. Two meta-analyses [72, 75] found no significant difference in LDL-c when comparing LCDs and low-fat diets, whereas two other meta-analyses [65, 76] and one recent systematic review [77] observed significant increases in LDL-c in LCDs or KDs when compared to low-fat or moderate-CHO diets.

2.2.3 Weight Loss

Recent meta-analyses have demonstrated a non-significant effect of CHO-restricted diets on weight long-term [65-67, 75]. However, sub-analyses by McCardle *et al.* [66] and Sainsbury *et al.* [67] found significant between-group differences in weight loss, favouring CHO-restricted diet groups at 3 months. This superiority however was not maintained long-term, as sub-analyses at 6 and 12 months showed no significant differences in weight loss between CHO-restricted and moderate-CHO diets [67]. These findings are largely supported by previous other meta-analyses [72-74, 78, 79].

There are important methodological limitations of the RCTs included in these meta-analyses, notably the differing energy intakes between study arms. Many of the LCD or KD interventions were hypocaloric compared to the control diet, which may explain weight differences [66]. Moreover, the majority of trials did not report or adjust for physical activity levels in their analysis which may also confound weight changes [66]. Lastly, poor long-term dietary compliance to LCDs or KDs has been demonstrated in many RCTs, thus whether or not significant weight loss achieved by CHO-restricted diets can be maintained is debatable [76].

2.2.4 Diabetes Medication

In meta-analyses conducted by Goldenberg *et al.* [65] and Sainsbury *et al.* [67], changes in diabetes medication use were assessed as a secondary outcome. Overall, LCDs showed clinically significant reductions in dosage of OHAs and/or insulin, or cessation of one or both of these medications. These findings remain evident despite difficulties in comparing studies due to inconsistencies in measurement or reporting of medication use. However, the majority of RCTs either did not report usable data or did not permit medication reduction during the trials, thus the analysis was limited to less than half of the RCTs included [65, 67].

CHAPTER 3

Manuscript 1

Ketogenic Diet as a Normal Way of Eating by Adults with Type 1 and Type 2 Diabetes: A Qualitative Study

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KEY MESSAGES

- Adults with diabetes who experience positive outcomes from the ketogenic diet are motivated to follow it long-term.
- Despite the lack of safety information available, health care professionals are encouraged to actively listen, remain non-judgemental, and inform patients who wish to follow the ketogenic diet.

ABSTRACT

Objectives: There are currently no recommendations on following the ketogenic diet (KD) in the context of diabetes and, therefore, health-care professionals may not be comfortable in supporting this dietary regimen. In this qualitative study, we aim to understand the perspective of patients with diabetes when following the KD, particularly with regard to reasons for starting the diet, motivators, support systems, sources of information, and challenges.

Methods: Adults diagnosed with type 1 or type 2 diabetes who followed a KD for ≥3 months were recruited for inclusion in this study. Semistructured interviews were conducted, audio recorded, and transcribed. Themes were analyzed using concept mapping until theme saturation was achieved.

Results: Participants were 54.5 (standard deviation 10.1) years old, on average, and had been following the KD for 6-19 (median 5) months; 43% were male and 79% had type 2 diabetes. The main motivation to start the diet was to improve blood glucose control or to reduce/stop taking diabetes medications, followed by weight loss and diabetes reversal. Participants reported benefits of the diet, such as improved glycemic control, weight loss, and satiety, which appeared to strongly prevail over challenges, such as lack of support from health-care professionals and lack of information sources. Most participants expressed the KD as a normalized way of eating that they would continue for the rest of their lives. **Conclusion:** A wide range of reported benefits, either expected or that emerged, strongly motivated individuals to follow the KD despite the lack of safety information and/or support. Further studies are needed to establish guidelines that health-care professionals can use to provide direction for individuals with diabetes who wish to follow the KD.

RÉSUMÉ

Objectifs : Il n'existe aucune recommandation sur le régime cétogène (RC) dans le contexte du diabète. Par conséquent, les professionnels de la santé ne sont pas à l'aise de conseiller ce régime alimentaire. Dans la présente étude qualitative, notre objectif est de comprendre le point de vue des patients diabétiques sur le RC, notamment les raisons de le commencer, les motivations, les systèmes de soutien, les sources d'information et les enjeux.

Méthodes : Pour cette étude, nous avons recruté des adultes ayant un diagnostic de diabète de type 1 ou de type 2 qui suivaient le RC depuis 3 mois. Nous avons mené des entrevues semi-structurées que nous avons enregistrées et transcrites. Nous avons analysé les thèmes au moyen de la cartographie conceptuelle jusqu'à leur saturation.

Résultats : Les participants avaient en moyenne 54,5 (écart type 10,1) ans et avaient suivi le RC durant 6 à 19 (médiane 5) mois; 43 % étaient des hommes et 79 % avaient le diabète de type 2. La principale motivation à commencer le régime était l'amélioration de la régulation de la glycémie, ou la réduction ou l'arrêt de la prise de médicaments contre le diabète, ainsi que la perte de poids et la régression du diabète. Les participants ont rapporté les avantages du régime tels que la régulation de la glycémie, la perte de poids et la satiété, qui semblaient fortement l'emporter sur les enjeux comme le manque de soutien de la part des professionnels de la santé et le manque de sources d'information. La plupart des participants considéraient qu'il était normal de suivre le RC et qu'ils pourraient le poursuivre pour le reste de leur vie.

Conclusions : Le large éventail d'avantages rapportés, soit escomptés ou nouveaux, a fortement motivé les individus à suivre le RC en dépit du manque d'information ou de soutien sur l'innocuité, ou les deux. D'autres études sont nécessaires pour établir des lignes directrices que les

professionnels de la santé pourront utiliser pour donner des conseils aux individus diabétiques qui souhaitent suivre le RC.

INTRODUCTION

Over the past decade, there has been increased interest in the ketogenic diet (KD) as a quick and effective weight loss strategy [1]. The KD was originally proposed by physicians in the 1920s as a treatment for drug-resistant epilepsy in children, which remains the only validated clinical indication to date [2]. The KD is defined as a very-low carbohydrate (<50 g/day or <10% of daily energy intake), high-fat (>75% of total energy) diet that induces nutritional ketosis. Ketosis is the metabolic formation of ketone bodies by the liver, which occurs when the body shifts its primary fuel source from carbohydrates to fatty acids in response to a scarce supply of glucose. Ketosis induced by the KD is hypothesized to have an appetite suppressing effect, which has prompted many individuals to try this diet to lose weight [3]. The KD is primarily composed of high-fat foods such as meat, poultry, fish, eggs, nuts and seeds, and foods that are abundantly seasoned with oils, mayonnaise, and full-fat dairy products. Grain products, fruits, starchy vegetables, sugar-containing beverages, and foods with added sugars are avoided. Due to these restrictions, multivitamin supplements are recommended to prevent nutritional deficiencies [4].

The KD has also gained interest in the diabetes community, particularly for its effect on blood glucose and weight. Several studies have shown positive health outcomes in individuals with diabetes who have followed the KD such as weight loss, improved glycemic control, and decreases in medication dosages [5-7]. In a systematic review and meta-analysis of nine randomized-controlled trials, pooled results suggest that very low/low-carbohydrate diets (<130 g/day) were associated with significantly reduced glycated hemoglobin and short-term weight loss compared with high- or normal-carbohydrate diets [6]. Moreover, significant reduction or cessation of diabetes-related medication doses were observed in overweight or obese individuals with type 2

diabetes in 2 studies [7, 8]. Despite the significant increase in the literature investigating the KD in diabetes, the long-term safety and efficacy of this dietary approach remain unknown.

To date, there is no research on the long-term risks and benefits for individuals with diabetes following the KD. For any diet that restricts certain food groups, such as the KD, there is the risk of developing nutritional deficiencies, such as vitamin B-complex, vitamin D, beta-carotene, calcium, and antioxidant deficiencies. Furthermore, individuals who are taking insulin or medications that may cause hypoglycemia need to be cautious when following this diet [9]. Moreover, the consequences of following a high-fat diet such as the KD on lipid profiles are not well known and represent a major concern, especially when the lifetime risk of cardiovascular disease is higher in individuals with diabetes compared to those without diabetes [6, 10]. In addition, one can argue that this diet is not suitable in the context of a chronic disease such as diabetes, in which the diet is part of the treatment and needs to be followed for life.

Currently, there are no clinical recommendations to support the use of the KD in the context of diabetes. Consequently, health care professionals (HCPs), such as physicians, nurses, and dietitians, may not be comfortable in supporting the use of this diet upon being confronted by patients who wish to try it. A greater understanding of the patients' experience with the diet could help them support and guide their patients in making their decision. The current literature gives us insight on the potential clinical outcomes and health benefits of the KD but does not provide information about the participants' experience, such as motivation to start the diet, support systems, challenges in adhering to the diet, side effects, and reasons for discontinuation. Furthermore, it is not well known where individuals obtain their information on the KD, and it is unclear whether they are getting their information from non-reputable sources or from HCPs. In

addition, it remains unclear whether or not individuals on the KD are being supported or monitored by their HCPs. Our objective in this study was to better understand the experience of individuals with diabetes who have followed or are currently following the KD.

METHODS

Study Design and Recruitment

This was a descriptive qualitative cross-sectional study using semistructured interviews to explore the experience of individuals living with diabetes who have followed or follow the KD. The study was reported according to the Consolidated Criteria for Reporting Qualitative studies checklist.

A combination of purposive and convenience sampling was used. Potential participants were recruited through advertisements at endocrinology clinics, in online advertisements on social media platforms (e.g. Facebook), on websites of diabetes' organizations (e.g. Diabète Québec), and through word of mouth. Inclusion criteria included being 18 years or older, living with type 1 or type 2 diabetes, and having followed the KD for at least 3 consecutive months. Exclusion criteria were: inability to speak English or French and inability to meet for an in-person interview. Potential participants were screened through a 10-minute telephone call after completing an eligibility questionnaire that included a 24-hour dietary recall or usual intake to estimate adherence to the KD (daily intake of carbohydrates <50 g/day). A sample target of 10 to 15 participants was estimated to reach a saturation of information in the interviews. Eligible participants were then recontacted to schedule an in-person interview.

Data Collection

Setting

Semistructured interviews were conducted in-person in Montréal, Québec, at a location convenient for the participant (e.g. home, workplace, or coffee shop) during the summer and fall

months of 2018. Two researchers were present for the interview: the interviewer (a dietetics student trained for interviewing), and a registered dietitian (with experience in clinical diabetes). Written informed consent was obtained and background information was collected by all participants before conducting the interview. Background data was collected through a short questionnaire that included demographic characteristics and anthropometrics (e.g. weight history) as well as past dieting history.

Interview Structure

The interview guide was composed of 4 main topics of open-ended questions to direct the discussion (Supplementary Appendix). The interview guide was developed by clinicians based on patient interactions, and then reviewed by an external group of dietitians and endocrinologists and sequentially pilot-tested. Semistructured interviews were preferred to allow for a free-flowing, 2-way conversation in which the interviewer could guide the conversation, but diverge from the script when necessary, and the participants could discuss the proposed topics or share their experiences at liberty [11]. Interviews averaged 33.5 (standard deviation [SD] 7.8) minutes in duration and were audio-recorded and transcribed verbatim within 24 hours. Narrative accuracy checks were completed by a second researcher.

Data Analysis

The interview transcripts were analyzed through inductive thematic analysis and concept mapping. Each transcript was coded individually by 2 researchers using NVivo (QSR International, Melbourne, Australia), a data management software program, in which each idea or concept is

coded, and recurrent codes are further analyzed into categories and themes. The first three transcripts were coded as part of the initial coding process, in which both researchers met to discuss preliminary codes that had emerged to ensure uniformity and to establish a base framework of codes. Following the coding of 10 transcripts, the researchers met again and used concept mapping to categorize the codes and discuss emerging themes. Concept mapping is a visual conceptualization process that reduces interview data into themes and patterns, which allows for a better understanding of the meaning and interconnections within the data [12]. Researchers met for a third and final time once the remainder of the interviews were analyzed. Once data saturation was obtained, recruitment was terminated and researchers conducted a second round of concept mapping to establish the final themes and categories. After analysis of the interviews, a focus group session was held with HCPs experienced in diabetes care, including 2 physicians, 2 nurses and 5 dietitians, to validate the categories and themes and ensure cohesiveness.

RESULTS

The sample consisted of 14 participants (6 men, 8 women), most living with type 2 diabetes (78.6%). **Table 1** presents the participant characteristics. The average age was 54.5 (SD 10.1) years. Twelve participants (85.7%) were overweight or obese before the diet (body mass index ≥ 25 kg/m^2). Ten participants (71.4%) had previously attempted at least 1 other diet in the past, ranging from 1 to more than 6 diets. Twelve participants were following the diet at the time of the interview, 11 of whom were monitoring their ketones, with an average daily carbohydrate target of 22 (SD 12) g/day. Participants followed the diet for a median duration of 5 (range 3 to 19) months.

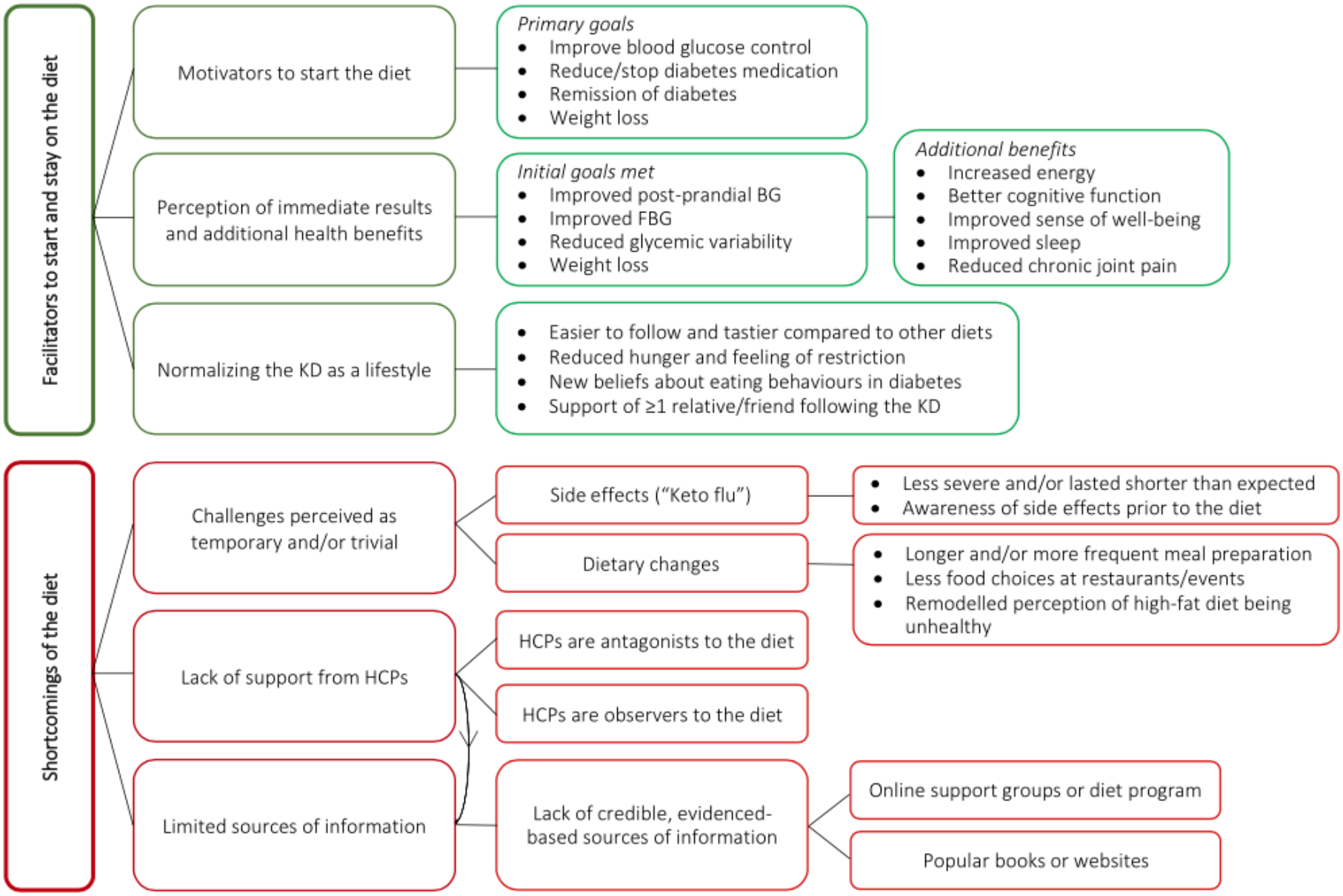
Six themes emerged from the analysis of the transcripts, and these themes were separated into two main categories: (I) Facilitators to start and stay on the ketogenic diet, and (II) Shortcomings of the ketogenic diet (**Figure 1**). Examples of themes are reflected through direct quotes from participants (**Table 2**).

Table 1 - Participants' Characteristics

Sample size, n	14 participants
Age, years, mean (SD)	54.5 (10.1)
Sex	
Males	6 of 14
Females	8 of 14
BMI before starting the KD, kg/m^2, mean (SD)	31.5 (5.1)
Overweight/obese (BMI >25kg/m^2)	12 of 14
Race	100% Caucasian
Type of diabetes	
Type 1	3 of 14
Type 2	11 of 14
Daily carbohydrate intake target, g/day, mean (SD)	22 (12.3)
Daily target <20 g/day	10 of 14
Following the KD at the time of interview	12 of 14
Followed at least 1 diet in the past	10 of 14
Monitoring ketones at the time of interview	11 of 14
Duration of the KD, months, median and range	5, range 3-19

Abbreviations: *BMI*, Body Mass Index; *KD*, Ketogenic Diet

Figure 1 - Schematic Representation of Different Themes



Abbreviations *BG,* Blood glucose; *FBG,* Fasting blood glucose; *HCP,* Health-care provider; *KD*, Ketogenic diet

Table 2 - Quotes from Participants' Interview Transcripts

Categories	Themes	Quotes
Facilitators to Start and Stay on the Ketogenic Diet	**Motivators to Start the Diet**	*So that's the main reason; it was to control my diabetes.* (Participant 8, 53-year old male, Type 2 diabetes) *The personal motivation [to start the diet] was to reverse diabetes, to stop taking medication and weight loss.* (Participant 10, 68-year-old male, Type 2 diabetes)
	Experience of Immediate Results and Additional Health Benefits	(When asked what keeps them on track with the diet) *"Results. Knowing that it works. Seeing blood results that were going into normal range. It felt good. It was like I'm doing the right thing."* (Participant 5, 50-year-old woman, Type 2 diabetes) *We decided to start the diet in February, and already after 3 days, I started skipping my medication, half a pill in the morning, and half a pill in the evening. After 2 weeks I stopped taking anything.* (Participant 2, 55 year-old male, Type 2 diabetes) *We saw impressive results, related to our level of attention, concentration, and in how we manage our emotions.* (Participant 3, 46-year-old female, Type 2 diabetes) *I felt [the effects of the diet] pretty quickly. Fairly quickly in the joints and inflammation. Just to give you an example, there were exercises that I couldn't do anymore. And that came back.* (Participant 10, 68-year-old male, Type 2 diabetes) *Since I started the ketogenic diet, it's.. it's drastic the difference. Normally at meals, I would take between 14 and 16 units of insulin with each meal. (…) With the ketogenic diet, and also with intermittent fasting, when I eat, I normally give myself between 4-6 units. So it's 4 times less.* (Participant 14, 41-year-old male, Type 1 diabetes)

	Normalizing the Ketogenic Diet as a Lifestyle	*The taste is good. It's easy to eat this way. You are not hungry. We had a period of adaptation that maybe took one month or a month and a half. […] It's been 50 years that they tell us that [fat] is not good. But when you read well about it, it's sugar that is the poison, it's not fat. So [the ketogenic diet] is easy.* (Participant 2, 55-year-old male, Type 2 diabetes) *I went full force, it was... it was pretty incredible because.... you weren't---* *I was not hungry the way I would if I eat carbohydrates.* (Participant 5, 50-year-old female, Type 2 diabetes) *After my 2nd pneumonia, I ... I gave myself the chance to stay alive in the best possible condition. Then in that, I'm ... really very very very happy to be ketogenic. I know I will never go back to carbs again.* (Participant 7, 52-year-old female, Type 2 diabetes)
Shortcomings of the Ketogenic Diet	Challenges Perceived as Temporary and Trivial	*What I found most difficult part at the beginning was changing our paradigms of all of our beliefs about nutrition.* (Participant 3, 46-year-old female, Type 2 diabetes) *Not really, sometimes you get in a rut that you're eating the same thing everyday and you get fed up of that, and then you try something else, then you get in that rut. But it's fine, it's easy, it's not difficult*. (Participant 1, 67 year-old male, Type 2 diabetes) *When I see my family… I know that there will be plenty of carbs, so I will eat cheese and vegetables. And the nice thing about the ketogenic diet is that I'm not hungry, so I can eat less, just eat a bit socially and it's going to be alright.* (Participant 7, 52-year-old female, Type 2 diabetes)
	Lack of Support from Health-Care Providers	*[My friends and family] disapprove [of the diet]. Even those who work in the healthcare system really disapprove.* (Participant 10, 68-year-old male, Type 2 diabetes)

		I can no longer trust my doctors. They should have told me since the beginning that if I do not eat sugar, I will not become diabetic. Why didn't they tell me? (Participant 11, 77-year-old male, Type 2 diabetes)
	Limited Sources of Information	*I read the book by Jason Fung … Then, I read a book that was called The Ketogenic Bible, since you can find it easily on the internet. There is also a website called Plumette in France…* (Participant 10, 68-year-old male, Type 2 Diabetes) *I mostly went on internet, listened to conferences by Jason Fung, I read books… his book the Obesity Code, you should read that….I do a lot of research on my own.* (Participant 11, 77-year-old male, Type 2 diabetes) *Yeah, a Facebook group called Type 1 Diabetes Quebec, I often read publications there… On there, some people posted an article that came from another website that was related to the website 'Long Live Bacon'…* (Participant 4, 43-year-old female, Type 1 diabetes)

Facilitators to Start and Stay on the Ketogenic Diet

Motivators to Start the Diet

Participants were asked about their personal motivations for starting the diet. Most participants expressed concerns about their health and responded that their primary goal was to improve their blood glucose management, and some participants with type 2 diabetes mentioned hope for remission of diabetes. For others, the primary goals were to decrease their dose of diabetes-related medication, and/or weight loss. Primary motivators were similar among participants with type 1 and type 2 diabetes, except for diabetes reversal, which was only expressed by participants with type 2 diabetes. One participant noted:

> *"For me, it's really because of my diabetes… honestly it was the only reason to start."* (Participant 9, 41-year-old woman, Type 2 diabetes)

Perception of Immediate Results and Additional Health Benefits

Participants expressed feeling immediate results which were related to their primary goals. They reported positive effects on blood glucose levels, such as reductions in fasting blood glucose, postprandial blood glucose, and blood glucose fluctuations. Consequently, some participants reported reductions in their dose of diabetes medication, either as self-prescribed or as suggested by their physician.

> *"It's been 3 days that my blood sugar levels are below 7, either after a meal or when I wake up. In the morning, I used to be at 8.6-8.8-8.9, and all of a sudden I was below 7, simply be eating this way for 3 days."* (Participant 3, 46-year-old female, Type 2 diabetes)

Beyond experiencing benefits related to their primary goals, most participants mentioned additional health benefits of following the KD. Some participants reported improvements in

cognitive abilities, most often in areas of concentration. Others indicated a reduction in chronic pain levels that were most often related to inflammation and arthritis. Other perceived benefits included an increase in overall well-being and energy levels and an improvement in quality of sleep.

Many participants expressed that the immediate experience of the positive results affirmed their belief in the KD and motivated them to continue following the diet.

Normalizing the Ketogenic Diet as a Lifestyle

Many participants described having difficulty adjusting to the KD in the beginning, partly due to going against conventional belief that high fat diets are unhealthy. Many participants explained that it took time before they were able to shift their mindset from their previous conceptions of dieting and to be able to fully adopt the principles of the KD.

Participants explained that, in comparison to other diets they had tried in the past, the KD was easier to follow, tastier, and overall more enjoyable. Almost all participants reported not feeling hungry on the KD and as a result, some mentioned that they would naturally progress to intermittent fasting. Many participants did not consider being on a diet, as previous diets made them feel hungry and felt restrictive and unsustainable. Some participants stated that they were less preoccupied with the thought of food and described an overall improved experience with food.

Following the KD prompted participants to develop new beliefs concerning what they consider as a healthy diet for people with diabetes. They claimed that the diet could heal diabetes and other negative symptoms, such as joint pain and migraines. They assigned new meanings to

"sugar," claiming that sugar was a poison, a drug and/or an allergy. These characteristics ultimately made them feel that the KD was a normal way to eat and that it was a suitable lifestyle rather than a short-term diet.

Shortcomings of the Ketogenic Diet

Challenges Perceived as Temporary and Trivial

Participants were faced with challenges when going out to eat at restaurants or at friends' or family's houses, where there are limited food choices consistent with the strict requirements of the KD. In addition, participants reported the challenge of adjusting to more meal preparation. Despite these changes to their daily lives, participants appeared to overcome these challenges over time by adjusting their routine, such as bringing their own "keto-friendly" meals to social events or choosing restaurants that offer wider selections that fit their dietary requirements.

Some participants reported side effects of the "keto flu" at the beginning of the diet. "Keto flu" is described as flu-like symptoms that occur within the first weeks of implementing the diet, such as nausea, vomiting, fatigue, headaches, and hypoglycemic episodes [13]. Participants reported experiencing fatigue, headaches, dizziness, and constipation. Almost all participants reported being aware of these side effects before starting the diet – with many reporting side effects to be less severe and lasting shorter than expected. Participants also reported elevated cholesterol levels or no change in their cholesterol levels, but did not seem concerned by this outcome. Overall, all the negative side effects were not perceived as barriers to continuing the diet.

Despite the challenges of adjusting to a new way of eating and its initial side effects, participants often found these challenges to be temporary and/or trivial. The challenges that were present at the beginning of their diet were no longer perceived to be so at the time of the interview. Participants appeared to adjust their lifestyles to fit the diet, as the perceived benefits appeared to override any challenges of following the diet.

> *"At the restaurant, it's quite simple. Because you know uh ... a steak with a salad, it's super good and ... it's fine. There is always something in the menu which is accessible [for a ketogenic diet]. (…) I don't find it difficult."* (Participant 4, 43-year-old female, Type 1 diabetes)

The two participants that were not following the diet at the time of the interview both expressed an intention to restart the diet in the future. Reasons for discontinuing the diet were personal stressors or an active, on-the-go lifestyle, which affected their ability to fully devote and comply with the diet. Ultimately, these participants viewed these challenges to be minor, compared to the benefits of following the diet.

Lack of Support from Health Care Providers

Almost all participants reported having support from at least one close family member within their household, who sometimes would also follow the KD. Some received encouragement from friends and co-workers. Many participants received support from Facebook groups, made up of other individuals on the KD, which serves as a place to ask questions, share recipes and individual experiences, and help motivate each other.

Many participants reported a lack of support from their HCP, mainly their physicians. Most frequently, participants expressed that their HCP acted as an antagonist to the diet, often

dismissive and discouraging to the participants. Some HCPs offered no support in terms of information, guidance, or structured follow-up for their patients on the KD.

> *"Absolutely not. My doctor is one of those "by the book", in fact I'm just changing, but she's by the book and "one size fits all," you know? Like a lot of them are. So I don't even tell her."* (Participant 1, 67-year-old female, Type 2 diabetes)

Some participants revealed that their HCP acted more as observers. The HCPs were impressed with the blood glucose results and encouraging about the diet but offered no professional guidance in terms of information, evaluation of risk and benefit of the diet, or follow ups specific to the diet.

Limited Sources of Information

Due in part to the lack of support from their HCPs, participants reported having limited sources of information that were credible and evidence-based. Participants mentioned the same sources of information (books, websites, and social media networks) repeatedly and were often recycled. No sources from health authorities seemed to be available or referenced. Some participants paid to be enrolled in a program offered by a private clinic promoting the KD, where they received support from a physician and a kinesiologist.

DISCUSSION

The main objective of this study was to better understand the experiences of individuals living with diabetes who were successful in following the KD for at least 3 months. The overall experience of the participants was positive, where benefits of the diet appeared to strongly outweigh the challenges.

The participants' experience of following the KD appeared to emphasize facilitators over challenges incurred with the diet. Participants experienced immediate positive health results after starting the KD, which were all related to their primary goals such as improved glycemic control, diabetes medication reduction, and weight loss. Similarly, in a recent randomized-controlled trial investigating a KD program in obese individuals with type 2 diabetes, Morris *et al.* reported that a strong motivator for participants to follow the diet was the potential to reduce or stop medications [14]. Participants reported improved motivation and confidence upon seeing initial rapid results, such as improvements in blood glucose, blood pressure, emotional and psychological well-being, and appearance. The results served as a continuing motivator for these participants [14]. This sense of increased self-efficacy, as observed by Morris *et al.* as well as in the current study, may explain in part why participants predominantly expressed positive experiences of following the diet. According to the social cognitive theory and as observed in other studies, people who experience high self-efficacy in lifestyle change are more likely to identify facilitators than barriers to change [15, 16].

The benefits expressed by the participants, including increase in psychological well-being and satiety when following the KD, are similar to what has been described in other studies on the KD in diabetes. Two studies that investigated the KD as a weight-loss strategy and its effect on

quality of life in overweight or obese individuals showed notable improvements in psychological well-being after following the diet for 4 or 6 months [17, 18]. Both studies hypothesized this improvement to be partly attributed to decreased levels of hunger when following the KD. A possible correlation between satiety and well-being when following a KD may also be suggested in this study alike, as participants who expressed high levels of satiety also reported improved overall well-being. Other benefits, such as reduced appetite and improved energy levels and well-being, were also reported in an 8-month, low-carbohydrate diet trial in individuals with type 2 diabetes and pre-diabetes [19].

Another facilitator for staying on the diet was the experience of reframing. Participants expressed that it was challenging at the beginning to consume high fat foods, which went against their conventional beliefs of what constitutes a healthy diet. However, as time passed by, they discerned characteristics of the KD that were beneficial to their health. These characteristics included but were not limited to weight loss, improvements in glycemic control, levels of energy, and quality of sleep, as well as reductions in diabetes medication doses and chronic pain. These perceived health benefits enabled them to shift their concept of a healthy diet for diabetes; ultimately, they felt that the KD was a normal way to eat and a suitable diet for their diabetes, rather than a short-term diet. This shift in paradigm and reframing is also apparent and a key to success for long-term maintenance of healthy behavior change in people who attempt diets for weight loss [20].

Participants often described the challenges they faced on the diet as temporary or trivial, and not enough to incur frustration and derail the diet. This contributed to the overall positive experience of the diet, where challenges were of little importance. Although some of these

challenges were innocuous (fewer food choices at restaurants, more meal preparation), some were potentially harmful, such as loss of hunger, prolonged fasting, constipation, "keto flu" symptoms, and reported elevated cholesterol levels. Participants appeared to be more preoccupied with the benefits of the diet that they did not acknowledge or report concerns for its possible long-term side effects.

The shortcomings of the KD in this study are predominantly the lack of support from HCPs, namely physicians and dietitians, and having limited sources of information. Indeed, participants reported receiving little to no support from their HCP and described their HCPs as antagonists or observers to their diet. Despite these challenges, participants continued to follow the diet and were inclined to find other sources of information and support. This perspective further emphasizes the need for HCPs to support their patients on the KD despite the absence of strong scientific evidence, as individuals are strongly motivated to continue to follow the diet with or without their support. Moreover, if patients do not feel supported by their HCPs, they are forced to search for other resources, some which may be disreputable. In the recently published position statement on low-carbohydrate diets, Diabetes Canada recommends that HCPs support their patients who wish to follow a low-carbohydrate diet, as this may help with adoption of a healthier KD that is also more culturally appropriate and aligns with individualized values, preferences, needs and treatment goals. HCPs can support their patients by making appropriate recommendations or changes to their diabetes management, and can properly inform individuals on how to reduce adverse effects and nutritional deficiencies [21].

This qualitative study adds to the previous literature by offering insights on the motivators, facilitators and shortcomings of patient's experience with the KD. The participants recruited in this

study have chosen to follow this diet. However, our findings may be limited in generalizability, due to the inclusion of only Caucasian participants. Selection bias may also limit external validity, as participants included in the study were exclusively those who were successful in following the diet. Furthermore, the interviews did not include the perspective of confounding factors such as physical activity level, an important factor to consider in blood glucose and weight management.

The long-term safety and efficacy of the KD in individuals with diabetes remains unknown, notably its effect on cardiovascular risk factors and frequency of hypoglycemia [6, 10, 22]. Further long-term studies with strong methodologic rigour, such as randomized, controlled trials, on the KD in the context of diabetes are required in order to establish safe, effective recommendations. As interest in the KD continues to rise, HCPs can still engage with their patients who are motivated to follow the KD by providing guidance and regular follow up.

CONCLUSION

In conclusion, we found that participants expressed a strong desire and motivation to follow the KD on a long-term basis. Many of the participants described the KD as a lifelong way of eating. When people have success at adhering to a diet after 3 months, they develop high self-efficacy and reframe their experience as positive [18]. This sense of self-efficacy, success in attaining the goals of their diet, and experiencing additional benefits of the KD appeared to strongly overrule the challenges of lacking support from their healthcare team and of the lack of informational resources on the KD.

Despite the lack of strong scientific evidence to support the use of KD in the context of diabetes, researchers remind HCPs to actively listen, remain open-minded, and collaborate with their patients if they intend to follow a KD. HCPs are encouraged to present evidence-based information to help patients in making informed decisions, guide them to safely initiate or discontinue the diet, and ensure regular follow up and monitoring of their care.

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AUTHOR DISCLOSURES

Conflicts of interest: None.

AUTHOR CONTRIBUTION STATEMENT

K.W., A.F-R, and A.-S.B. contributed to the design and implementation of the research. K.W. and M.R. were involved in data collection and analysis and drafting the initial manuscript. All authors were involved in critically revising the manuscript and approval of the final draft.

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SUPPLEMENTARY APPENDIX

Semi-Structured Interview Guide for Participants

1. REASONS TO START

   Why are/were you interested in starting a ketogenic diet?

   Probes

   - What is your personal motivation for starting this diet?
   - How did you hear of the ketogenic diet?
   - Have you been advised by a doctor to lose weight or improve a specific health marker?
   - Have you tried other diets? If yes, which kinds?:
     - Paleo, high CHO low fat, low CHO, high protein, Atkins, Whole 30, Mediterranean, South Beach, Weight Watchers, Vegetarian…
     - What was your experience with those diets?

2. KNOWLEDGE OF THE KETOGENIC DIET

   How did/do you obtain information on the ketogenic diet?

   Probes

   - Where did you find information about the ketogenic diet?
   - Where do you find keto recipes?
   - Do you receive support from a HCP? If so, who is it (e.g. dietitian, doctor, etc.)? What was your experience with discussing the ketogenic diet with your HCP? Was your HCP supportive?
   - Are you a part of support groups on social media (e.g. Facebook, forums, etc.)?
     - If so, are these helpful to you?
       - If yes, how does it help you (e.g. keeps you motivated, helps you to try new recipes, etc.)
       - If no, why was it not helpful?

3. (Facilitators) MOTIVATING FACTORS & SOCIAL NETWORK

   What helped you stay on track with your diet?

   Probes

   - Do your friends and family approve, disapprove, or are indifferent about your diet? Why or why not?
   - Has your diet influenced people around you (family, friends, coworkers) to change their dietary habits?
   - Do you have days when you are less strict with your diet? Do you have days where you take a break from the diet entirely?

- What did you like about the diet? Do you think the diet had/has a positive impact on your health?

4. (Challenges) SIDE EFFECTS & REASONS FOR STOPPING

   Are you still on a ketogenic diet?

   If yes, what are some challenges that you face?

   If no, what are your reasons for stopping?

   Probes

   - Did you experience any of the keto flu symptoms?
     - Constipation, dizziness, headaches, nausea…
   - Were you aware of side effects of the diet prior to starting it?
   - Would you recommend this diet to a friend or family member?
   - Did the diet have an impact on your social life?
   - Is the diet more expensive, less expensive, or no different than before (e.g. your habitual diet)?

CHAPTER 4
Bridge

In Chapter 3, we established that in a small sample of adults with T1D and T2D, individuals are strongly motivated to follow a KD due to its perceived benefits and contribution to individual goals, such as glycemic control, weight loss, or reduction or cessation of diabetes medications. The qualitative study found that these benefits prevailed over self-reported challenges, including disapproval from HCPs, in which some participants reported not disclosing to their HCP that they were following a KD in fear of disapproval. This may have negative health repercussions as patients may receive less follow-up from their HCP, with particular concern in those living with T1D. People living with T1D or using insulin need to take caution when following LCDs due to the potential impacts on hypoglycemia and IAH as described in Chapter 2.1.1, which are still not fully understood. In Chapter 4, Manuscript 2 aims to explore associations with LCDs, glycemic control, and CV risk factors with the use of a LCD score to establish levels of CHO restriction in a sample of adults with T1D.

CHAPTER 5

Manuscript 2

Associations Between Low-Carbohydrate-Diet Score, Glycemic Control and Cardiovascular Risk Factors in Adults with Type 1 Diabetes

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ABSTRACT

Low-carbohydrate-diets (LCD; less than 30% of energy from carbohydrates) are gaining popularity in individuals with type 1 diabetes (T1D). However, the impact of such diet on glucose control and cardiovascular (CV) risk factors is debated.

Objective: To evaluate associations between LCD score, glycemic control and CV risk factors in adults with T1D using a registry in Québec, Canada.

Research Design and Methods: Cross-sectional study using 24-hour dietary recalls to calculate LCD scores, self-reported or measured anthropometric data including waist circumference, moderate and severe hypoglycemic episodes, impaired awareness of hypoglycemia (Clarke score ≥4) and biochemical data (HbA1c, LDL-cholesterol and non-HDL-cholesterol). Participants were divided into quartiles (Q) based on LCD scores.

Results: 285 adults (aged 48.2±15.0 years; T1D duration of 25.9±16.2 years) were included. Overall, participants reported low carbohydrate and fiber intakes and high fat intake compared to recommendations. Mean carbohydrate intake ranged from 31.2±6.9% (Q1) to 56.5±6.8% of total energy (Q4). Compared to Q4, more people in Q1 reported HbA1c ≤7% (Q1: 53.4% vs Q4: 29.4%; *P*=0.011). Compared to Q3, more people in Q1 reported no history of severe hypoglycemia (Q1: 60.0% vs Q3: 31.0%; *P*=0.004). There were no differences between quartiles for frequency of moderate hypoglycemia events (*P*=0.784), impaired awareness of hypoglycemia (*P*=0.269) and lipid profile: LDL-cholesterol (*P*=0.290) and non-HDL-cholesterol (*P*=0.118).

Conclusions: Low carbohydrate intake is associated with a higher probability of reaching HbA1c target and lower frequency of history of severe hypoglycemia, but not with moderate hypoglycemia frequency, impaired hypoglycemia awareness, nor CV risk factors.

INTRODUCTION

Strict glycemic control has been demonstrated to significantly decrease microvascular and macrovascular complications in type 1 diabetes (T1D) as observed in the landmark Diabetes Control and Complications Trial (DCCT) [1, 2]. Glycemic improvements were superior in the intensive insulin therapy group; however, this was also associated with an increased risk of severe hypoglycemia, weight gain, and abdominal obesity. Despite advancements in diabetes treatment and technologies seen today, the percentage of people living with T1D (PWT1D) reaching optimal glucose control still remains low [3] with a high incidence of hypoglycemia [4] and increasing rates of abdominal obesity and CV risk factors [1, 5]. In addition, carbohydrate (CHO) counting, a key component of intensive insulin therapy, remains a complex task prone to frequent errors leading to glycemic variability [6, 7]. Therefore, PWT1D are avidly looking for strategies to improve glucose control while reducing the burden of CHO counting and the risk of weight gain.

Recent meta-analyses have demonstrated benefits of following low-CHO diets (LCDs) in people living with type 2 diabetes (T2D) [8, 9], and have subsequently gained popularity among the T1D community. Many studies have evaluated the impact of LCDs in people living with T2D [8, 9], however the current literature is lacking evidence in the context of T1D. The few studies that exist have demonstrated improved glycemic control in PWT1D, however the majority of these studies are observational and limited in sample size [10, 11]. In a retrospective chart review of 48 participants following a low-CHO educational program, Nielsen *et al.* reported improvements in hemoglobin A1c (HbA1c) in participants with good adherence to a LCD [11]. In this subsample (*n*=23, 48%), significant HbA1c improvements observed at 3 months (mean change -0.7 ± 0.4%) were sustained over 4 years, resulting in a mean HbA1c of 6.9 ± 0.8% in adherent participants.

Similar improvements were found in 2 observational studies in which participants with T1D followed a very-low-CHO diet for over a year on average [10, 11]. In an online survey conducted by Lennerz *et al.*, mean HbA1c was 5.7 ± 0.7% in 316 respondents who followed the diet for a mean duration of 2.2 years [12]. Furthermore, Leow *et al.* demonstrated glycemic benefits in 11 participants who followed a very-low-CHO diet for a mean of 1.5 years, where blinded continuous glucose monitoring (CGM) revealed optimal HbA1c at 5.3 ± 0.4% [10]. This improvement was however associated with a mean rate of hypoglycemia (<54 mg/dl; 3.0 mmol/L) at 6.3 episodes per week, higher than average rates of 1-2 episodes per week observed in T1D populations [13].

There is no precise definition of a LCD, however literature suggests that LCDs are composed of <30% of energy from CHO or about 150 g of CHO per day [14]. Although Diabetes Canada's Clinical Guidelines suggest that CHO should represent 45-60% of daily energy [15], this recommendation varies worldwide [16]. In response to the high popularity of LCDs in the diabetes population, diabetes organizations have adapted their guidelines which state that LCDs may be suitable for people living with diabetes, given that patients consult their HCP in order to individualize recommendations based on goals and preferences [17-19]. Yet for PWT1D, the impact of adopting a LCD on hypoglycemic risk (severe and moderate), CV risk factors, obesity, and its android repartition is still largely unknown. Accordingly, many healthcare professionals may be reluctant to recommend these diets to people with diabetes due to lack of long-term evidence and information on their safety [20, 21]. Given the increased interest in limiting CHO intake for diabetes management, further evidence is needed on benefits and risks of adopting a LCD.

The impact of a LCD is not only defined by CHO intake, but dietary composition of fat and protein as well. The LCD score is a method to objectively measure the adherence of a LCD while

considering all proportions of macronutrients [22]. It has been used by several large cohort studies to assess the association of a LCD and chronic diseases, such as CV disease (CVD) [22-24] and risk of T2D [22, 25]. However, this methodology is yet to be used in a T1D population. Using 24-hour dietary recalls (R24H), individual LCD scores are computed according to CHO, fat, and protein intakes as a percentage of total energy. The current cross-sectional study aims to examine the associations between the LCD score, glycemic control, and CV risk factors in a sample of Canadian adults with T1D.

RESEARCH DESIGN AND METHODS

Study Design

The cross-sectional study collected baseline data from the BETTER Registry in Québec, Canada (https://www.maelstrom-research.org/study/better). To enroll, individuals ≥14 years old can self-register if they received clinical diagnosis of T1D or self-report LADA (latent autoimmune diabetes in adults), are living in the province of Québec, and are able to read French or English. Through online questionnaires, participants provide information on socio-demographics, clinical characteristics, treatment regimens, history of hypoglycemia, lifestyle habits, physical activity, and dietary intake (Supplemental Table S1).

For this study, inclusion criteria were adults (≥18 years old) with T1D who had completed a R24H from one of the registry's questionnaires. Exclusion criterion was pregnant women. Participants who reported dietary recalls of very low (<600 kcal for women, <650 kcal for men) and very high (>4400 kcal for women, >5500 kcal for men) energy intakes were excluded using cut-off criteria from the Automated Self-Administered 24-Hour (ASA-24) dietary assessment tool (26). Data available from February 2019 to April 2021 was used for this analysis.

Dietary Assessment

Dietary assessments using a validated, web-based R24H is based on an automated multiple-pass method inspired by methods developed by the United States Department of Agriculture (USDA) [27]. Food items, beverages and recipes are linked to a nutritional database sourced from the Canadian Nutrient File, and from the Nutrition Data System for Research from

the University of Minnesota when data was not available. All food items were also coded to enable automatic calculation for Canada's Food Guide's (CFG version 2007) food group servings.

Using a personal web link, each participant completed one R24H. Food items, beverages and recipes were selected by using the search tool or by browsing through 16 main categories and 98 subcategories. Portion-size images were available to help participants estimate their serving size for each item. Detailed nutritional values and CFG's food group servings were automatically extracted and summed up to assess daily dietary intake. Participants did not receive any direct feedback from their dietary assessment.

Calculation of the Low-Carbohydrate-Diet Score

LCD scores were calculated based on macronutrient intake from R24H. Participants were divided into 11 strata for each CHO, fat and protein intake, expressed as a percentage of total energy intake (Supplemental Table S2). A score of 0 to 10 points (11 strata) was given for each macronutrient for a total of 30 points. For CHO, participants with lowest intakes were given 10 points, and the next stratum received 9 points and so on, descending to the stratum with the highest CHO intake being given 0 points. For fat and protein intakes, the point allocation was reversed, such that the strata with the highest intakes of fat or protein were given 10 points, and the strata with the lowest received 0 points each. Points for each macronutrient were then summed to total the LCD score, ranging from 0 points (highest CHO intake, lowest fat and protein intakes) to 30 points (lowest CHO intake, highest fat and protein intakes). Participants were then divided into quartiles based on their LCD score.

Outcomes

Medical history, medication use, insulin treatment regimen, CGM use, and history of hypoglycemia-related events were self-reported by participants. Furthermore, hypoglycemia awareness was assessed by the Clarke method [28], using a score ≥ 4 to define impaired awareness of hypoglycemia (IAH). In a subsample of participants, laboratory tests of HbA1c, LDL-cholesterol (LDL-c), and non-HDL-cholesterol (non-HDL-c) were reported from participants' online health booklets (*Carnet Santé Québec, CSQ,* https://carnetsante.gouv.qc.ca/) if taken within the last 6 months. When HbA1c tests from CSQ were not available, self-reported HbA1c, expressed as a range, was used.

In addition, sociodemographic characteristics and self-reported information on total weekly physical activity (defined as doing activities for more than 10 minutes and that made one sweat a little and breathe harder and considered below recommendations if <150 min/week [29]), alcohol consumption (defined as active drinkers and considered above recommendations if > 9 drinks/week for women and 15 drinks/week for men [30]), and smoking status were collected. The recommended alcohol limit for women is 10 drinks/week, however alcohol consumption was reported in the registry as predefined ranges, thus 9 drinks/week was used as the cut-off instead.

Anthropometric Measurements

Anthropometric data was self-reported by participants, expressed in kilograms and meters. Body Mass Index (BMI) was calculated by dividing body mass (kg) by squared height (m^2) and rounded to the nearest 0.1 kg/m^2. Overweight is defined as BMI between 25.0-29.9 kg/m^2 and obese is defined as BMI ≥30 kg/m^2. To measure waist circumference (WC), participants were each

sent measuring tape, an instructional pamphlet and a link for a video on proper measuring technique using the superior border of the iliac crest as the anatomic reference. Abdominal obesity was defined as WC ≥88.0 cm for women or ≥102.0 cm for men [31].

Statistical Analysis

Statistical analyses were performed using SPSS (IBM Corp., version 27.0, Armonk, NY, USA). Participants' characteristics were expressed as mean ± SD for continuous variables and as a count and proportions for categorical variables, unless otherwise specified. Number of observations was specified when data for the variables were not available for the full sample.

A two-sided *P* value α-level of <0.05 was defined as statistically significant. For comparisons across quartiles, categorical variables were analyzed using Chi-squared (χ^2) or Fisher's Exact tests, and continuous variables were analyzed using One-way Analysis Of VAriance (ANOVA) tests. Sensitivity analyses (parametric and non-parametric analyses) were performed for all continuous variables. When outliers were identified, such as in total energy intake and symptomatic nocturnal hypoglycemia, Kruskall-Wallis tests were used instead. Binomial logistic regression models were used to analyze HbA1c and experience of severe hypoglycemia between all quartiles. Models estimated crude (unadjusted) and adjusted odds ratios (OR). For multivariate analysis, model I adjusted for age, sex, and duration of T1D, and model II included model I with physical activity added as a covariate.

RESULTS

Participant Characteristics

A total of 285 adults (62.9% women) with a mean duration of T1D of 25.9 ± 16.2 years met inclusion criteria for the study (**Table 1**). The mean age of participants was 48.1 ± 15.0 years old, 94.4% were Caucasian, 30.2% had an annual household income of >$100,000 and 48.4% had a Bachelor's degree or above (**Table 1**). Medical history included self-reported CVD (12.3%), hypercholesterolemia (46.7%), and microvascular complications (38.6%, defined as reporting one or more: neuropathy, nephropathy, or retinopathy). For insulin administration, 40.4% of participants reported using an insulin pump. In addition, the majority of participants (72.6%) reported using CGM on a regular basis (defined as use >75% of the time). Participant characteristics according to sex are reported in **Supplemental Table S3**.

Dietary Intake and Lifestyle Habits

LCD score ranged from a median of 24 points in Q1 and 6 points in Q4. In our sample, 10.5% (*n* = 30) of the participants followed a LCD (<30% of total energy as CHO), and 1.0% (*n* = 2) followed a very-low-CHO diet (<10% of energy as CHO). Mean daily CHO intake was 43.8 ± 10.7% of total energy or 229.9 ± 84.3 g/day (**Table 1**), ranging from 31.2 ± 6.9% or 167.0 ± 60.6 g/day in Q1 to 56.5 ± 6.8% or 270.9 ± 84.6 g/day in Q4 (**Table 2**). Overall, mean daily fat and protein intake were 38.6 ± 9.6% and 17.2 ± 4.1% of total energy respectively. Fiber intake averaged 10.8 ± 4.6 g/1000 kcal/day for all participants. Saturated fat (SFA), trans fat, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) were significantly higher in Q1 compared to Q4.

Participants in Q1 consumed 16.7 ± 5.2% of total energy as SFA and 0.8 ± 0.4% of total energy as trans fat compared to Q4 that consumed 9.9 ± 3.3% and 0.3 ± 0.3% of total energy respectively.

Dietary intake was also characterized by food group portions, where significant differences were observed across quartiles in all food groups. Fruit intake was significantly (P <0.001) lower in Q1 (1.3 ± 1.2 portions) compared to Q4 (2.8 ± 2.8 portions), while vegetable intake did not significantly differ between quartiles. Intake of grain products was also lower (P <0.001) in Q1 compared to the other quartiles, including intake of whole grain products that differed significantly (P = 0.044) between Q1 (1.1 ± 1.4 portions) and Q2 (1.9 ± 2.0 portions). For milk and alternatives and meat and alternatives groups, Q4 consumed significantly (P = 0.005 and P <0.001 respectively) fewer portions than the rest of the quartiles.

In terms of participants' characteristics, there were no significant differences in sociodemographic characteristics and medical histories across quartiles (Table 3). Mean total daily insulin dose was 0.7 ± 0.4 U/kg, where Q2 used the least amount (0.57 ± 0.18 U/kg) and Q4 used the most (0.79 ± 0.37 U/kg). About half the sample reported using statins (51.2%) or antihypertensive medication (41.4%) for cardiorenal protection and/or treatment of CV risk factors. Lifestyle habits included physical activity, smoking status, and alcohol intake. Mean physical activity was variable at 100 ± 131 min/week, with about three quarters (73.2%) of participants not meeting recommended weekly activity. 8.8% of participants were active smokers. Although most participants were active drinkers (86.7%), few (7.6%) of them were above recommendations.

Glycemic Control and Treatment Modalities

Proportions of participants achieving a HbA1c ≤7.0% was greater in Q1 (53.4%) compared to Q4 (29.4%) (*P* = 0.011). In the non-adjusted logistic regression analysis, participants in the lowest CHO intake quartile (Q1) were 2.75 (95% CI 1.37-5.52) more likely to have a HbA1c ≤7.0% compared to those in Q4 (Table 4). These odds were similar when adjusting for age, sex, and duration of T1D (model I), however, they were further exemplified when adjusted for physical activity (model II; adjusted OR [aOR] 2.87; 95% CI 1.41-5.86).

History of hypoglycemic events did not significantly differ between quartiles when accounting for self-treatable moderate hypoglycemia (<54.0 mg/dL; <3.0 mmol/L) and symptomatic nocturnal hypoglycemia. However, compared to Q3, Q1 had a significantly higher frequency of never having experienced severe hypoglycemia (defined as requiring external help from a third party or needing glucagon or intravenous glucose to treat). In the non-adjusted logistic regression analysis, Q3 was significantly more likely to have experienced a severe hypoglycemia than Q4 ([OR] 0.41; 95% CI 0.21-0.82) with similar odds in model I ([aOR] 0.32; 95% CI 0.15-0.68) and model II ([aOR] 0.32; 95% CI 0.15-0.69) (Table 4). IAH as assessed by a Clarke score ≥ 4 was non-significantly different but numerically higher in Q1 vs. Q4 (24.0% vs. 15.7%, *P* = 0.269).

CGM use and treatment regimens including insulin administration method, insulin dose, statin and antihypertensive medication use, as well as lifestyle habits, did not significantly differ between quartiles.

Obesity and Other Risk Factors

Mean BMI of participants was 26.2 ± 4.7 kg/m^2 with overall 37.5% being overweight and 18.5% obese. Using self-measured WC data, 44.1% participants were considered having abdominal obesity (**Table 1**). Mean BMI (*P* = 0.354) and prevalence of abdominal obesity (*P* = 0.210) did not significantly differ between quartiles (**Table 3**). Mean LDL-c (*P* = 0.290) and non-HDL-c (*P* = 0.118) values were not significantly different among quartiles (**Table 3**). However, in sub-analysis of the participants subgroup with available lipid profile data, differences were found between statin and non-statin users, with a more adverse profile in participants adhering to LCD for both LDL-c 76 ± 31 mg/dL vs. 92 ± 31 mg/dL (*n* = 51 vs. *n* = 38; *P* = 0.020) and non-HDL-c 93 ± 35 mg/dL vs. 110 ± 34 mg/dL (*n* = 50 vs. *n* = 35; *P* = 0.031).

CONCLUSIONS

Among a large sample of Canadian adults living with T1D in Québec, adhering to a LCD as measured by the LCD score was associated with a higher likelihood of reaching the recommended HbA1c target and a higher likelihood of never having experienced severe hypoglycemia. No difference was observed in moderate hypoglycemia risk, IAH, or reported or measured CV risk factors.

The use of the LCD score allows us to not only describe the diet by its CHO intake, but also by its fat and protein composition to better assess the impact of the diet as a whole. In addition, evaluating macronutrient intake as a percentage of energy instead of absolute intake reduces the risk of bias of underreporting food portions.

Compared to guidelines, participants' average dietary intake is on the lower end of recommendations (45-60% of daily energy) for CHO, below recommendations (≥20 g/1000 kcal per day) for fiber intake, and above recommendations (20-35% energy) for fat [15]. Mean SFA intake was above clinical recommendations, which recommend <9% of total energy as SFA in order to reduce CVD risk [15], with Q1 consuming higher proportions for all types of fat (SFA, trans fat, MUFA, and PUFA). In the general population, such dietary profile is associated with a higher CV risk [32]. In our sample, adherence to a LCD (<30% of energy as CHO) is quite high at 11.5% (*n* = 32), with an additional 8.0% (*n* = 23) approaching this threshold (<35% of energy as CHO). In other large cohort studies using LCD scores, their LCD group with the highest score consumed more CHO (36.8-53.0% vs 31.2%) and had lower fat intake (32.0-41.3% vs 48.7%) compared to our Q1, with similar protein intake (15.5-22.8% vs 19.9%) [22-25]. These PWT1D following a LCD consume fewer fruits and grain products and higher proportions of milk and meat and alternatives. This data

suggests that PWT1D have overall low diet quality and that those who follow LCDs to facilitate glucose control and/or CHO counting have even lower diet quality.

We found that more than half the participants in Q1 reported meeting therapeutic HbA1c goals ≤7.0% compared to 29.4% participants in Q4. These findings are consistent with some other observational studies that have shown glycemic control within target in PWT1D following a LCD [10-12]. This adequate HbA1c level was not obtained at the expense of hypoglycemic risk as hypoglycemia <54 mg/dL (<3.0 mmol/L), symptomatic nocturnal hypoglycemia, and Clarke scores did not significantly differ between quartiles. In addition, there was a significantly higher percentage of participants in Q1 that had never experienced a severe hypoglycemic episode. Due to the theoretical increased risk of severe hypoglycemia with a LCD, it is possible that patients with a previous episode are less likely to consider a LCD as a dietary option. Still, in individuals who adhere to a very-low-CHO diet, IAH may be a consequence of increased cerebral exposure to circulating ketones [33]. In fact, a recent study suggested an increase of non-perceived hypoglycemic episodes in patients following a very-low-CHO diet long-term [10]. The high percentage (75%) of patients using CGM in our study reduced this risk of bias, however the potential risk of IAH with long-term adherence to low-CHO intake still warrants attention.

Another potential concern of following LCDs is the long-term CV risk. Although blood lipids were not significantly different across quartiles, participants in Q1 to Q3 did not meet the most frequent therapeutic targets for LDL-c <77 mg/dL (<2.0 mmol/L) and non-HDL-c <100 mg/dL (<2.6 mmol/L) [34], however Q4 met these targets. This difference may be mitigated by statin use in half of participants. The small sub-analysis of non-statin users with available biochemical data suggests that LDL-c and non-HDL-c are higher in patients adhering to LCD. These findings are

consistent with other studies that report LDL-c above target in observational studies of LCDs in T1D [10-12]. A very important proportion of this population presented an increased body weight with android repartition, as approximately 55% of the total sample was classified as overweight or obese and 44% with abdominal obesity. In patients adhering to a LCD (Q1), there was a non-significant numerical trend for lower values for both BMI and WC. In addition, a very small fraction of patients (26.8%) met physical activity recommendations. Thus, overall PWT1D are exposed to a high CV risk without evidence of additional significant positive or adverse effect of adhering to LCD on reported or measured CV risk factors. Statin therapy may mitigate some awaited adverse effects on lipid profile.

The current study has some important limitations. Due to the cross-sectional nature of the study, causal associations cannot be determined. In addition, the inclusion of only one R24H and the lack of information on diet duration limits our ability to accurately describe our populations' long-term dietary intake. In addition, an individual's adherence to a dietary intervention may reflect a better overall adherence to diabetes management and thus indirectly be responsible of observed higher achievement for reaching HbA1c target. Worse lipid profile in patients adhering to LCDs was only available on a small sample of participants, thus larger studies with objective measures of atherosclerosis are needed to better assess potential adverse impacts of LCDs on CV risk. Finally, long-term adherence to LCDs and validation of the optimal method to assess it remains to be established. On the other hand, our study is the first to use the LCD score to assess the overall impact of LCDs in PWT1D. Our large sample size and use of validated methods provides further insight of real-world adherence and possible impact of LCDs.

Our findings suggest that adhering to a LCD is associated with a higher likelihood of achieving recommended HbA1c goals without observing adverse impacts on hypoglycemic risk. This favourable impact on glucose control justifies further attention for this dietary approach. We observed no adverse impact on measured or reported CV risk factors. Nonetheless, this patient group is at high CV risk and further studies are needed to assess the impact of LCDs on long-term glucose control and CV risk.

TABLES

Table 1: Participants' Characteristics

Characteristic	[n]	Full sample – mean ± SD (min-max) or n (%)
Age – yrs	[285]	48.2 ± 15.0 (18-80)
Female	[285]	180 (63.2)
Ethnicity	[285]	
Caucasian		269 (94.4)
Other[1]		16 (5.6)
Household income	[285]	
< $60,000		95 (33.3)
$60,000 to $100,000		71 (24.9)
> $100,000		86 (30.2)
I don't know/I prefer not to answer		33 (11.6)
Highest level of education	[285]	
High school diploma or lower		40 (14.0)
Associate's degree[2]		104 (36.5)
Bachelor's degree or above		138 (48.4)
I don't know/I prefer not to answer		3 (1.1)
BMI – kg/m^2	[259]	26.2 ± 4.7 (16.9-44.4)
Overweight (25-29.9 kg/m^2)		97 (37.5)
Obese (≥30 kg/m^2)		48 (18.5)
Abdominal obesity[3]	[213]	94 (44.1)
Duration of T1D – yrs	[284]	25.9 ± 16.2 (0.0-68.0)
Microvascular complications[4]	[280][5]	110 (39.3)
Cardiovascular disease[6]	[281]**	35 (12.5)
Hypercholesterolemia[7]	[284]**	133 (46.8)
Active smokers	[285]	25 (8.8)
Active drinkers	[285]	247 (86.7)
Alcohol intake above recommendations[8] – of active drinkers		19 (7.6)

Abbreviations: *BMI*, Body Mass Index. *CGM*, Continuous Glucose Monitoring. *HbA1c*, Glycated hemoglobin A_1c. *SD*, Standard Deviation. *T1D*, Type 1 Diabetes.

** Responses of "I prefer not to answer" or "I don't know" were coded as missing data

[1] Includes Black, Arab, Latin American, West Asian, Aboriginal, Other, I don't/know/prefer not to say.
[2] Includes Vocational school, Diploma from CEGEP or community college, University certificate.
[3] Defined as a waist circumference (WC) ≥88 cm (women) or ≥102 cm (men).
[4] Defined as reporting one or more of the following: neuropathy, nephropathy, retinopathy or receiving eye injections related to diabetes damage.
[5] Responses of "I prefer not to answer" or "I don't know" were coded as missing data
[6] Defined as heart attack, need a bypass or dilation of an artery, stroke, surgery for a blocked vessel in a leg, etc.
[7] Defined as high levels of blood cholesterol
[8] Alcohol intake over recommended limits: F≥9 drinks/week, M≥15 drinks/week.

Physical activity – min/wk	[280]	100 ± 131 (0-600)
Physical activity below recommendations[9]		205 (73.2)
Insulin Administration Device – Use of insulin pump only	[281][10]	115 (40.9)
Insulin Dose – units/kg	[148]	0.7 ± 0.4 (0.1-3.1)
CGM Regular Use (>75% of the time)	[242]	207 (85.5)
Medication Use		
Statins	[284]**	146 (51.4)
Anti-hypertensive and cardiorenal protection	[283]**	118 (41.7)
Labs		
HbA1c[11]	[285]	
≤7%		103 (36.1)
>7%		121 (60.4)
I don't know		10 (3.5)
LDL-cholesterol[12] – mmol/L	[89]	2.14 ± 0.82 (0.81-4.56)
Non-HDL-cholesterol[12] – mmol/L	[85]	2.59 ± 0.92 (1.20-5.70)
Dietary intake	[285]	
Energy intake – kcal/day		2131 ± 678 (808-4882)
Carbohydrate intake – % of energy		43.8 ± 10.7 (8.0-76.3)
Carbohydrates – g/day		229.9 ± 84.3 (34.3-573.3)
Fiber – g per 1000 kcal/day		10.8 ± 4.6 (1.3-27.8)
Fat intake – % of energy		38.6 ± 9.6 (15.0-77.1)
Saturated fat – % of energy		13.1 ± 4.7 (2.6-36.3)
Trans fat – % of energy		0.5 ± 0.4 (0.0-2.7)
Monounsaturated fat – % of energy		14.4 ± 4.8 (2.3-33.7)
Polyunsaturated fat – % of energy		8.0 ± 3.3 (1.5-24.7)
Protein intake – % of energy		17.2 ± 4.1 (5.3-29.5)

Abbreviations: *HDL*, High-density lipoprotein. *LDL*, Low-density lipoprotein. *SD*, Standard Deviation.

** Responses of "I prefer not to answer" or "I don't know" were coded as missing data

[9] Defined as total physical activity <150 min/week.

[10] Responses of "Both" or "None" (no insulin use) were coded as missing data

[11] HbA1C based on health booklet (Carnet Santé Québec) when available (n=141), otherwise self-reported (n=135)

[12] Reported by participants from their health booklet (Carnet Santé Québec)

Table 2: Dietary Intake of Adults with Type 1 Diabetes Among Quartiles of LCD Score

	Quartiles of Low-Carbohydrate-Diet Score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
LCD Score range	21-30	15-20	10-14	0-9	
Participants – n	75	68	72	70	
Dietary intake* – mean ± SD					
Energy intake – kcal/day	2138 ± 717	2203 ± 592	2201 ± 678	1942 ± 616	0.061
Carbohydrate intake – % of energy	31.2[a] ± 6.9	41.7[b] ± 3.3	46.4[c] ± 4.4	56.5[d] ± 6.8	**<0.001**
Carbohydrates – g/day	167.0 ± 60.6	229.1 ± 60.5	256.3 ± 87.4	270.9 ± 84.6	**<0.001**
Fiber – g per 1000 kcal/day	10.6 ± 4.3	10.5 ± 4.1	11.7 ± 4.9	10.5 ± 5.0	0.330
Fat intake – % of energy	48.7[a] ± 8.3	39.5[b] ± 5.8	36.1[c] ± 5.8	29.8[d] ± 6.3	**<0.001**
Saturated fat – % of energy	16.7[a] ± 5.2	13.0[b] ± 3.9	12.4[b] ± 3.3	9.9[c] ± 3.3	**<0.001**
Trans fat – % of energy	0.8[a] ± 0.4	0.5[b] ± 0.3	0.5[b] ± 0.3	0.3[c] ± 0.3	**<0.001**
Monounsaturated fat – % of energy	18.7[a] ± 4.9	14.8[b] ± 3.7	13.1[c] ± 3.3	10.8[d] ± 3.3	**<0.001**
Polyunsaturated fat – % of energy	9.4[a] ± 3.8	8.5[a] ± 2.9	7.7[b] ± 3.1	6.5[c] ± 2.6	**<0.001**
Protein intake – % of energy	19.9[a] ± 3.3	18.6[a] ± 3.9	16.3[b] ± 3.3	14.0[c] ± 3.0	**<0.001**
Intake of food group servings – mean ± SD, portions					
Fruits and vegetables	4.9 ± 2.7	5.6 ± 3.1	5.3 ± 3.2	5.9 ± 3.9	0.246
Fruits	1.3[a] ± 1.2	1.8 ± 1.6	1.8 ± 1.5	2.8[b] ± 2.8	**<0.001**
Vegetables	3.5 ± 2.1	3.8 ± 2.3	3.5 ± 2.5	3.1 ± 2.5	0.398
Grain products	3.5[a] ± 2.0	5.1[b] ± 2.4	5.4[b] ± 2.7	5.0[b] ± 2.4	**<0.001**
Whole grain products	1.1[a] ± 1.4	1.9[b] ± 2.0	1.5 ± 1.8	1.4 ± 1.8	**0.044**
Milk and alternatives	2.3[b] ± 1.6	2.6[b] ± 2.1	2.2 ± 1.5	1.6[a] ± 1.1	**0.005**
Meat and alternatives	3.3[b,c] ± 2.0	2.8[b,c] ± 1.4	2.2[b] ± 1.2	1.5[a,d] ± 1.1	**<0.001**

Abbreviations: *kcal*, Kilocalories. *SD*, Standard Deviation

* Based on one 24-hour dietary recall.

Table 3: Characteristics of Adults with Type 1 Diabetes Among Quartiles of LCD Score

		Quartiles of Low-Carbohydrate-Diet Scores				
	[n]	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
LCD Score range		21-30	15-20	10-14	0-9	
Participants – n	[285]	75	68	72	70	
Age – mean ± SD, yrs		48.7 ± 13.6	47.7 ± 14.7	49.6 ± 16.3	46.6 ± 15.5	0.674
Female – n (%)		45 (60.0)	50[a] (73.5)	37[b] (51.4)	48 (68.6)	**0.035**
Ethnicity – n (%)						0.453
Caucasian		72 (96.0)	66 (97.1)	67 (93.1)	64 (91.4)	
Other		3 (4.0)	2 (2.9)	5 (6.9)	6 (8.6)	
Household income – n (%)	[252]*					0.148
< $60,000 per year		18 (26.9)	20 (35.7)	28 (44.4)	29 (43.9)	
$60,000 to $100,000 per year		17 (25.4)	19 (33.9)	17 (27.0)	18 (27.3)	
> $100,000 per year		32 (47.8)	17 (30.4)	18 (28.6)	19 (28.8)	
Highest level of education – n (%)	[282]*					0.653
High school diploma or lower		10 (13.5)	5 (7.5)	12 (16.7)	13 (18.8)	
Associate's degree†		28 (37.8)	27 (40.3)	25 (34.7)	24 (34.8)	
Bachelor's degree or above		36 (48.6)	35 (52.2)	35 (48.6)	32 (46.4)	
BMI – mean ± SD, kg/m^2	[259]	26.0 ± 4.8	25.4 ± 4.7	26.9 ± 5.4	26.2 ± 3.6	0.354
Overweight – n (%)		24 (38.1)	14[a] (23.0)	27 (39.1)	32[b] (48.5)	0.135
Obese – n (%)		12 (19.0)	12 (19.7)	14 (20.3)	10 (15.2)	
Abdominal obesity‡ – n (%)	[213]	21 (41.2)	21 (40.4)	22 (38.6)	30 (56.6)	0.210
Duration of T1D – mean ± SD, yrs	[284]	24.4 ± 15.8	24.6 ± 16.4	26.9 ± 16.0	27.9 ± 16.6	0.489
Microvascular complications§ – n (%)	[280]*	28 (37.8)	22 (33.3)	28 (39.4)	32 (46.4)	0.475
Cardiovascular disease – n (%)	[281]*	11 (14.9)	7 (10.6)	9 (12.7)	8 (11.4)	0.880
Hypercholesteremia – n (%)	[284]*	35 (47.3)	33 (48.5)	34 (47.2)	31 (44.3)	0.965
Active smokers – n (%)		7 (9.3)	7 (10.3)	5 (6.9)	6 (8.6)	0.912
Alcohol intake above recommendations** – n (%)	[249]	2 (2.9)	4 (6.9)	6 (9.0)	7 (12.5)	0.222
Physical activity – mean ± SD, min/wk	[280]	97 ± 121	86 ± 115	105 ± 136	111 ± 152	0.709

Abbreviations: *BMI*, Body Mass Index. *SD*, Standard Deviation. *T1D*, Type 1 Diabetes.

[a,b]: Letters represent significant differences ($P<0.05$) between groups

* Responses of "I prefer not to answer" or "I don't know" were coded as missing data

† Includes Vocational school, Diploma from CEGEP or community college, University certificate.

‡ Defined as a waist circumference (WC) ≥88 cm (women) or ≥102 cm (men).

§ Defined as reporting one or more of the following: neuropathy, nephropathy, retinopathy, or receiving eye injections related to diabetes damage.

** Alcohol intake over recommended limits: F≥9 drinks/week, M≥15 drinks/week

Physical activity below recommendations[††] – n (%)		54 (72.0)	51 (77.3)	49 (71.0)	51 (72.9)	0.853
Insulin Administration Device – Use of insulin pump only – n (%)	[281][*]	31 (41.9)	28 (42.4)	23 (31.9)	33 (47.8)	0.278
Insulin dose – mean ± SD, units/kg	[147]	0.64 ± 0.28	0.57 ± 0.18	0.69 ± 0.47	0.79 ± 0.37	0.061
CGM Regular Use (>75% of the time) – n (%)	[242]	56 (84.8)	53 (91.4)	52 (85.2)	46 (80.7)	0.439
Medication Use						
Statins – n (%)	[284][‡‡]	38 (50.7)	34 (50.0)	39 (54.9)	35 (50.0)	0.924
Anti-hypertensive – n (%)	[283][‡‡]	33 (45.2)	23 (33.8)	33 (45.8)	29 (41.4)	0.455
Labs						
HbA1c ≤7%[§§] – n (%)	[275]	39[a] (53.4)	23 (34.3)	21 (31.3)	20[b] (29.4)	**0.011**
LDL-cholesterol, CSQ[***] – mean ± SD, mg/dL	[89]	81 ± 29	91 ± 36	85 ± 35	73 ± 27	0.290
Non-HDL-cholesterol, CSQ[***] – mean ± SD, mg/dL	[85]	101 ± 30	109 ± 42	107 ± 43	85 ± 23	0.118
Hypoglycemia Management & Complications						
Hypoglycemia <54 mg/dL – mean ± SD, episodes in past month	[267]	6.9 ± 10.2	8.0 ± 8.3	7.4 ± 7.4	6.6 ± 6.4	0.784
Symptomatic nocturnal hypoglycemia – mean ± SD, episodes in past month	[278]	3.0 ± 4.8	2.8 ± 3.9	1.5 ± 1.9	3.5 ± 5.7	0.420
Never experienced a severe hypoglycemia – n (%)	[283]	45[a] (60.0)	35 (51.5)	22[b] (31.0)	36 (52.2)	**0.004**
Clarke score ≥4[†††] – n (%)		18 (24.0)	18 (26.5)	21 (29.2)	11 (15.7)	0.269

Abbreviations: *CGM*, Continuous Glucose Monitoring. *HbA1c*, Glycated hemoglobin A_1c. *HDL*, High-density lipoprotein. *LDL*, Low-density lipoprotein. *SD*, Standard Deviation.

[a,b]: Letters represent significant differences ($P<0.05$) between groups

[††] Defined as total physical activity <150 min/week.

[‡‡] Responses of "I prefer not to answer" or "I don't know" were coded as missing data

[§§] HbA1C based health booklet (Carte Santé Québec) reported by participants when available (n=141), otherwise self-reported (n=135)

[***] Reported by participants from their health booklet (Carte Santé Québec)

[†††] Clarke questionnaire is comprised of 8 questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia with scores ranging from 0 to 7. A score ≥4 implies impaired awareness of hypoglycemia (IAH).

Table 4: Odds Ratio and 95% Confidence Interval (CI) of A1c and History of Severe Hypoglycemia Across LCD Score Quartiles

	(n) Odds Ratio (OR) [95% CI]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}*
LCD Score (range)	21-30	15-20	10-14	0-9	
HbA1c ≤7.0%					
Crude	(73) 2.75[a] [1.37-5.52]	(67) 1.26 [0.61-2.60]	(67) 1.10 [0.53-2.28]	(68) 1[b]	**0.012**
Model I†	(73) 2.73[a] [1.35-5.52]	(67) 1.30 [0.63-2.71]	(66) 1.07 [0.51-2.26]	(68) 1[b]	**0.039**
Model II‡	(73) 2.87[a] [1.41-5.86]	(65) 1.45 [0.69-3.04]	(64) 0.98 [0.46-2.10]	(68) 1[b]	**0.018**
Never experienced severe hypoglycemia					
Crude	(75) 1.38 [0.71-2.66]	(68) 0.97 [0.50-1.90]	(71) 0.41[a] [0.21-0.82]	(69) 1[b]	**0.004**
Model I†	(75) 1.17 [0.57-2.41]	(68) 0.78 [0.37-1.62]	(70) 0.32[a] [0.15-0.68]	(69) 1[b]	**<0.001**
Model II‡	(75) 1.20 [0.58-2.47]	(66) 0.81 [0.39-1.72]	(68) 0.32[a] [0.15-0.69]	(69) 1[b]	**<0.001**

[a,b]: Letters represent significant differences (P<0.05) between groups

Abbreviations: *HbA1c*, Glycated hemoglobin A_1c.

* Percentage of explained variance

† Adjusted for age, sex, and duration of type 1 diabetes.

‡ Adjusted for age, sex, duration of type 1 diabetes and physical activity.

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SUPPLEMENTAL MATERIAL

Supplemental Table S1: Data Collected from the BETTER Registry Questionnaires

Questionnaire 1	Questionnaire 2	Questionnaire 3
Socio-demographics data • Age • Sex at birth • Gender they identify with • Ethnicity • Level of education • Employment status • Household income Diabetes duration Family history of T1D Current treatment modalities • Multiple daily injections (MDI) or Continuous subcutaneous insulin infusion (CSII) • Blood glucose monitoring (self-monitoring of capillary blood glucose [SMBG] or continuous glucose monitoring [CGM]) Reported • HbA1c • Diabetes complications • History of non-severe and severe hypoglycemia • Medication for hypertension, dyslipidemia, thyroid gland disorders or depression/anxiety Hypoglycemia unawareness using the Gold score [39] Glucagon usage	Diabetes treatment • Type of insulin used • Number of insulin injections per day • Model of insulin pump and/or CGM device • Reasons to use CSII and/or CGM Usual management of hypoglycemia Validated questionnaires • Hypoglycemia Fear Survey II [35] • Hypoglycemia Confidence Scale [36] • Diabetes Distress Scale [37] • Clarke questionnaire [38] Lifestyle habits • Physical activity • Eating habits • Weight at different stages of life • Smoking status • Alcohol consumption • Use of drugs Number of pregnancy and deliveries Circumstances, actions and consequences of last level-2 and level-3 hypoglycemia	Diabetes treatment • Number of insulin boluses per day • Timing of insulin bolus in relation to the meal • Insulin-to-carbohydrate ratio • Carbohydrate counting Knowledge about insulin action Treatment satisfaction Other medication taken for diabetes treatment • Victoza®, Trulicity®, Ozempic® • Invokana®, Forxiga®, Jardiance®, Steglatro® • Glucophage® or Glumetza® • Soliqua®, Xultophy® Type of food primarily used to treat hypoglycemia Strategies used to prevent exercise-induced hypoglycemia Participant's assessment of the potential of new therapies and technologies to reduce hypoglycemia frequency Validated questionnaires • Hyperglycemia Avoidance Scale [40] • Pittsburgh Sleep Quality Index (PSQI) • Patient Health Questionnaire-9 (PHQ-9) to assess depression [41] • Diabetes Stigma Assessment Scale (DSAS-1) [42] • Social support survey developed in the Medical Outcomes Study (MOS) [43]

- International Physical Activity Questionnaire (IPAQ) [44]
- Barriers to Physical Activity in Type 1 Diabetes scale (BAPAD-1) [45]

Objective measurements

- Food intake [46]
- Physical activity [47]
- Waist circumference

Official reports for:

- Latest blood and urine tests
- Medication list

Supplemental Table S2: Criteria for Determining the Low-Carbohydrate-Diet Score

Points	Macronutrient Intake (% of total energy)		
	Carbohydrates	Fat	Protein
0	>57.7%	<27.0%	<12.5%
1	53.3-57.7%	27.3-30.4%	12.5-13.6%
2	49.3-53.1%	30.6-33.1%	13.7-14.7%
3	47.0-49.2%	33.2-35.0%	14.8-15.6%
4	44.9-46.7%	35.1-37.0%	15.7-16.4%
5	43.4-44.8%	37.1-39.2%	16.5-17.2%
6	40.9-43.2%	39.3-41.2%	17.3-18.1%
7	38.0-40.6%	41.3-43.6%	18.2-19.3%
8	35.2-38.0%	43.8-46.4%	19.4-20.7%
9	30.1-34.7%	46.8-50.3%	20.8-22.8%
10	<30.1%	>50.3%	>22.8%

Supplemental Table S3: Characteristics of Adults with Type 1 Diabetes Among According to Sex

Characteristic	[n]	Male – mean ± SD or n (%)	Female – mean ± SD or n (%)	*P* value
Participants	[285]	105	180	
Age – yrs	[285]	52.4 ± 15.0	45.7 ± 14.5	**<0.001**
Ethnicity	[285]			0.312
Caucasian		101 (96.2)	168 (93.3)	
Other*		4 (3.8)	12 (6.7)	
Household income	[285]			0.090
< $60,000		27 (25.7)	68 (37.8)	
$60,000 to $100,000		32 (30.5)	39 (21.7)	
> $100,000		36 (34.3)	50 (27.8)	
I don't know/I prefer not to answer		10 (9.5)	23 (12.8)	
Highest level of education	[285]			0.841
High school diploma or lower		17 (16.2)	23 (12.8)	
Associate's degree†		39 (37.1)	65 (36.1)	
Bachelor's degree or above		48 (45.7)	90 (50.0)	
I don't know/I prefer not to answer		1 (1.0)	2 (1.1)	
BMI – kg/m^2	[259]	26.6 ± 4.4	25.9 ± 4.9	0.203
Overweight (25-29.9 kg/m^2)		45 (46.4)	52 (32.1)	**0.021**
Obese (≥30 kg/m^2)		19 (19.6)	29 (17.9)	0.735
Abdominal obesity‡	[213]	31 (38.3)	63 (47.7)	0.177
Duration of T1D – yrs	[284]	28.2 ± 16.3	24.6 ± 16.0	0.071
Microvascular complications§	[280]**	44 (42.7)	66 (37.3)	0.370
Cardiovascular disease††	[281]**	16 (15.4)	19 (10.7)	0.254
Hypercholesterolemia‡‡	[284]**	48 (45.7)	85 (47.5)	0.773
Active smokers	[285]	8 (7.6)	17 (9.4)	0.599

Abbreviations: *BMI*, Body Mass Index. *SD*, Standard Deviation. *T1D*, Type 1 Diabetes.

* Includes Black, Arab, Latin American, West Asian, Aboriginal, Other, I don't/know/prefer not to say.
† Includes Vocational school, Diploma from CEGEP or community college, University certificate.
‡ Defined as a waist circumference (WC) ≥88 cm (women) or ≥102 cm (men).
§ Defined as reporting one or more of the following: neuropathy, nephropathy, retinopathy or receiving eye injections related to diabetes damage.
** Responses of "I prefer not to answer" or "I don't know" were coded as missing data
†† Defined as heart attack, need a bypass or dilation of an artery, stroke, surgery for a blocked vessel in a leg, etc.
‡‡ Defined as high levels of blood cholesterol

Alcohol intake above recommendations[§§] – of active drinkers	[285]	7 (7.2)	12 (7.9)	0.844
Physical activity – min/wk	[280]	111 ± 148	93 ± 120	0.267
Physical activity below recommendations[***]		74 (71.2)	131 (74.4)	0.550
Insulin Administration Device – Use of insulin pump only	[281][†††]	41 (39.4)	74 (41.8)	0.695
Insulin Dose – units/kg	[148]	0.7 ± 0.3	0.7 ± 0.4	0.728
CGM Regular Use (>75% of the time)	[242]	84 (90.3)	123 (82.6)	0.094
Medication Use				
Statins	[284][‡‡‡]	59 (56.7)	87 (48.3)	0.173
Anti-hypertensive and cardiorenal protection	[283][‡‡‡]	57 (54.3)	61 (34.3)	**0.001**
Labs				
HbA1c ≤7%[§§§]	[275]	44 (43.6)	59 (33.9)	0.111
LDL-cholesterol, CSQ[****] – mg/dL	[89]	74 ± 31	87 ± 31	0.065
Non-HDL-cholesterol, CSQ[****] – mg/dL	[85]	91 ± 32	105 ± 37	0.097
Dietary intake	[285]			
Energy intake – kcal/day		2429 ± 752	1957 ± 565	**<0.001**
Carbohydrate intake – % of energy		42.7 ± 11.4	44.4 ± 10.3	0.188
Carbohydrates – g/day		256.1 ± 98.0	214.6 ± 71.1	**<0.001**
Fiber – g/day		23.0 ± 11.1	22.1 ± 10.2	0.517
Fat intake – % of energy		38.7 ± 9.7	38.6 ± 9.5	0.924
Saturated fat – % of energy		13.4 ± 5.0	12.8 ± 4.6	0.333
Trans fat – % of energy		0.6 ± 0.4	0.5 ± 0.3	0.073
Monounsaturated fat – % of energy		14.3 ± 4.5	14.5 ± 5.0	0.672
Polyunsaturated fat – % of energy		7.8 ± 2.9	8.2 ± 3.5	0.391
Protein intake – % of energy		17.1 ± 4.5	17.3 ± 3.8	0.680

[§§] Alcohol intake over recommended limits: F≥9 drinks/week, M≥15 drinks/week.

Abbreviations: *CGM*, Continuous Glucose Monitoring. *CSQ*, Carnet Santé Québec. *HbA1c*, Glycated hemoglobin A_1c. *HDL*, High-density lipoprotein. *LDL*, Low-density lipoprotein. *SD*, Standard Deviation.

[***] Defined as physical activity <150 min/week.

[†††] Responses of "Both" or "None" (no insulin use) were coded as missing data

[‡‡‡] Responses of "I prefer not to answer" or "I don't know" were coded as missing data

[§§§] HbA1C based on health booklet data (Carte Santé Québec) reported by participants, if available (n=141), or self-reported (n=135)

[****] Reported by participants from health booklet data (Carte Santé Québec)

CHAPTER 6
Discussion

6.1 MAIN FINDINGS

In Manuscript 1, our qualitative study used semistructured interviews to evaluate the patients' perspective of following a KD for a short period of time (median 5 months) in adults living with T1D and T2D. Our findings were consistent with other studies in the literature which demonstrated that adults with diabetes reported improved glycemic control [65, 67], a reduction or cessation of diabetes medications [65, 67], weight loss [66, 67], reduced hunger [80-83], and improved well-being [81, 84] after following a KD.

A strong observation noted in almost all participants was an overall positive experience with the diet and that they viewed the KD as a lifestyle, not a diet, that they would follow for the rest of their lives. One factor that may attribute to participants' positive experience with the KD is the fact that half of participants reported weight loss as a reason for initiating the diet; of whom, 6 of these 7 participants reported a history of "yo-yo dieting" or weight cycling (see addendum, Appendix 4.1). In our study, weight cycling was defined as a significant weight loss of >5% of usual body weight on 2 or more occasions. Given the high rate of reported weight loss (*n*=8; 57.1%), dieting history (*n*=10; 71.4%) and overall satisfaction with the KD, it may be inferred that the KD was the sole diet that participants deemed to be successful in achieving a certain weight loss goal. This is supported by the findings of researchers in Australia who found that in weight-reduced patients following a KD, ketosis altered appetite-regulating hormones in a manner that opposed weight regain [85]. Compensatory changes that favour weight regain after losing weight, such as

increases in hunger hormones (i.e. ghrelin) and appetite, were mitigated against when participants were in a ketotic state. Although the effect of the KD on hunger and appetite regulation is still being debated, this hunger-suppressing effect of the KD proposed by Sumithran *et al.* [85] and others [80] may explain our participants' success in weight loss achieved by the KD superior to other attempted diets.

While observations were generally positive and seemingly beneficial to health, a common observation among participants was the lack of acknowledgement or concern for long-term side effects. Our sample primarily consisted of participants with T2D not using insulin; in fact only half of participants reported currently taking diabetes medications (Appendix 1.4). This may in part explain why adverse effects, aside from temporary "keto flu" side effects associated with initiating the diet, were not reported, as risk for hypoglycemia is generally not a concern in individuals who are not taking insulin or insulin secretagogues [17]. In people living with T1D, taking insulin or insulin secretagogues, the risk of hypoglycemia is higher, and individuals need to pay close attention to CHO intake and insulin dosing in order to prevent hypoglycemia.

In Manuscript 2, we aimed to cross-sectionally assess glycemic control and CV risk factors in adults with T1D by characterizing their dietary intake with the use of the LCD score. Quartiles were used to represent different macronutrient distributions, where Q1 was representative of a typical high-fat LCD seen in the literature, and Q4 was representative of a classically defined moderate-CHO diet. In the quartile with lowest CHO and highest fat intake (Q1), we hypothesized that participants would demonstrate better glycemic control and CV risk factors, such as BMI, abdominal obesity, and blood lipids, at the expense of more frequent episodes of hypoglycemia and prevalence of IAH.

Compared to Q4, participants in Q1 were significantly more like to have HbA1c within targets ≤7.0%, without significant differences in hypoglycemia outcomes. Although there were no associations between LCD score quartile and CV risk factors, we observed differences in dietary quality. Notably, participants in Q1 demonstrated a significantly higher SFA and trans intake compared to other quartiles. Coupled with inadequate fibre intake, the dietary patterns observed in Q1 may be concerning to CV health.

The current study had important methodological limitations and consequently, we were unable to thoroughly evaluate the relationship between clinical outcomes and level of CHO-restriction. Nonetheless, we did observe a high prevalence of CV risk factors in our overall sample such as overweight/obesity, abdominal obesity, abnormal blood lipids, and low levels of physical activity, regardless of dietary pattern. The majority of our sample reported physical activity below recommendations and did not meet therapeutic targets for blood lipids, despite half of participants reported using a statin. Moreover, overall fibre intake and SFA intake did not meet dietary recommendations. These findings should be interpreted with prudence as our study is limited by its cross-sectional nature, use of self-reported data, and inability to thoroughly assess usual dietary intakes with the use of one R24H. However, our findings may further emphasize the need for CVD prevention in individuals with T1D, although future studies in ethnically diverse populations are needed.

In summary, the first manuscript demonstrated short-term benefits of following a KD in adults with T1D and T2D from a qualitative study design, whereas the second manuscript showed improved glycemic control when evaluating LCDs in adults with T1D from a quantitative, cross-sectional view. Our conclusions remain limited due to the observational study design and reliance

on self-reported data, however we observed in both studies a strong motivation for people with diabetes to follow LCDs or KDs. Our studies thus further iterate the need for evidence to inform HCPs on how to support patients with diabetes wishing to follow such diets.

6.2 FUTURE DIRECTIONS

As documented in Chapter 2, there is currently a paucity of long-term studies that assess the impact of LCDs and KDs in T1D and T2D populations. In T1D, the current literature is mainly of observational nature assessing short-term outcomes and limited in size. Furthermore, the effect on hypoglycemia-related outcomes are obscured by differences in measurement (e.g. weekly or monthly frequency vs. incidence by persons per year) and cut-off values that define hypoglycemia, and use of self-reported hypoglycemic events. Blinded CGM may be preferable to measure levels of hypoglycemia, as individual differences in perception and history of IAH may skew data related to reporting hypoglycemic events. Lastly, RCTs of longer-term in larger sample sizes are warranted in T1D to better understand the implications of LCDs.

In T2D, many RCTs exist which examine the effects of a LCD or KD compared to a control diet, however these studies are not without limitations. The current findings are confounded by poor dietary compliance, absence of isocaloric study arms, and differences in dietary assessment methods and macronutrient composition of the LCD/KD. Future long-term studies beyond 2 years are needed, in addition to considerations on macronutrient quality and distribution, namely on CHO (refined vs. whole grain) and fat (unsaturated vs. SFA) intake, and methods to more accurately assess or encourage dietary adherence.

CHAPTER 7
Conclusion

With the rising interest and popularity of LCDs and KDs, it is important to be keep in mind that the current literature remains limited in the scope of clinical recommendations in people living with diabetes. While the literature is more robust and extensive in T2D, the long-term consequences of LCDs and KDs in the context of diabetes are still inconclusive. Nonetheless, some people living with diabetes are still strongly motivated to follow a LCD or KD as observed in our qualitative study.

Both studies demonstrated certain benefits and challenges from following a LCD or KD, however these findings are largely limited by study design. Nevertheless, our studies affirm the large interest in LCDs in people living with diabetes as seen in the literature, and further emphasize the need for clinical studies to investigate the short- and long-term consequences of LCDs and KDs as well as the impact on hypoglycemia and CV risk factors. Future studies are needed to help guide HCPs in how to better support their patients with diabetes on achieving their goals when following a LCD or KD.

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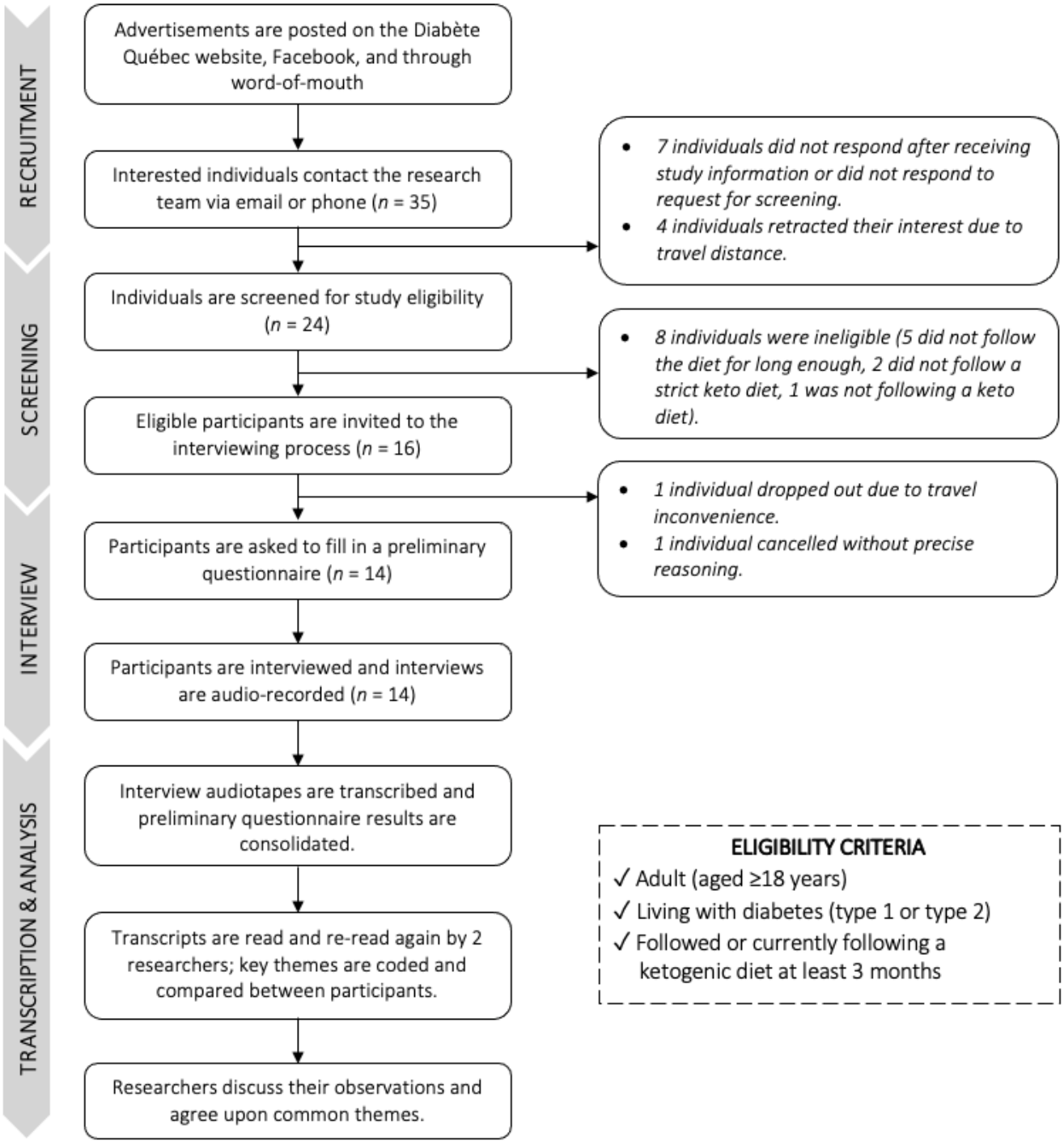
APPENDICES

APPENDIX 1
Supplementary Materials for Manuscript 1

Appendix 1.1 – Methodology Flowchart



Appendix 1.2 – Consent Form

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Consent Form

Patients' Experience with the Ketogenic Diet and Diabetes

Investigators: Anne-Sophie Brazeau RD, PhD, Sarah Blunden RD, CDE and Sondra Sherman RD, CDE
Student: Kayla Wong
Supervisor: Anne-Sophie Brazeau RD, PhD of McGill University School of Human Nutrition

Thank you for agreeing to receive information about our research study. Before agreeing to participate, please read the information below that will help you understand the study and what will happen if you agree to participate. If you have any questions or comments that you would like us to answer before you proceed with participating in the study, please contact us by phone or email (contact information are at the end of the document).

Purpose: The purpose of this study is to better understand the experience of individuals with diabetes who have followed or are currently following a ketogenic diet. A ketogenic diet is a diet with very low intake of carbohydrates that result in your liver producing ketone bodies as a source of energy. Our goal is to understand your personal experience with this diet to better assist you with your diet and your healthcare needs.

Procedures:
If you agree to participate: you will sign your consent at the end of this form. Then:

1: You will be asked to answer a short questionnaire with questions about your age, gender, anthropometrics (height and weight), type of diabetes, and personal history of dieting. You may answer the questionnaire yourself, or it can be read to you and you can tell us the answers out loud. All this information will remain confidential. Your questionnaire will be identified by a number and your name will not be associated with the answers you give.

2: A research assistant will conduct a one-on-one interview with you. The interview will take place at a public place of your convenience or if you prefer, at the Mary Emily Clinical Nutrition Research Unit. It will last around 30 minutes and will be audio recorded. The audio tape will be transcribed and reviewed by our research team for further analysis. Your interview transcript will be identified by a research number and your name will not be used. The questions will ask about your interest in the ketogenic diet, your social network and relationships with your health care providers, and challenges or side effects that you may have faced while following the diet. You do not have to answer every question if any of them make you uncomfortable.

Potential Benefits: You will not benefit directly from this study, however you will help the research team to better understand the ketogenic diet experience of individuals with diabetes and therefore help to educate health care professionals on the real life experience of the diet.

Risk and Discomforts: There are no risks associated with this study. One inconvenience will be the time that it takes to complete the interview. We will use password protection to protect your personal information.

Compensation: There will be no compensation for your participation in the study.

Voluntary Participation and/or Withdrawal: Your participation in this study is strictly voluntary. You may refuse to answer any questions that you are uncomfortable answering. You may refuse to participate or you may discontinue your participation at any time without explanation.

Confidentiality:

All information obtained during the study will be kept confidential as required or permitted by law. Your identity will be protected by replacing your name with a research number. Only the research team at McGill University will have access to the code linking your name to this number. Only the research number will be linked to the interview audiotape and transcript. Furthermore, the audio tapes will be destroyed once the study is completed, and only the transcripts identified by numbers will be kept on a password-protected hard drive accessible only by study personnel.

The results of this research study may be presented at scientific or professional meetings or published in scientific journals. We will potentially quote what you have said during the interview; however your name will never be used.

In order to ensure your protection and quality control of the research project, the following organizations could consult your research records:

Research ethics committee or a person mandated by them;

This organization adheres to a confidentiality policy.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The principal investigator, Anne-Sophie Brazeau, will be responsible for securely storing all the research data for 7 years.

Contact information:

If you have any questions you may call us at 514 398-7848 or email us at ketogenicstudy@gmail.com to speak with a study research assistant (Ms. Kayla Wong) or the Principal Investigator (Dr. Anne-Sophie Brazeau).

DECLARATION OF CONSENT FOR THE INTERVIEW

Please indicate YES or NO

I give consent to be audio taped during the interview ☐ Yes ☐ No

DECLARATION OF CONSENT

I have read the contents of this consent form, and I agree to participate in this research study. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I have been given sufficient time to consider the above information and to seek advice if I choose to do so. I understand that I will be given a copy of this signed consent form and one will be kept at McGill University. By signing the consent form, I have not given up any of my legal rights.

Participant's Signature: _____ Date: _____

Printed Name: _____

I have explained the research to the participant and, to the best of my knowledge; the participant has understood the proposed research and freely consented to research participation.

Delegate Signature: _____ Date: _____

Printed Name: _____

Version 2: June 20, 2018

McGill

PRELIMINARY STUDY QUESTIONNAIRE

Patients' Perspective on the Ketogenic Diet and Diabetes

1. When were you born? (date/month/year) _____
2. I identify as a:
   - ☐ Man
   - ☐ Woman
   - ☐ Other; you may specify: _____
3. How tall are you? _____ cm or ____ ft ____ in
4. How much do you currently weight? _____ lbs or _____ kg or ☐ Unsure
   If unsure, when was the last time you weighed yourself? _____
   How much did you weight? _____ lbs or _____ kg
5. What is your usual body weight? (please specify dates if applicable): _____
6. Please indicate your highest education level completed (check one response)
   - ☐ Have not completed Grade 12 (Secondary 5 in Quebec)
   - ☐ Grade 12 (Secondary 5 in Quebec)
   - ☐ College (including CEGEP in Quebec) or technical school
   - ☐ A University degree
   - ☐ Post-graduate studies
7. People living in Canada come from many different cultural and ethnic backgrounds. Please circle all that apply and if none do, check 'other' and write in your response:

a. White	b. Chinese	c. South Asian
d. Black	e. Filipino	f. Latin American
g. Southeast Asian	h. Arab	i. West Asian
j. Korean	k. Japanese	

   l. Other; you may specify: _____

8. Which type of diabetes do you have?
   - ☐ Type 1 diabetes (juvenile-onset diabetes or insulin-dependent diabetes)
   - ☐ Type 2 diabetes (adult-onset diabetes or noninsulin-dependent diabetes)
9. Are you taking any medications for your diabetes?
   - ☐ Yes (please specify below):
     _____
   - ☐ No
10. Have you ever experienced significant weight loss? (>5% of your usual weight)
    - ☐ Yes

- If yes, how many times have you experienced this level of weight loss in your life?
  - ☐ Once
  - ☐ Twice
  - ☐ Three times
  - ☐ More than three times

☐ No
☐ Not sure

11. Have you ever followed specific diet from the following list?:

☐ Low carb (a diet containing less than 100 g/d of carbs)
☐ Mediterranean (a diet focused on fish, olive oil, nuts, legumes, fruits/veggies and unrefined cereals)
☐ Intermittent fasting (whole day fasting or restrictive eating for more than 16 hours daily)
☐ Paleo (a diet focused on meat, fruits/veggies, and nuts which excludes dairy, legumes, grains and sugar)
☐ Whole 30 (a diet which excludes sugar, alcohol, grains, legumes, soy and dairy)
☐ Veganism (a diet which excludes all animal products)
☐ Vegetarianism (a diet which excludes meat products)
☐ Raw foods (a diet focused on the consumption of raw food)
☐ Gluten-free (a diet which excludes gluten-containing foods such as wheat, barley, rye and oat)
☐ Others; you may specify: _____

12. When did you start to follow a ketogenic diet? _____
13. Are you still following the ketogenic diet? Yes / No
    If no, when did you stop? _____
14. What is your daily carbohydrate goal? _____ g
15. Do you monitor ketone bodies? Yes / No
    If yes, how? (urine or blood tests) _____
    How often?
    - ☐ Once a week
    - ☐ 2-3 times a week
    - ☐ 4-7 times a week
    - ☐ Every 2 weeks
    - ☐ Once a month
    - ☐ Other (please specify); _____

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Appendix 1.4 – Participants' Characteristics

Addendum from Table 1

Sample size, n	14
Age, years, mean (SD)	54.5 (10.1)
Sex	
Males	6 (42.9)
Females	8 (57.1)
BMI before starting the KD, kg/m^2, mean (SD)	31.5 (5.1)
Overweight/obese (BMI >25kg/m^2)	12 (85.7)
Race	100% Caucasian
Type of diabetes, n (%)	
Type 1	3 (21.4)
Type 2	11 (78.6)
Current use of diabetes medications, n (%)	7 (50.0)
Insulin	2 (14.3)
Oral hyperglycemic agents (OHA)	3 (21.4)
Both (insulin and OHA)	2 (14.3)
Daily carbohydrate intake target, g/day, mean (SD)	22 (12.3)
Daily target <20 g/day, n (%)	10 (71.4)
Following the KD at the time of interview	12 (85.7)
Followed at least 1 diet in the past	10 (71.4)
History of significant weight loss§§§§§§§§§§	
Yes, once	1 (7.1)
Yes, twice	3 (21.4)
Yes, on ≥3 occasions	8 (57.1)
No	2 (14.3)
Monitoring ketones at the time of interview	11 (78.6)
Duration of the KD, months, median and range	5, range 3-19

Abbreviations: *BMI*, Body Mass Index; *KD*, Ketogenic Diet

§§§§§§§§§§ Defined as >5% of usual body weight.

APPENDICES

APPENDIX 2
Supplementary Materials for Manuscript 2

Appendix 2.1 – Flowchart of Participants Included