Human Salivary Nerve Growth Factor associated with Painful Temporomandibular Disorders

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DEDICATION

This thesis is dedicated to the memory of my beloved father, Alberto Fernando Monteiro do Nascimento and to my precious stillborn daughter. I miss them incredibly every second of my life, but I feel immensely blessed to have had their presence in my life; owing to them, I am a better person every day.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

TMD – Temporomandibular Disorder

pTMD – Painful Temporomandibular Disorder

TMJ – Temporomandibular Joint

NGF – Nerve Growth Factor

sNGF – Salivary Nerve Growth Factor

MP – Myofascial Pain

DD – Disc Displacement

RDC/TMD – Research Diagnostic Criteria for Temporomandibular disorders

CMI – Craniomandibular Index

GCPS – Graded Chronic Pain Scale

NIH – National Institute of Health

NIDCR's TIRR – National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository

UMN – University of Minnesota

RSBO – Réseau de recherche en santé buccodentaire et osseuse

FRSQ – Fonds de recherche en santé du Québec

ELISA – Enzyme-Linked Immunosorbent Assay

OR – Odds Ratio

CI – Confidence Interval

SD – Standard Deviation

ICC – Intraclass Correlation Coefficients

NRS – Numeric Rating Scale

ABSTRACT

Objective: Inflammatory mediators have been proposed to be biomarkers of painful Temporomandibular Disorders (pTMD). The aim of this study was to identify if salivary nerve growth factor (sNGF), an inflammatory mediator, is a marker of pTMD.

Methods: Data from 124 participants with TMD and 97 controls were obtained from the National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository. pTMD diagnosis was determined by clinical examination conducted by calibrated clinicians using a Modified Craniomandibular Index (CMI), wherein the CMI examination items were redesigned to conform precisely to those specified for the Research Diagnostic Criteria for TMD. Participants completed questionnaires to assess pain, medical history, oral habits and demographics. Five milliliters of unstimulated whole saliva were collected from all participants on the same day of the clinical examination. Blinded laboratory assays were performed to measure the sNGF levels using commercially available ELISA kits.

Results: The pTMD group contained more females (109/124; $P = 0.0003$) and was older ($P < 0.0001$) than the control group. Participants with pTMD did not show greater likelihood to have higher levels of sNGF than controls (OR = 0.92; $P = 0.43$). However, older participants with high sNGF levels were almost twice as likely to have pTMD as controls (OR = 1.87; $P = 0.01$). Moreover, pain intensity was positively associated ($\beta = 0.38$; $P = 0.008$) with sNGF levels in pTMD participants who reported pain greater than 4 (0-10 Numeric Rating Scale). pTMD participants taking anti-inflammatories had significantly lower levels of sNGF than those who did not ($\beta = -0.73$; $P = 0.0004$).

Conclusion: Our results show that the likelihood of having pTMD is not related to higher levels of sNGF, except among older participants, high sNGF levels may contribute to worsening the pain severity.

RÉSUMÉ

Objectif : Les médiateurs inflammatoires ont été proposés comme marqueurs biologiques des désordres de l'articulation temporo-mandibulaire (DTM). Le but de cette étude est d'identifier si le facteur de croissance nerveuse présent dans la salive (sFCN), un médiateur inflammatoire, est un marqueur de DTM.

Méthode: Les données de 124 participants avec DTM et 97 témoins, sans DTM, ont été obtenues du « National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository ». Le diagnostique de DTM a été réalisé par examen clinique effectué par des examinateurs calibrées en utilisant l'indice craniomandibular (ICM) modifiée, dans lequel les questions de ICM ont été redessinés afin de se conformer exactement à celles spécifiées pour les Critères Diagnostiques de Recherche des Désordres Temporo-mandibulaires. Les participants ont rempli des questionnaires destinés à évaluer la douleur, les antécédents médicaux, les habitudes orales et la démographie. Cinq ml de salive non-stimulée ont été recueillis le même jour de l'examen clinique. Des tests de laboratoire en aveugle ont été réalisés pour mesurer les niveaux de sFCN en utilisant des kits « ELISA » disponibles sur le marché commercial.

Résultats: La majorité des 124 participants dans le groupe de DTM étaient des femmes (P = 0.0003), et plus âgés que les 97 témoins (P < 0.0001). Les participants atteint de DTM n'étaient pas plus probables d'avoir des niveaux de sFCN significativement plus élevés que les témoins (OR = 0.92; P = 0.43). Toutefois, les participants plus âgés avec des niveaux plus élevés de sFCN étaient presque deux fois plus susceptibles d'être atteints de DTM que les témoins (OR = 1.87; P = 0.01). En outre, l'intensité de la douleur était associée positivement (β = 0.38; P = 0.008) avec les niveaux de sFCN quand la douleur reportée variait de modérée à sévère (>4; 0-10 échelle d'évaluation numérique). Les participants prenant des anti-inflammatoires avaient des niveaux significativement inférieurs de sFCN à ceux qui n'en prenait pas (β = -0.73; P = 0.0004).

Conclusion: Nos résultats indiquent que la probabilité d'avoir DTM n'est pas liée à des niveaux plus élevés de sFCN, sauf chez les participants plus âgés et les niveaux plus élevés de sFCN peuvent contribuer à l'aggravation de la sévérité de la douleur.

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PREFACE

The format of this thesis follows a manuscript-based format thesis. The manuscript included in this thesis discusses the original study on the levels of a salivary biomarker (i.e., nerve growth factor) associated with painful temporomandibular disorders. The first chapter consists of a brief introduction of the topic, which is followed, in the second chapter, by an up-to-date background regarding temporomandibular disorders, saliva samples and biomarkers. The aims of the study are presented in the third chapter, and a discussion about the methodology applied in this study is proposed in the fourth chapter, which is followed by the manuscript *per se*. Finally, the final discussion and conclusions are presented in the sixth and seventh chapters.

The recognition of every author's contribution to the manuscript of this study is presented in the next section.

CONTRIBUTIONS OF AUTHORS

Manuscript:

Human salivary Nerve Growth Factor associated with Painful Temporomandibular Disorders: a Case-Control Study

Priscila Sander, DDS, M.Sc. Candidate, McGill University, Faculty of Dentistry: performed the literature review, carried out statistical analyses, and wrote the manuscript.

James Fricton, Professor Emeritus, University of Minnesota, School of Dentistry: director of the NIDCR's TIRR database which was used to recruit the data.

Mervyn Gornitsky, Professor Emeritus, McGill University, Faculty of Dentistry and Jewish General Hospital, Department of Dentistry: contributed to manuscript writing.

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Mike Giovinazzo, Research Assistant, Jewish General Hospital, Lady Davis Institute: conducted the laboratory assays and provided comments on the manuscript.

Ana Miriam Velly, Associate Professor, McGill University, Faculty of Dentistry and Department of Dentistry, Jewish General Hospital: designed and supervised

the NIDCR's TIRR study, contributed to statistical analyses, provided statistical and epidemiological expertise, and reviewed and contributed to manuscript writing.

CHAPTER 1 – INTRODUCTION

Temporomandibular disorder (TMD) is nowadays an increasingly reported condition within populations worldwide. In the general population, where the prevalence of painful TMD (pTMD) ranges from 5% to 10% (3, 4), it is the second most commonly occurring musculoskeletal disorder, after back pain (5) and is more frequent among women (2%-18%) than men (0-10%) (6-8). pTMD is characterized by musculoskeletal pain in the muscles of mastication, the temporomandibular joint (TMJ), or both, and is often aggravated during jaw function (9). One in three individuals seeking care for pTMD still report persistent pain after 5 years of the treatment (10, 11).

The specific mechanisms implicated in the persistence of pTMD are not clear (12). In fact, pTMD has been related to the dysregulation of pain modulatory systems involving the central and peripheral nervous systems and the immune system (13). A number of animal and human studies have been performed to identify biomarkers of pTMD (14-17). A biomarker is defined as a pharmacological or a physiological measurement that is used to indicate a normal biological or toxic event and has a particular feature that makes it useful for measuring disease progression or the effect of treatments (18-20).

Nerve Growth Factor (NGF), a neurotropic protein often employed as an indicator of mechanical injury and inflammation, has been suggested as a possible pTMD biomarker (21). NGF is naturally found in certain glands and fluids of the body (e.g. blood and saliva), and is produced by mast cells, macrophages and

Schwann cells (22). NGF stimulates growth and maintenance of sympathetic and sensory nerve cells (23, 24). Cells deprived of NGF may undergo apoptotic changes and death (25). In addition, NGF is present in many forms of inflammation (22, 26), and is taken up by the tissues leading to hyperalgesia (27).

In fact, pain is a very subjective experience that can vary greatly among individuals (28). Hence, it would be crucial to have a biomarker of pain status. We therefore evaluated the relationship between salivary NGF (sNGF) levels and pTMD. More specifically, we investigated whether:

1) Participants with high levels of sNGF were more likely to have pTMD, regardless of the number of putative confounders;

2) Levels of sNGF were positively related to pain status - pain intensity, pain subgroups (persistent and recurrent) and pain upon muscle palpation - regardless of the number of putative confounders.

To our knowledge, no research exists addressing the magnitude of variations in sNGF levels between individuals with and without pTMD.

CHAPTER 2 – LITERATURE REVIEW

2.1 Painful Temporomandibular Disorders

It has been reported that TMDs have an impact on over 10 million to as many as 36 million adults in the United States of America (29, 30). TMDs are a group of disorders that affect the TMJ, the muscles of mastication or both (8). pTMD is characterized by musculoskeletal pain in the muscles of mastication, the TMJ, or both and is often aggravated during jaw function (9). TMDs are reported to be more common in females (2-18%) as compared to males (0-10%), with a female to male ratio ranging from 1.2 to 2.6 (7).

Among those affected, approximately half to two-thirds will seek professional care, with an annual cost estimated at $4 billion dollars (5). A number of individuals seeking treatment for TMD will progress to chronic pain, which is defined as a pain that has persisted beyond normal tissue healing time up to 3 to 6 months (31). In addition, many studies have demonstrated that pTMDs may cause individuals to be debilitated in relation to mastication, speech, and sleep; thus, pTMDs have an influence on decreasing individuals' quality of life (32). The field of pTMD is experiencing countless changes in terms of etiology and treatment.

2.2 Epidemiology of Temporomandibular Disorders

2.2.1 Prevalence of Painful Temporomandibular Disorders

Prevalence is a term commonly used in epidemiological studies, and is defined as the proportion of a population found to have a condition within a particular period of time; thus, it is considered as a "measure of disease status" (33). Within literature, prevalence is usually separated in two different terms: period prevalence and point prevalence. Period prevalence is the number of people with a specific disease or condition in a period of time (34). Point prevalence is a measure of the proportion of people in a population who have a disease at a specific date (35).

A great number of epidemiological studies have estimated the prevalence of TMD (Table 2.2.1). A study performed among 677 random Canadian adults (67% participation rate) reported an overall prevalence of 5.5% (pain in the TMJ while opening) and 7.5% (pain in the TMJ while chewing) (36).

In a survey among 1,016 subjects from the Health Maintenance Organization (80% of participation rate) 12% of individuals reported pain in the muscles of the face, joint, and jaw in the last 6 months (37).

A survey conducted among 897 Quebecers (64% response rate) showed that 30% of participants reported at least one episode of pain in the muscles of mastication and jaw joints (38).

A telephone survey conducted among 19,586 adult women in New York metropolitan area (60% participation rate) found that about 10% of those

participants reported pain in face or in the front of the jaw in the last six months (3).

A population-based survey among 30,978 individuals (79% participation rate) from the National Health Institute Survey reported a prevalence of 5% of facial ache or pain in the jaw muscles or the joint in front of the ear (4).

An OPPERA study among 3,263 participants showed that females aged between 35 and 44 years old reported the highest prevalence of pTMD (7.1%) in comparison to females aged 18 - 24 years old (3.5%). However, the authors did not show the overall prevalence for the total population (39).

Table 2.2.1. Prevalence of Painful Temporomandibular Disorders

Authors, Year	Study Design	Sample Size	Age	Assessment	Condition	Prevalence %
Locker *et al*., 1988	Survey	677	18-65	Telephone Survey/ Questionnaire	TMJ pain while opening mouth	7.5
Von Korff *et al*., 1988	Cohort/ Survey	1,016	18-75	Symptom Checklist	Orofacial Pain	12
Goulet *et al*., 1995	Survey	897	18+	Telephone Survey/ Questionnaire	TMD Pain	30
Janal *et al*., 2008	Survey	782	18-75	Telephone Survey/Clinical examination	Myofascial TMD	10
Isong *et al*., 2008	Survey	30,987	-	Self-reported	Myofascial TMD	5
Slade *et al.,* 2011	Cohort/ Survey	3,263	35-44	RDC/TMD	TMD-like pain	7.1

2.2.2 Incidence of Painful Temporomandibular Disorders

Incidence is the proportion or rate of new conditions or diseases occurring in a defined population during a specified time period (34). Within the literature, two types of incidence can be found: incidence rate or density and cumulative

incidence. Incidence rate is the number of new cases of a disease during a specific period of time divided by the total persons-time of observation (34). The denominator for incidence rate changes as persons originally at risk develop a disease during the period of observation. Cumulative incidence gives an estimation of the probability that an individual will develop a condition during a specific period of time (34).

Some studies have assessed the incidence of TMD (Table 2.2.2). A cohort study performed in 1016 subjects from the Health Maintenance Organization aged between 18-65 reported a annual incidence of TMD of approximately 2.2% (40).

Another study reported an overall annual incidence of 2.9% among 2,255 adolescents 12 to 19 years of age over three years, and the annual incidence was higher among females (4.5%) as compared to males (1.3%) (41).

More recently, a cohort study among 2,737 subjects in the USA reported an annual incidence of 3.9%. However, this cumulative incidence increased from 2.5% (age 18 - 24) to 4.5% (age 35 - 44) *per annum* with increasing age (42).

Table 2.2.2. Incidence of Painful Temporomandibular Disorders

Authors, Year	Study Design	Sample Size	Condition	Annual Incidence %
Von Korff *et al*., 1993	Cohort	1,016	Painful TMD	2.2
Nilsson *et al.,* 2007	Cohort	2,255	Painful TMD	2.9
Slade *et al.,* 2013	Cohort	2,737	Painful TMD	3.9

2.3 Diagnostic of Temporomandibular Disorders

A number of classification systems have been proposed for the diagnosis of TMD including both systems used in this study: the Craniomandibular index (CMI) and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD).

2.3.1 Craniomandibular Index

Fricton *et al*. were the first group to suggest the CMI in order to stipulate a standardized measurement of limitation of mandibular movement, muscle and joint tenderness, and TMJ sounds (43). In addition, similar to the RDC/TMD, this classification was based on clinical examination (43). The CMI was separated into two categories: Palpation Index, which is calculated by adding scores of tenderness on palpation of the muscles of mastication and TMJ; and Dysfunction Index, which is based on the examination of the TMJ function (43).

2.3.1.1 Reliability and Validity of CMI Classification

Several studies have been performed in order to validate the CMI. A study conducted by Fricton *et al.* presented that the validity of the CMI was reasonably accurate and could be used in clinical studies, but strict precautions should be taken into account by the examiners to ensure the replicability of results (44).

Pehling *et al.* analyzed the correspondence between the CMI and the RDC/TMD, and found a great significant agreement between them for the measurement of TMD severity (ICC = 0.97, $P < 0.001$). For all 12 participants in this study, the mean TMI score was 0.26 (SD 0.18) and CMI score was 0.26 (SD 0.19) (45).

2.3.2 Research Diagnostic Criteria for Temporomandibular Disorders

More than 20 years ago, Dworkin and LeResche established an important classification for TMD, the well-known RDC/TMD, in order to reduce the variability of examination methods that was frequently noticed within studies (46). The RDC/TMD is a dual-axis method, wherein clinical examination (Axis I), as well as psychological status and pain-related disability (Axis II) are assessed among all subjects of a study (47).

The RDC categorize TMD into three specific groups according to the frequency of factors among conditions:

Group I: Muscle Disorders – a) Myofascial pain (MP) and b) MP with limited mouth opening. Myofascial pain is defined as a pain in the muscles of mastication or pain at palpation in at least three sites, with one of them at least on the same side as the reported pain. Myofascial pain with limited mouth opening is the pain in the mandibular area and/or muscles of mastication with limitation of the mouth opening, such as pain-free <40mm in unassisted opening and ≥5mm in passive stretch.

Group II: Disc Displacements (DD) – which can be: a) with reduction, characterized by stretching of the ligaments that hold the disc in place, producing a clicking-like sound and the joint is pain-free; b) DD without reduction with limited opening, characterized by absence of TMJ clicking and/or painful opening of ≤35mm and passive stretch of ≤4mm; c) DD without reduction without limited opening in which the ligaments are extended to the limit, and painful opening >35mm and passive stretch >4mm with contralateral excursion of more than 7mm. DD is often defined as an abnormal relationship of the articular disc to the mandibular condyle and the articular eminence of the TMJ (46).

Group III: Other common Joint disorders – such as arthralgia, which is the pain in the joint without crepitus; osteoarthritis that is a pain in the joint with crepitus; and osteoarthrosis, which is pain-free joint with crepitus.

2.3.2.1 Reliability and Validity of RDC/TMD Classification

A satisfactory measurement should provide exactly the same value if applied repeatedly by different examiners or by the same study group at a different point in time (48). Thus, reliability is also called reproducibility. Validity deals with the truthfulness of the measurement (49).

The RDC/TMD diagnostic system has been widely used and translated into 21 languages. A study conducted by John *et al.* investigated the reliability of clinical TMD diagnosis using definitions contained in the RDC/TMD. They looked into 10 assessment trials conducted by international clinical centers

(San Francisco, Portland, USA; Singapore; Sydney, Australia; Amsterdam, The Netherlands; Heidelberg, Germany; Zurich, Switzerland; Naples, Italy; Linkoping and Malmo, Sweden), which involved 30 clinical TMD specialist examiners who assessed 230 subjects. Volunteers were included as healthy controls. Reliability assessment for RDC/TMD was conducted within each clinical center and between centers by computing the Intraclass Correlation Coefficients (ICC), which is a measure of similarity of units that share the same quantification procedure. Results showed fair to good reliability for MFP with and without limited mouth opening (ICC = 0.51 and 0.60), disc displacement with reduction (ICC = 0.61), and arthralgia (ICC = 0.47). The reliability of diagnostic classification improved when diagnoses were grouped into pain versus non-pain diagnosis (ICC = 0.72) (50).

A study conducted by Schiffman *et al.* presented a modified version of the RDC/TMD currently called Diagnostic Criteria for TMD (DC/TMD). They found a satisfactory sensitivity and specificity for myalgia (0.90 and 0.99, respectively), arthralgia (0.89 and 0.98, respectively), myofascial pain (0.86 and 0.98 respectively), and headache attributed to TMD (0.89 and 0.87 respectively). On the other hand, a medium sensitivity and specificity were found for DD with reduction (0.34 and 0.92, respectively), DD with reduction with intermittent locking (0.38 and 0.98, respectively), DD without reduction with limited opening (0.80 and 0.97, respectively), DD without reduction without limited opening (0.54 and 0.79, respectively), and degenerative disease (0.55 and 0.61, respectively) (51).

2.4 Etiopathogenesis of Temporomandibular Disorders

Initially, TMD was believed to be related simply to malocclusion and unsuitable jaw position (52). Over the years, improvements in the understanding of the biomechanics, neuromuscular physiology, and mechanisms of pain led to significant changes in the rationale related to the cause of TMDs (30).

Nowadays, TMDs are described as having a multifactorial etiology (53, 54). Engel *et al.* first proposed the term biopsychosocial, which compiles biological psychological, and social factors (55). Dworkin and LeResche suggested a biopsychological model of chronic pain development and understanding of pTMD. This model described the variability in the individual pain experience (46).

Contemporary biopsychosocial models of chronic pain attribute an important role of psychosocial factors in contributing to the experience of chronic pain (56). In fact, chronic pain is a multidimensional and complex condition since it is related to subjectivity and private experience, such as the implication of the emotional-affective system, pain behavior, and environmental factors (57). In recent years, based on the biopsychosocial model, several contributing factors have been proposed for pTMD, such as grinding, clenching, comorbidities, trauma, psychological factors, gender and age. The model that succeeded the one proposed by Dworkin and LeResche presented that TMD is also affected by risk factors as suggested by biopsychosocial models, such as pain amplification, pro-inflammatory states, and impaired pain regulation (58).

2.5 Mechanisms of Pain

2.5.1 Peripheral Mechanisms and Sensitization

The facial muscles and TMJ are innerved by nerve afferent fibers of the trigeminal nerve and, in the orofacial tissues, these afferent fibers finish as free nerve endings (59). Free nerve endings are considered nociceptors since they are activated by noxious stimuli which is defined as "an actually or potentially tissue damaging event" (60). These fibers respond to peripheral stimulation of tissues (61, 62), and recognize the occurrence of noxious stimulus (59). Two fiber types (Aδ and C-fibers) are in charge of conducting nerve impulses into central nervous system (63). In fact, Aδ fibers are myelinated, medium-diameter fibers, responsible for fast conduction, acute and sharp pain. While C-fibers are non-myelinated, small-diameter, responsible for slow conduction and diffuse pain (64).

Damage or injury to tissue is always followed by an inflammatory process (65). Immediately after the damage, some chemical mediators (e.g., NGF, histamines – Figure 2.5.1) are released at the site of injury and increase the excitability (66, 67). The activation of the afferent fibers

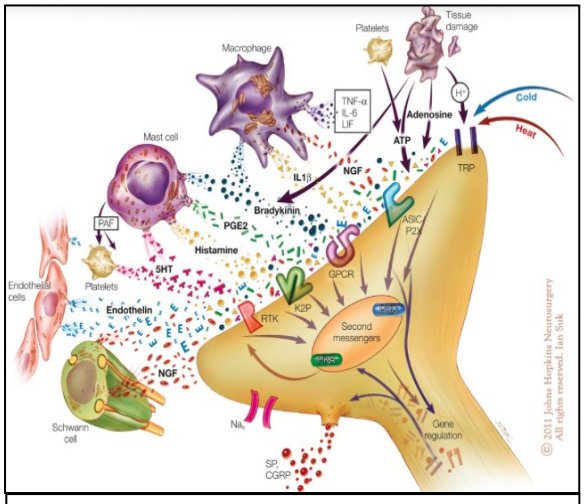

Figure 2.5.1. Chemical mediators involved in inflammation-related peripheral sensitization. From Ringkamp *et al.* Copyright 2011 by Ian Suk. Reproduced with permissions (1).

initiates the conduction of nerve impulses to the central nervous system (63). In the case of the persistence of the stimulus, a considerable modification of the peripheral nervous system and a sensitization of the nerve fibers will occur, consequently leading to a hyperalgesia of the nociceptors (65) to such an extent that even a low intensity stimulus can trigger them; in fact, this phenomenon is extensively reported as peripheral sensitization (68). This event comes after the activation of many mediators, including inflammatory mediators, and is followed by the reduction of the threshold of nociceptors (65). Some chemical irritants, such as capsaicin, when applied to a tissue may display a similar mechanism of action (hyperalgesia), as well as an intense response to an innocuous noxious stimuli (allodynia) and even spontaneous activity (63).

Therefore, nociceptors may translate thermic, chemical, or mechanical stimuli into an electrical stimulus which will pass on to the central nervous system and be interpreted by the cerebral cortex as pain (65). The mechanisms involved in the peripheral sensitization of orofacial nociceptive endings have been studied for over two decades; however, they have not been completely elucidated (1, 63).

2.5.2 Central Mechanisms and Sensitization

During the pathway of pain from nerve cells into the central nervous system (Figure 2.5.2) some changes may occur in the spinal cord showing that this is a dynamic process (64, 69) which leads to an expanded response of the neurons in the central nervous system or, in the case of orofacial pain, in the trigeminal

nerve. After this process there is a facilitation of the passage of the signal, which will then be recognized as pain.

Central sensitization is characterized by pronounced changes of the response effects of the neurons in superficial, profound and ventral cords during inflammation (70). It is usually observed after cutaneous inflammation, cutaneous capsaicin application and inflammation in the joint, muscle and viscera (70).

In fact, a number of neurons respond to stimulation in damaged tissue after sensitization. Furthermore, central sensitization may persist for days or even weeks considering the variety of stages of neurons' acute and chronic inflammation (71, 72).

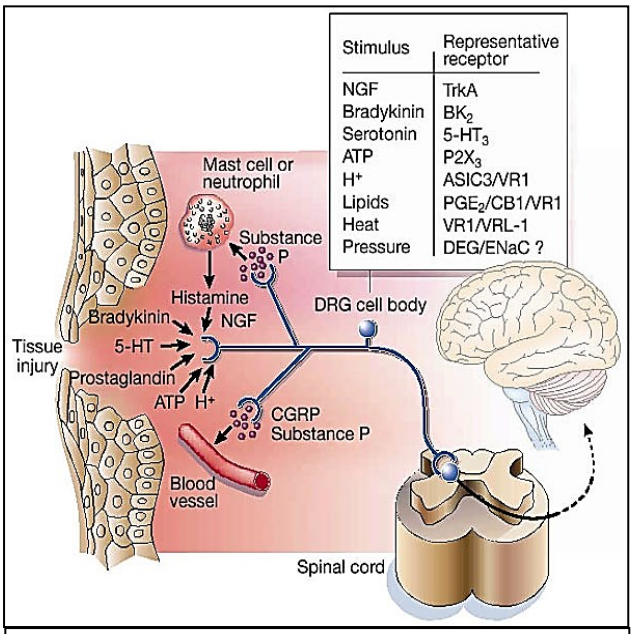

Figure 2.5.2. Scheme showing inflammatory mediators released at the site of tissue injury that go through peripheral (nerve fibers) to central mechanisms (spinal cord and brain). Reproduced with permissions (2).

2.6 Pain Mediators

As illustrated in the figures 2.5.1 and 2.5.2, there are many mediators involved in peripheral and central mechanisms of pain, such as histamine, bradykinin, prostaglandin, substance P and NGF.

2.6.1 Nerve Growth Factor

A well-known pain mediator assayed in this study was NGF. It was first tracked down more than six decades ago and was described as a substance present in the body that is capable of inducing neuritis outgrowth in explants from sympathetic and sensory ganglia (73). Nowadays, NGF is defined as a neurotropic protein naturally found in certain glands and body compartments (e.g., synovial fluid, blood, saliva and muscles tissues), and that stimulates the growth of sympathetic and small diameter sensory nerve cells (23, 24). NGF is mostly produced in the mast cells, macrophages and Schwann cells (22), and plays an essential role for the survival and maintenance of sympathetic neurons (74). The cells deprived on NGF may undergo apoptotic changes and death (25, 75).

2.6.1.1 NGF: Peripheral and Central Mechanisms of Pain

NGF is evident in many forms of inflammation (22, 26), and is taken up by the tissues leading to hyperalgesia (27). A number of previous studies have reported that the injection of NGF leads to pain responses like hyperalgesia, allodynia and muscle sensitization (27, 76-79).

Malik *et al.* observed a rapid onset hyperalgesia with a significant decrease in mechanical nociceptive threshold after 10 minutes of the injection of NGF on the dorsum of the hind paw of male rats (76).

A recent experimental study conducted by Wu *et al.* on rats showed that hippocampal NGF was upregulated by TMJ inflammation induced by complete

Freund adjuvant injection into the bilateral TMJs and it may be involved in allodynia of inflammatory TMJ pain (79).

Svensson *et al*., in a randomized double-blind placebo study among 12 healthy male subjects (mean age of 24.8 ± 2.8 years), found that NGF injection in the masseter muscle was associated with a decrease in pressure pain threshold, and with local signs of mechanical allodynia and hyperalgesia within seven days after administration of the substance (27).

Andersen *et al.*, also in a double–blinded placebo controlled study among 20 healthy individuals, noticed a local hyperalgesia and increased muscle soreness after the injection of NGF in the tibialis anterior muscle in comparison to the contralateral site (77).

In another randomized and placebo controlled experiment among 10 healthy subjects, Nie *et al.* noted higher pain ratings during temporal summation, and muscle soreness responses in the NGF-injected side of the trapezius in comparison to the contralateral side (78).

However, a case-control study did not find a significant difference in the levels of NGF in plasma, synovial fluid and masseter muscle, between 27 pTMD participants and 23 controls without TMD (16). This discrepancy between studies may be related to TMD pain characteristics and/or confounders, and body compartments since the mean levels of NGF in human body vary largely within studies and fluids of assessment (16, 80-85). Salivary glands represent the largest source of circulating NGF in animal models (68).

2.7 Saliva as a Diagnostic Tool

Blood is historically and widely the chosen fluid for assessing any systemic condition until now. However, blood collection may imply some risks to subjects, which includes pain, discomfort and possible infection (86). These risks make the collection of this type of body fluid less recommendable for children and older subjects. Hence, saliva has many advantages compared to other bodily fluids, such as blood.

Collecting saliva samples has numerous advantages: a) it is basically non-invasive, thus generally preferred by individuals, especially children; b) it has a great participation rate (>70%) obtained in previous studies, which reduces the chances of selection bias (87, 88); c) it is stress-free and safe; d) it can also allow repeated sampling for serial measurement; and e) it is usually performed by the subject of analysis with the supervision of a trained person, which makes this method less costly since it does not require a trained phlebotomist. However, salivary flow and diurnal rhythm can vary and this may affect some parameters of investigation (89).

Human saliva is composed of 98% water and 2% of other compounds, such as antibacterial composites and multiples enzymes (90). It has multiple functions including: food digestion, food and bacterial clearance, lubrication of soft tissues, bolus formation, dilution of detritus, swallowing, immune-related functions, speech, taste and facilitation of mastication (86, 90, 91).

Even though all these functional components have been identified in saliva, numerous molecular functions in the oral cavity remain unknown. Recent evolution in proteomic, genomic and metabolomic techniques has advanced the sensitivity and improved the extension of usefulness in the diagnosis (90). For the past 25 years, salivary diagnostics have been explored for the detection of oral diseases, permitting the assessment of periodontal diseases, as well as caries' risk (92-99).

Salivary biomarkers can be analyzed from unstimulated whole saliva, resting saliva or stimulated saliva from specific gland pairs (such as parotid or submandibular-sublingual pairs) (86). Unstimulated whole saliva is defined as the saliva present in the oral cavity for the majority of a 24-hour period. Unstimulated whole saliva is usually correlated to systemic conditions more accurately than stimulated saliva because the materials used to stimulate flow may change salivary composition (as it induces a higher production of saliva resulting in diluted composition) (100). Whole saliva is mainly composed of fluids produced by major and minor salivary glands (101). Major salivary glands including parotid, submandibular, and sublingual glands, secrete fluid transported from serum and glandular tissues (101).

A number of measurement tools can be applied to analyze salivary composition. Despite that, in the literature the majority of analyses in saliva are done using Enzyme-Linked Immunosorbent Assays (ELISAs) because of their feasibility, reliability, and precision (86, 90, 101-103).

However, traditional ELISAs generally measure a single biological marker; thus, sample volume requirements increase dramatically if multiple biomarkers are to be measured (86).

CHAPTER 3 – STUDY OBJECTIVES

The main objective of this study was to evaluate the relationship between sNGF levels and pTMD.

More specifically, we investigated whether:

1) Participants with high levels of sNGF were more likely to have pTMD, regardless of the number of putative confounders;

2) Levels of sNGF were positively related to a difference in pain status - pain intensity, pain subgroups (persistent and recurrent) and pain upon muscle palpation - regardless of the number of putative confounders.

CHAPTER 4 – METHODOLOGY

In this chapter, a painstaking description of the database, ethics, study design and population, data collection, saliva collection, saliva and statistical analysis applied in this study was accomplished.

4.1 Database – National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository

pTMD participants (cases) and controls were selected from the National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository (NIDCR's TIRR). This database is held by University of Minnesota (UMN), Minneapolis, Minnesota, United States of America. NIDCR's TIRR retains clinical information including TMD signs and symptoms, other medical findings, laboratory data, fluid samples (i.e., saliva and serum), imaging and dental records, surgical and implant data, as well as demographics (104).

4.2 Ethics

The first protocol of this study was approved by the UMN's research ethics committee before the beginning of this study. After having been explained about their participation in the study, all participants who agreed to participate signed a consent form (Appendix). The research ethics committee and institutional review board of the Jewish General Hospital, Montreal, Canada approved the second

protocol of this study since the database and saliva samples were kept at the Jewish General Hospital on a secured computer and laboratory, respectively.

4.3 Study Design and Population

In this case-control study, 124 pTMD case participants and 97 controls were selected from the NIDCR's TIRR. These NIDCR's TIRR participants consisted of those recruited between 2006 and 2009 from the UMN.

Participants who agreed to participate signed a consent form. The Institutional Review Boards from the University of Minnesota (UMN), Minneapolis, USA, and from the Jewish General Hospital, Montreal, Canada, approved this study.

All participants who were unable to read in English, under 18 years of age and/or with rare diseases such as tuberculosis, liver diseases, hepatitis, Parkinson's disease, multiple sclerosis, sickle cell anemia, sexually transmitted disease, and human immunodeficiency virus were excluded from the NIDCR's TIRR. Myers *et al.* have published detailed data about the NIDCR's TIRR (104).

Only pTMD subjects and controls who had received clinical examinations between 2006 and 2009 participated in this case-control study. The objective of this approach was two-fold: 1) to recruit controls from the same time period as the cases and 2) have both groups examined by the same calibrated examiners.

4.3.1 Cases Selection

In this study, the CMI examination was performed by calibrated examiners at the UMN Oral Health Research Center. According to the NIDCR's TIRR examiners, the pTMD case group was composed of individuals diagnosed with pTMD (see section 2.3). It was decided to recruit cases only between 2006 and 2009 in order to have cases and controls selected from the same base and time period, since controls were only recruited in this specific time frame.

4.3.2 Controls Selection

Controls, individuals without TMD, were outpatients selected from the dental clinic at UMN between 2006 and 2009 for problems other than pTMD. These participants could not have any orofacial pain.

4.4 Assessments and Data Collection

4.4.1 Diagnosis – Primary Outcome

The primary outcome, pTMD diagnosis, was determined by clinical examination using a modified CMI wherein the items were redesigned to conform to those found on the RDC/TMD (46).

4.4.1.1 Pain Assessment

Another primary outcome in this study is current pain intensity which was assessed using the question from the Graded Chronic Pain Scale (GCPS) (105) (Appendix): "How would you rate the worst pain at present time?". Pain intensity was a measure that was considered in this study as being more susceptible to the incurrence of recall bias since participants had to report the level of pain intensity of their pain in the past 6 months; thus, we only performed additional analyses on current pain intensity.

Worst and average pain intensities in the past six months were secondary outcomes and were assessed using the following questions from the GCPS:

1) "In the past six months how intense was your worst pain?";

2) "In the past six months, on the average, how intense was your pain?"

The purpose of each of the above questions is to inquire about participants' rating of their pain intensity in a range from 0 (no pain) to 10 (pain as bad as it could be).

pTMD was classified in pain subgroups as persistent or recurrent using the question from the NIDCR's TIRR questionnaire and RDC/TMD (Appendix):

1) "What is the pattern of your worst problem?", possible answers: recurrent, persistent or one time only.

4.4.2 Putative Confounders

Confounding is a distortion of the exposure-outcome association due to its mutual association with another factor (49). More specifically, a confounder must be associated with E and D and cannot be in the causal pathway between E and D.

The following putative confounders, measured using a detailed NIDCR's TIRR questionnaire (self-reported assessment - see appendix), were included in the analyses:

Oral habits - clenching or grinding - since previous studies demonstrated that injection of NGF into the masseter muscle causes hyperalgesia as well as pain during jaw movement (21), and clenching appears to be associated with craniofacial pain (106).

Periodontal treatment, which has been described as a factor that can influence the levels of many mediators in saliva (92, 98) and is associated with pain and oral inflammation.

Alcohol intake (yes/no), which can influence the amount of saliva and many inflammatory oral diseases (107).

Back pain, which has been related to the odds of having pTMD (9, 109) and degenerated disc tissues were showed as containing high levels of NGF (108).

Stress was also taken into account because it has been indicated that stressful events induce an increase of NGF into the bloodstream (110) and has been related to TMD (111).

4.4.3 Saliva Collection

Participants were instructed to avoid eating, chewing gum, or drinking any liquid, except water, for two hours before the sampling.

On the day of the clinical examination, unstimulated whole saliva was obtained in the morning between 8am and 12pm by asking participants to swish and rinse mouth with clean water and expectorate, then the water was discarded. After the oral rinse they were asked to spit saliva into a 50 cc Falcon tube for 5 minutes. Participants should sit quietly without talking, with the head tilted slightly forward. Collection should be without effort; the participant should not try to work up saliva. As soon as some saliva collects in the mouth, the participant should spit into the tube, and the Falcon tube is then placed on ice during the collection.

At the end of 5 minutes, the ice bucket with the saliva sample was transported to the Repository laboratory. The saliva was transferred to microcentrifuge tubes and centrifuged at 10,000g for 20 minutes at 4ºC. The supernatant was then transferred to microcentrifuge tubes, into 0.5 ml aliquots which were then stored at -80ºC (0.5 ±0.1 ml volume/aliquot). Saliva specimens were sent in a frozen container from the NIDCR's TIRR in Minnesota to the Jewish General Hospital in Montreal, where they were kept in the laboratory directed by Drs. Gornitsky and Schipper at -80ºC until analyzed.

4.5 Saliva Analysis

In this investigation, free mature NGF concentrations in saliva were measured using ELISA (NGF Emax® ImmunoAssay System, Promega, Madison, USA). In the laboratory, the ELISA plates were coated with Anti-NGF Polyclonal Antibody and incubated overnight at 4ºC. The freshly prepared NGF standards and samples were loaded; the plate was sealed and incubated for six hours at room temperature. The second specific monoclonal antibody was added to the plate and incubated overnight at 4°C. Then, the plate was incubated with Anti-Rat IgG HRP Conjugate for 2.5 hours at room temperature. Absorbance values were measured in a microplate reader at 450nm, within 30 minutes of stopping the reaction (Bio-Rad Benchmark Plus, Hercules, USA). The limit of detection was 1 pg/ml.

4.6 Statistical Analysis

Descriptive analyses were performed to evaluate the distribution of sNGF levels within groups. Chi-square was used to compare dichotomous (e.g., gender) or categorical variables (e.g., anti-inflammatory intake) between pTMD and control groups. Student's t-test was used to compare the means of samples between case and controls or between pain status and controls.

Univariate and multivariate logistic regression analyses were performed in order to determine the likelihood that pTMD cases (dependent variable) would have higher levels of sNGF (independent variable) in comparison to controls. These analyses were adjusted by putative confounders (see section 4.5.2).

Odds ratios (OR) and their 95% confidence intervals (95% CI) were estimated. OR is defined as the ratio of exposure odds among cases to exposure odds among controls (33), and odds is the chance or likelihood of something happening or being the case. A logarithmic transformation was applied to the sNGF values to achieve a normal distribution (Figure 1).

Pearson product-moment correlation coefficients were used to assess linear associations between sNGF levels, periodontal disease, headache, pain frequency, pain upon muscle palpation, TMJ surgery and TMJ implant procedures.

Analysis of variance (ANOVA) was used to assess the mean difference of sNGF (dependent variable) between participants exposed and not exposed to the putative confounders. Means and 95% confidence intervals (CI) were estimated.

Multivariate linear regression analyses were used to determine if changes in sNGF levels (independent variables) are associated with pain intensity (dependent variables). Beta and 95% CI were estimated in those analyses.

These logistic and linear regression analyses were both performed for the following groups: 1) TMD cases versus controls, and 2) among pTMD participants with pain greater than 4 (0-10 NRS) and controls. These analyses were also stratified by gender and age. For this study, any participant 50 years of age and above was considered as an older person.

Analyses were performed with SAS version 9.3 software (Statistical Analysis System; Institute Inc, Cary, North Carolina, USA) and the level of significance was set at $\alpha = 0.05$.

4.7 Power Analysis

Post-hoc power analyses were executed for the results presented in the manuscript and are described in this section.

We do not have any prior study describing the sizes of correlation or OR, nor the difference in means of sNGF between pTMD and controls, to calculate the appropriate sample size for the primary analysis: logistic regression (Table 1) and linear regression (Table 2).

Our hypothesis was that high levels of sNGF were moderately correlated with pTMD (from 0.25 to 0.40). Another hypothesis was that high levels of sNGF were positively correlated to current pain intensity with a correlation rating from 0.30 to 0.40, and that this correlation would be high among TMD participants with moderate to severe pain intensity (>0.30). Using these correlations and $\alpha = 0.05$ (two sided test), the required sample size with power of 80% would range between 85 and 123. This sample size was calculated based on the form described by Lachin (1981) (112).

Another hypothesis was that if the true difference between cases and controls means is 0.15, and that standard deviation is 1.34, it would be necessary to include 1128 cases and 1410 controls to be able to reject the null hypothesis that the population means between these groups are equal with probability (power) of 80%. The Type I error probability associated with this test of this null hypothesis is 0.05. The software Power Samples size version 3.0 was used for conducting this analysis.

4.7.1 Post-hoc Power Analysis

4.7.1.1 pTMD and Log sNGF

In our study, we found a very low correlation of 0.05 between pTMD and log sNGF, as well as OR = 1.00 (Table 1). Note that the necessary sample size would be 2500 participants per group in order to obtain a power of 80%, considering these effects and alpha of 5%.

4.7.1.2 Current Pain and Log sNGF

We also found a very low correlation (r = 0.08) between current pain intensity and log sNGF. Taking into account this correlation and alpha of 5%, the required sample size for achieving a power of 80% would be 1224 participants per group.

The non-significant associations previously described (sections 4.7.1.1 and 4.7.1.2) are not due to a small sample size, but to a low magnitude of associations.

These low associations could be due to:

1) sNGF is not related to all TMD diagnosis, but to a sub-group. Our results suggest that sNGF is related to a subgroup that may be more common among elders, and cases with moderate to severe pain.

2) Low levels of sNGF were found among pTMD because they were using a medication to manage their pain. Even if this cannot be completely excluded; the magnitude of the effect almost did not change when the analysis was stratified by use (cases: β = 5.36, 95% CI: 4.58 – 6.13; and controls: β = 5.55, 95% CI:

3.70 – 7.40) or not of anti-inflammatories (cases: β = 6.53, 95% CI: 6.20 – 6.85; and controls: β = 6.62, 95% CI: 6.21 – 7.02) (P = 0.0005).

CHAPTER 5. MANUSCRIPT

Human Salivary Nerve Growth Factor Levels associated with Painful Temporomandibular Disorders: a Case-Control Study

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ABSTRACT

Inflammatory mediators have been proposed to be biomarkers of painful Temporomandibular Disorders (pTMD). The aim of this study was to identify salivary nerve growth factor (sNGF), an inflammatory mediator, as a marker of pTMD. Data from 124 participants with TMD and 97 controls were obtained from the National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository. pTMD diagnosis was determined by clinical examination conducted by calibrated clinicians using the Research Diagnostic Criteria for TMD. Participants completed questionnaires to assess pain, medical history, oral habits and demographics. Five milliliters of unstimulated whole saliva were collected from all participants on the same day of the clinical examination. Blinded laboratory assays were performed to measure the sNGF levels using commercially available ELISA kits. The pTMD group contained more females (109/124; $P = 0.0004$) and was older ($P < 0.0001$) than the control group. Participants with pTMD did not show greater likelihood to have higher levels of sNGF than controls (OR = 0.92; $P = 0.43$). However, older participants with high sNGF levels were almost twice as likely to have pTMD as controls (OR = 1.87; $P = 0.01$). Moreover, pain intensity was positively associated ($\beta = 0.38$; $P = 0.008$) with sNGF levels within pTMD participants who reported pain greater than 4 (0-10 Numeric Rating Scale). pTMD participants taking anti-inflammatories had significantly lower levels of sNGF than those who did not ($\beta = -0.73$; $P = 0.0004$). Our results show that the likelihood of having pTMD is not related to higher levels of sNGF, except among older participants, high sNGF levels may contribute to worsening the pain severity.

Keywords: Nerve Growth Factor; Human Saliva; Temporomandibular Disorders.

INTRODUCTION

Temporomandibular disorder (TMD) is a commonly and increasingly reported condition in the general population with a prevalence ranging from 5% to 10% (3, 4). It is the second most commonly occurring musculoskeletal disorder, after back pain (5), and is more frequent among women (2% - 18%) than men (0 - 10%) (6-8). Painful TMD (pTMD) is characterized by musculoskeletal pain in the muscles of mastication, the temporomandibular joint (TMJ), or both, and is often aggravated during jaw function (9). One in three individuals seeking care for pTMD reports persistent pain after 5 years of treatment (10, 11).

The specific mechanisms implicated in the persistence of pTMD are not completely explained (12), but have been related to the dysregulation of the pain modulatory systems (13).

A number of animal and human studies have been performed to identify biomarkers of pTMD (14-17). A biomarker is defined as a pharmacological or physiological measurement that is used to indicate a biological or toxic event and has a feature that makes it useful for measuring disease progression or the effect of treatments (18, 19).

Nerve Growth Factor (NGF), a neurotropic protein often employed as an indicator of mechanical injury and inflammation, has been suggested as a possible pTMD biomarker (21). NGF is naturally found in certain glands and fluids of the body (e.g. blood and saliva), and is produced by mast cells, macrophages and Schwann cells (22). NGF stimulates growth and maintenance of sympathetic and

sensory nerve cells (23, 24). Cells deprived of NGF may undergo apoptotic changes and death (25).

NGF is present in many forms of inflammation (22, 26), and is taken up by the tissues leading to hyperalgesia (27, 113, 114). Malik *et al.* observed a rapid onset hyperalgesia with a significant decrease in mechanical nociceptive threshold after 10 minutes of the injection of NGF on the dorsum of the hind paw of male rats (76). Nie *et al.* found, in a randomized and placebo controlled experiment among 10 healthy subjects, higher pain ratings during temporal summation, and muscle soreness responses in the NGF-injected side of the trapezius in comparison to the contralateral side (78).

However, in a case-control study including 23 TMD cases and 27 controls, levels of NGF in plasma, synovial fluid of TMJ and masseter muscle were not statistically significantly different between groups (16). This discrepancy among animal, healthy, and clinical TMD studies with respect to the role of NGF may be related to TMD pain characteristics and confounders (e.g., gender and age).

Pain is a very subjective experience and can vary considerably from one individual to another (28). Thus, it would be crucial to have a biomarker of pain status. Furthermore, it is important to assess which confounders might modify the association between pTMD and salivary NGF (sNGF). Only limited information is available about sNGF saliva in pTMD and we therefore evaluated the relationship between sNGF levels and pTMD in this study.

More specifically, we investigated whether:

1) Participants with high levels of sNGF were more likely to have pTMD, regardless of the number of putative confounders;

2) Levels of sNGF were positively related to pain status - pain intensity, pain frequency and pain upon muscle palpation - regardless of the number of putative confounders.

METHODS

Study Design and Population

We conducted a case-control study in which 124 pTMD participants and 97 controls were selected from the National Institute of Dental and Craniofacial Research's Temporomandibular Joint Implant Registry and Repository (NIDCR's TIRR).

Participants who agreed to participate signed a consent form. The Institutional Review Boards from the University of Minnesota (UMN), Minneapolis, USA, and from the Jewish General Hospital, Montreal, Canada, approved this study.

All participants who were unable to read in English, under 18 years of age and/or with rare diseases such as tuberculosis, liver diseases, hepatitis, Parkinson's disease, multiple sclerosis, sickle cell anemia, sexually transmitted disease, and human immunodeficiency virus were excluded from the NIDCR's TIRR. Myers *et al.* have published detailed data about the NIDCR's TIRR (104).

Only pTMD subjects and controls who had received clinical examinations between 2006 and 2009 participated in this case-control study. The objective of this approach was two-fold: 1) to recruit controls from the same time period as the cases and 2) have both groups examined by the same calibrated examiners.

Painful Temporomandibular Disorder Diagnosis

TMD diagnosis was determined by clinical examination performed by calibrated examiners at the UMN using Modified Craniomandibular Index (CMI), wherein the CMI examination items were redesigned to conform precisely to those specified for the Research Diagnostic Criteria for TMD (RDC/TMD) (46). Patients with pain in the muscles of mastication, the TMJ, or both, were included in this study. Controls were participants without the diagnosis of TMD and they could not have any orofacial pain.

Pain Assessment and Data Collection

Pain intensity was assessed using the Graded Chronic Pain Scale (GCPS), on a 0-10 numeric rating scale (NRS) in response to the following questions: 1) "How would you rate the worst pain at present time?" 2) "In the past six months how intense was your worst pain?" 3) "In the past six months, on the average, how intense was your pain?" (40). Based on a previous publication, specific cutoffs for pain intensity were determined (mild: 1-4, moderate: 5-6, and severe: 7-10) (115).

In addition, participants were classified into TMD subgroups of persistent or recurrent pTMD by answering the following questions: 1) "What is the pattern of your worst problem?", with the possible answers being: recurrent, persistent or one time only.

Putative Confounders

In this study, anti-inflammatory intake, oral habits (i.e., clenching or grinding), periodontal treatment, alcohol intake, back pain, gender, and age were considered putative confounders as previous studies have demonstrated that these variables may be related to NGF levels and pTMD (27, 108, 110, 116, 117).

Saliva Collection and Analysis

On the day of the clinical examination, unstimulated whole saliva was obtained in the morning between 8am and 12pm by asking participants - following oral rinsing - to spit for 5 minutes into a 50-ml graduated sterile tube that was then kept on ice. After collection, the saliva was transferred to microcentrifuge tubes and centrifuged at 10,000 rpm for 20 minutes at 4ºC. The supernatant was divided among microtubes, making 0.5ml aliquots, which were then stored at -80ºC (0.5 ±0.1 ml volume/aliquot). Saliva specimens were sent in a frozen container from the NIDCR's TIRR in Minnesota to the Jewish General Hospital in Montreal, where they were kept in the laboratory directed by Dr. Gornitsky and Dr. Schipper at -80ºC until analyzed.

A blinded laboratory assessment was performed by an expert researcher at the Lady Davis Institute, Jewish General Hospital. Free, mature NGF levels in saliva were measured by Enzyme-Linked Immunosorbent Assay (ELISA) as per the manufacturer's protocol (NGF Emax® ImmunoAssay System, Promega, Madison, USA). The plates were then read on a microplate reader at the

wavelength of 450 nm (Bio-Rad Benchmark Plus, Hercules, USA). The limit of detection was 1 pg/ml.

Statistical Analysis

Descriptive analyses were performed to evaluate the distribution of age, gender, and sNGF mean levels within groups. Chi-square tests were used to compare dichotomous or categorical variables between pTMD and control groups. Student's t-test was used to compare the means of samples (e.g., sNGF, age).

Univariate and multivariate logistic regression analyses were performed in order to determine the likelihood that pTMD cases (dependent variable) would have higher levels of sNGF (independent variable) in comparison to controls. These analyses were adjusted by putative confounders (i.e., anti-inflammatory intake, oral habits, periodontal treatment, alcohol intake, back pain, stress, gender and age). We preferred to adjust the analysis, instead of excluding or matching strategies to control confounders, as adjusted analysis allows for controlling the effect of a putative confounder while keeping all patients in the analysis. We also decided to adjust rather than match, as we wanted to evaluate the relationships between sNGF, age and gender, which would not be possible if matching was used.

Odds ratios (OR) and their 95% confidence intervals (95% CI) were estimated. A logarithmic transformation was applied to the sNGF values to achieve a normal distribution (Figure 1).

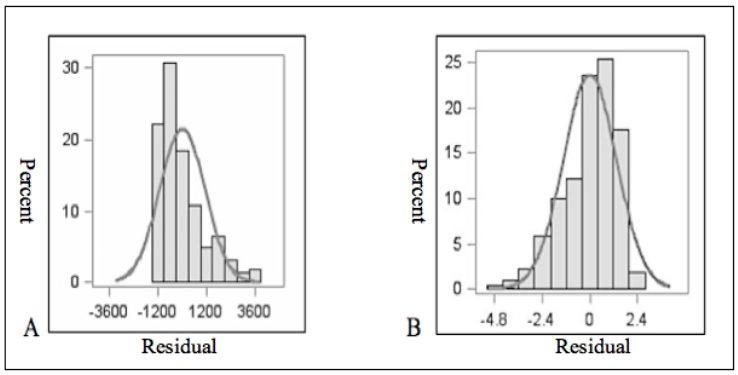

Figure 1. A: graphical demonstration of the distribution of sNGF levels skewed to the right; **B:** demonstration of a normal distribution after the logarithmic transformation.

Pearson product-moment correlation coefficients were used to assess linear associations between sNGF levels, periodontal disease, headache, pain frequency, pain upon muscle palpation, TMJ surgery and TMJ implant procedures.

Analysis of variance (ANOVA) was used to assess the mean difference of sNGF (dependent variable) between participants exposed and not exposed to the putative confounders. Means and 95% confidence intervals (CI) were estimated.

Multivariate linear regression analyses were used to determine if changes in sNGF levels (independent variables) are associated with pain intensity (dependent variables). Beta and 95% CI were estimated in those analyses.

These logistic and linear regression analyses were both performed for the following groups: 1) TMD cases versus controls, and 2) among pTMD participants with pain greater than 4 (0-10 NRS). These analyses were also stratified by gender and age. For this study, any participant 50 years of age and above was considered as an older individual.

Analyses were performed with SAS version 9.3 software (Statistical Analysis System; Institute Inc, Cary, North Carolina, USA) and the level of significance was set at $\alpha = 0.05$.

RESULTS

One hundred and twenty four pTMD cases and 97 controls were included in this case-control study. pTMD cases were significantly older (mean = 42.98 years, standard deviation [SD] = 15.31 years) than controls (mean = 33.89, SD = 13.77; $P < 0.0001$). As expected, participants in the pTMD group (88%) were more likely to be females in comparison to the control group (68%; $P = 0.0003$).

Among pTMD participants, 94 (78%) received the diagnosis of myofascial pain according to the RDC/TMD, 29 (24%) reported having undergone TMJ surgery and 19 (16%) had undergone TMJ implant procedures.

Based on the GCPS scale, the means of current (mean = 4.44, SD = 2.88), worst (mean = 6.67, SD = 2.79) and average pain intensity in the last 6 months (mean = 5.13, SD = 2.65) were moderate. pTMD participants reported persistent pain (n = 64/124, 52%) more frequently than recurrent pain (n = 54/124, 44%; $P < 0.0001$).

Salivary NGF levels and pTMD

The mean sNGF level was not significantly different between pTMD cases (mean = 1114.39 pg/ml, SD = 1120.29) and controls (mean = 1163.89 pg/ml, SD = 1127.28; $P = 0.68$) (Figure 2).

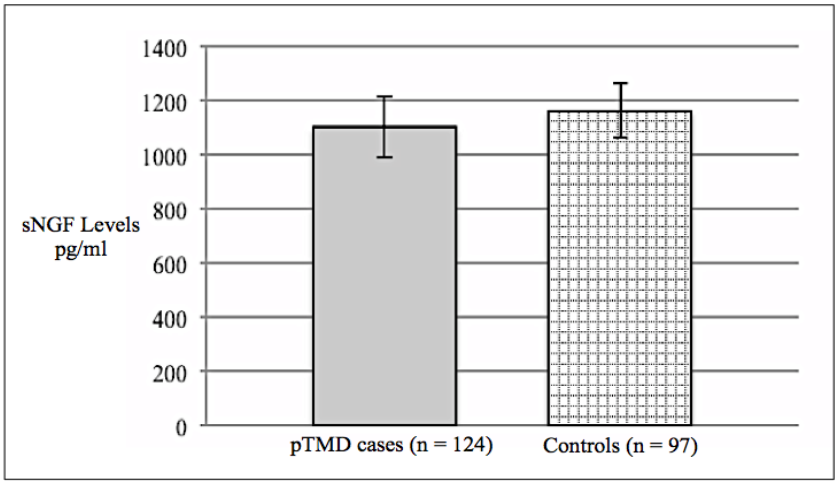

Figure 2. Mean levels of salivary NGF (sNGF) of TMD cases and controls. Error bars represent standard deviations.

This result remained after applying a logarithmic transformation to sNGF (pTMD: mean = 6.33 pg/ml, SD = 1.44 and controls: mean = 6.47 pg/ml, SD = 1.25; $P = 0.47$). Levels of log sNGF were not correlated with TMJ surgery ($r = -0.01$; $P = 0.86$) or TMJ implant ($r = -0.005$; $P = 0.93$).

Levels of log sNGF were also not correlated with pain subgroups (persistent and recurrent: $r = -0.04$; $P = 0.53$), and pain during palpation in the masseter and/or temporalis ($r = -0.06$; $P = 0.36$).

Crude and adjusted logistic regression analyses were conducted in order to identify the likelihood of higher levels of log sNGF in pTMD participants, regardless of the number of putative confounders (Table 1). In the crude (OR = 0.92; $P = 0.43$) and adjusted analyses (model I: OR = 0.98; $P = 0.89$ and model II: OR = 1.00; $P = 0.98$) participants with pTMD did not show a significant likelihood of higher levels of log sNGF. pTMD was associated with clenching ($P < 0.0001$), back pain ($P < 0.0001$), and age ($P = 0.009$).

We furthermore found that the likelihood of higher levels of log sNGF among pTMD participants remained statistically not significant when the analysis was stratified by gender (males: n = 45, OR = 0.59, 95% CI: 0.25 – 1.40; $P = 0.24$ and females: n = 167, OR = 1.05, 95% CI: 0.79 – 1.39; $P = 0.73$).

Among 63 individuals aged 50 years or over, participants with higher levels of log sNGF were almost twice as likely to have pTMD than controls (OR = 1.87, 95% CI: 1.12 – 3.12; $P = 0.01$). This analysis was adjusted by anti-inflammatory intake (OR = 4.49, 95% CI: 0.53 – 37.45; $P = 0.16$), clenching (OR = 11.67, 95% CI: 1.17 – 116.48; $P = 0.04$), back pain (OR = 5.06, 95% CI: 1.03 – 24.71; $P = 0.04$) and gender (OR = 13.60, 95% CI: 1.25 – 140.16; $P = 0.03$). No relationship was noted among 158 participants under 50 years of age (OR = 0.91, 95% CI: 0.67 – 1.24; $P = 0.58$) in a model adjusted by the same variables: anti-inflammatory intake (OR = 2.89, 95% CI: 0.79 – 10.50; $P = 0.11$), clenching (OR = 11.36, 95% CI: 4.46 – 28.91; $P < 0.0001$), back pain (OR = 10.72, 95% CI: 3.30 – 33.99; $P < 0.0001$), and gender (OR = 0.93, 95% CI: 0.35 – 2.47; $P = 0.88$).

Moderate to Severe TMD Pain

In the aforementioned results, we found that higher levels of sNGF are related to the likelihood of having pTMD only in older individuals. In this section, we would like to investigate whether high levels of sNGF would be affected by moderate to severe pain. The magnitude of the effect between log sNGF levels

and pTMD (OR = 0.99; P = 0.99) changed slightly (OR = 0.80, 95% CI: 0.58 – 1.10; P = 0.18) when the analysis included only 63 participants reporting moderate to severe pain (>4; 0-10 NRS). This model was adjusted by anti-inflammatory intake (OR = 2.30, 95% CI: 0.63 – 8.35; P = 0.21), clenching (OR = 16.16, 95% CI: 5.94 – 44.00; P < 0.0001), back pain (OR = 4.50, 95% CI: 1.53 – 13.29; P = 0.006), gender (OR = 1.47, 95% CI: 0.47 – 4.56; P = 0.50), and age (OR = 1.03, 95% CI: 1.00 – 1.06; P = 0.03). All these results remained in the analyses stratified by gender and age (results not presented).

Log Salivary NGF Levels and Pain Status

In these analyses, we investigated whether the level of current pain intensity, worst pain and average pain intensity in the last six months were affected by sNGF levels. In the crude analysis, current (β = -0.20; P = 0.18; Table 2), worst (β = -0.24, 95% CI: -0.63 – 0.14; P = 0.21) and average pain intensity (β = -0.20, 95% CI: -0.51 – 0.12; P = 0.22) were not associated with log sNGF. These results remained in the adjusted model (current: β = -0.13; P = 0.37; Table 2, worst: β = -0.12, 95% CI: -0.47 – 0.23; P = 0.49, and average pain: β = -0.10, 95% CI: -0.40 – 0.18; P = 0.46), regardless of number of putative confounders (Table 2). All these results remained in the analyses stratified by gender and age (results not presented).

Persistent (crude: n = 161, β = -0.13, 95% CI: -0.50 – 0.23; P = 0.47, and adjusted model: n = 157, β = 0.98, 95% CI: 0.68 – 1.41; P = 0.93) and recurrent

pTMD (crude: n = 151, β = -0.21, 95% CI: -0.51 – 0.09; P = 0.17, and adjusted model: n = 147, β = 0.95, 95% CI: 0.70 – 1.29; P = 0.77) were not associated with log sNGF, regardless of number of putative confounders.

Moderate to Severe TMD Pain and Pain Status

The results above show that current, worst and average pain in the last six months were not related to sNGF. In this section, we would like to see whether the severity of pain would be affected by sNGF levels including only 63 participants with current pain intensity greater than 4 (Table 3).

In the crude linear model, log sNGF levels were related to an increase in the levels of current pain intensity (β = 0.38; P = 0.008) (Figure 3).

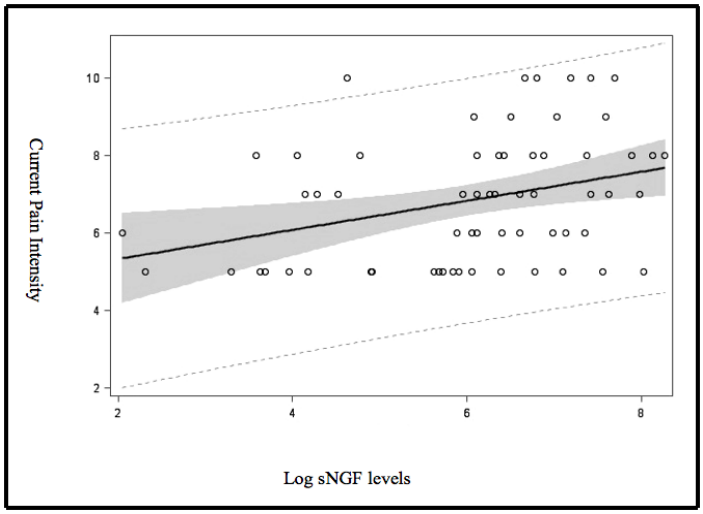

Figure 3. Scatter plot showing the linear association of log sNGF levels with current moderate to severe pain intensity.

We noted that, when the analysis was adjusted by potential confounders, this relationship was stronger and remained statistically significant (β = 0.59; $P < 0.0001$).

However, log sNGF levels remained not related to an increase in the worsening (β = 0.10, 95% CI: -0.21 – 0.40; P = 0.53) or the average pain intensity in the last 6 months (β = 0.11, 95% CI: -0.25 – 0.47; P = 0.55). These results remained in the model adjusted by putative confounders (worst: β = 0.08, 95% CI: -0.26 – 0.43; P = 0.65 and average pain intensity: β = 0.20, 95% CI: -0.21 – 0.62; P = 0.32).

Among females (n = 55), log sNGF levels were positively associated with current pain intensity (β = 0.47, 95% CI: 0.19 – 0.75; P = 0.001) in a model adjusted by anti-inflammatory intake (β = 0.20, 95% CI: -0.55 – 0.95; P = 0.59), clenching (β = -1.11, 95% CI: -1.89 – -0.33; P = 0.006), back pain (β = 0.66, 95% CI: -0.21 – 1.55; P = 0.13), and age (β = -0.04, 95% CI: -0.07 – -0.01; P = 0.004). Among males (n = 8), the magnitude of the slope was greater than that noted among females, but not significant, probably due to the very small sample size (β = 0.71, 95% CI: -0.15 – 1.58; P = 0.08)

Log sNGF levels were also positively associated with current pain intensity among older participants (n = 20, β = 0.91, 95% CI: 0.40 – 1.43; P = 0.001) and younger participants (n = 43, β = 0.31, 95% CI: 0.009 – 0.62; P = 0.04). These models were adjusted by anti-inflammatory intake (β = 0.17, 95% CI: -1.49 – 1.83; P = 0.83; β = 1.05, 95% CI: 0.30 – 1.80; P = 0.007), clenching (β = -0.37, 95% CI: -1.82 – 1.08; P = 0.59; β = -1.11, 95% CI: -2.04 – -0.18;

P = 0.02), back pain (β = 0.84, 95% CI: 0.78 – 2.45; P = 0.28; β = -0.23, 95% CI: -1.27 – 0.81; P = 0.66, and gender (β = 2.21, 95% CI: -0.80 – 5.23; P = 0.14; β = -0.77, 95% CI: -1.98 – 0.44; P = 0.20)

Secondary Analyses

In the following results, we evaluated whether the mean sNGF levels were different when taking into consideration a number of possible confounder – use of anti-inflammatories, oral habits, periodontal treatment, alcohol intake, back pain and stress – since NGF was measured in saliva. Neither periodontal disease (n = 12, r = -0.08; P = 0.23) nor headache (n = 145, r = -0.07; P = 0.28) were associated with log sNGF. Further results (means and 95% CI) for the following variables are presented in table 4.

In the crude analysis, as expected, log sNGF levels among 15 participants taking anti-inflammatories was significantly lower than among those who did not (P = 0.0004). In fact, anti-inflammatory intake showed a statistically significant difference in all models tested ($P \leq 0.003$). It was also interesting to note that the use of one anti-inflammatory does not appear to modify the levels of log sNGF (n = 5, β = 0.99, 95% CI: -0.19 – 2.17; P = 0.10), contrary to the use of two or more anti-inflammatories (n = 10, β = 1.37, 95% CI: 0.51 – 2.22; P = 0.001). These results therefore need to be interpreted with caution since we have small sample sizes in both groups.

Levels of log sNGF were neither associated with grinding (n = 51, crude: $P = 0.49$ and adjusted model: $P = 0.38$) nor clenching (n = 74, crude: $P = 0.80$ and adjusted: $P = 0.29$).

Participants reporting periodontal treatment (n = 19) showed lower log sNGF levels in comparison to those who did not (n = 198) in the crude analysis, this difference was close to the margin of statistical significance ($P = 0.09$), and did not remain associated with log sNGF in the adjusted model ($P = 0.31$).

In the crude analysis, log sNGF levels among participants who had reported drinking a beer or wine daily (n = 13) was higher than among those who did not (n = 206; $P = 0.03$). This significant difference did not remain in the adjusted model ($P = 0.11$).

In the crude analysis, the mean log sNGF levels among 66 participants who had reported back pain was significantly lower than those 149 without back pain ($P = 0.05$). This result did not remain in the adjusted model ($P = 0.29$) and was confounded by use of anti-inflammatory and gender.

In the crude analysis, the mean log sNGF levels among participants who had reported being stressed or overwhelmed (n = 70) was significantly lower in comparison to those who had not (n = 149; $P = 0.04$). This significant difference did not remain in the adjusted model ($P = 0.46$).

DISCUSSION

To our knowledge, this is the first study that investigated whether higher levels of sNGF modify the likelihood of having pTMD. The two main findings are: 1) the likelihood of having pTMD was not related to higher levels of sNGF, except among older participants, and 2) higher levels of sNGF were associated with the worsening of pain severity, among those reporting current moderate to severe pTMD (Table 3). This result supports our first hypothesis that, if the participant has a high level of sNGF, she/he is more likely to have severe pain. It is encouraging to compare this figure with those found by Svensson *et al*. in a randomized double-blind placebo study, which found that NGF injection in the masseter muscle is associated with hyperalgesia (27).

Abnormal high levels of sNGF in the control group could be one explanation for the non-significant likelihood difference found between pTMD cases and controls when all subjects were considered. In fact, in the current study, sNGF levels among controls (mean = 1163.89 pg/ml; SD = 1127.28) were slightly higher than the values reported by Nam *et al.* (mean = 901.4 pg/ml^{-1}; SD = 851.93), who assessed NGF concentrations in resting whole saliva (80). However, our results remained when the analysis were adjusted by a large number of potential confounders, such as anti-inflammatory intake, oral habits (e.g., grinding and clenching), periodontal treatment, alcohol intake, back pain, stress, gender and age. In our secondary analysis, we evaluated the role of sNGF and a number of putative confounders.

Safieh-Garabedian *et al.* showed that inflammation induced by subcutaneous injection of Freund's Complete Adjuvant into the plantar surface of the hind paw of male rats led to a significant increase in NGF levels in the skin of the hind paw (26). We found in the present study that participants taking anti-inflammatories and thereby supposedly having less inflammation, showed reduced levels of sNGF.

Our results further showed that participants who underwent periodontal treatment had lower levels of sNGF than those who did not, suggesting that the reduction of inflammation related to periodontal treatment leads to lower release of NGF in saliva. This result agrees with findings by Gašperšic *et al.*, where systemic anti-NGF treatment during provoked periodontitis in 18 female rats significantly reduced bilateral alveolar bone resorption. This indicates that NGF promotes periodontal inflammation (117).

In addition, participants reporting the habit of drinking alcohol had higher levels of sNGF than those who did not have this habit. This result might be related to the well-known fact that alcohol consumption may lead to xerostomia through dehydration (118), and the reduction of saliva can cause increased risk of caries, mouth soreness, and mucosal injury (107), resulting in an increased secretion of sNGF.

Lower levels of sNGF have also been detected in participants reporting back pain in this study. Contrasting with our result, Lee *et al*. performed western blot analysis using vertebral disc tissues and found greater levels of NGF in 10 patients with degenerated disc disease in comparison to 12 patients with herniated

nucleus pulposus. Unfortunately, this study (Lee *et al.*) did not present the means of NGF levels, preventing a proper comparison of the results (108).

Regarding the age profile, our study showed no significant difference in the levels of sNGF between young and old participants, similar to Nam *et al.* who also found no statistically significant difference between age groups (80). Nevertheless, it was interesting to find that older participants with higher levels of sNGF had a higher likelihood of pTMD. This greater likelihood may indicate a relationship with a specific type of pTMD (e.g., arthralgia, osteoarthritis) among those participants; this is in agreement with Spears *et al.* who found that induced inflammation of the TMJ was accompanied by an elevation on the concentration of NGF in 40 adult male rats (116), as well as with Aloe *et al*. who found that NGF was present in the synovial fluid of the knees from 22 patients with chronic arthritis, but was undetectable in synovial fluid of knee of two patients without chronic arthritis (119).

This study has several strengths. First, all participants received clinical examination by calibrated examiners for the diagnosis of pTMD, using the CMI on the same day as the saliva sample collection. This approach has the advantage of decreasing the chance of diagnosis misclassification among cases and controls since the diagnosis was determined by calibrated examiners. Second, controls for this study were also recruited from NIDCR's TIRR at the same time period as cases, which may decrease the chance of diagnosis misclassification and information bias, and help to ensure consistent assessment and confounder exposure. Third, saliva was collected by trained researchers who followed valid

collection, storage and transportation protocols. Finally, sNGF assays were conducted by the same researcher who was blinded to the study group and saliva outcome, performing them in the same run and day.

On the other hand, some limitations of the study have to be discussed. First of all, chances of misclassification of the subjects in a case-control study are possible, even though calibrated examiners conducted the clinical data collection based on the CMI protocol. However, this bias may be non-differential (toward underestimation) because TMD misclassification should not be related to the sNGF misclassification as the assays were conducted by the same researcher who was blinded to the study group and saliva outcome, and who performed the assays in the same run. Second, even if ELISA is often indicated as being a valid and reliable method to assess different biomarkers (80, 101, 103), measurement errors have to be considered. Third, changes in the concentration of sNGF over time were not studied and we have a prolonged period in which the saliva samples were kept stored, which may interfere with the stability of this biomarker. However, the direction of this bias may again be toward underestimation since the researcher who performed the assays was blind to TMD groups. Finally, although several statistical adjustments were executed to control confounders, unaccounted confounders still may have influenced the observations.

In conclusion, the present study demonstrated that older participants with pTMD were more likely to have higher levels of sNGF than those without TMD. In addition, high sNGF levels may contribute to worsening the pain severity, among participants reporting current moderate to severe pTMD, regardless of

anti-inflammatory intake, gender and age. The identification of human salivary biomarkers associated with pTMD, including NGF, may contribute to the identification of biological markers for chronic pain. This identification may also advance our knowledge of the prognostic factors related to pTMD, and may facilitate the understanding of the mechanisms involved in these conditions, thereby facilitating the identification of therapeutic targets for pain treatment.

CHAPTER 6. DISCUSSION

In this general discussion, a summary of the results showed in the manuscript, some further methodological considerations, as well as the strengths and limitations of this study will be addressed.

The main goal of this study was to identify the relationship between sNGF levels and pTMD. We investigated if high levels of sNGF would modify the likelihood of having pTMD (Table 1). In addition, we evaluated if high levels of sNGF were associated with pain intensity (Table 3). Finally, in a secondary analysis, we assessed whether the levels of sNGF were affected by putative confounders (Table 4).

6.1 Summary of the Results

6.1.1 pTMD and sNGF Levels

In this study, the mean levels of sNGF were not significantly different between pTMD cases and controls. Additionally, sNGF levels were not related to an increased likelihood of pTMD (Table 1).

However, it was interesting to note that among older individuals, participants with higher levels of log sNGF were almost twice as likely to have pTMD than controls. The likelihood of pTMD participants having higher levels of log sNGF remained not statistically significant among female, male and younger groups.

Furthermore, this study demonstrated that sNGF levels were related to an increase in the levels of current pain intensity if the pain was moderate to severe (>4; 0-10 NRS) (Table 3). These results remained in the models adjusted by anti-inflammatory intake, clenching, periodontal treatment, alcohol intake, back pain, stress, gender, and age (Table 3). This effect also remained among female, male, younger, and older participants. It was interesting to see that this relationship was stronger among older participants suggesting that these individuals may have more inflammatory conditions than other participants.

6.1.2 Secondary Analyses

Log sNGF levels among participants taking anti-inflammatories was significantly lower than among those who did not (Table 4). In addition, the use of one anti-inflammatory appears to not modify the levels of log sNGF, unlike the use of two or more anti-inflammatories, where we found elevated levels of sNGF.

Participants reporting grinding and/or clenching had no statistically significant difference in the mean levels of log sNGF in comparison to those who did not (Table 4).

In addition, participants reporting periodontal treatment showed a borderline difference in the mean log sNGF levels in comparison to those who did not (Table 4). In the crude analysis, the mean log sNGF levels among participants who had reported drinking a beer or wine daily was significantly higher than among those who did not (Table 4).

The mean log sNGF levels among participants who had reported back pain showed a borderline difference in comparison to those who had not. Moreover, among participants who had reported stress, the mean levels of log sNGF was significantly lower in comparison to those who did not.

6.2 Methodological Considerations

6.2.1 Bias

Bias is defined as a systematic error that leads to a distortion of the study results (120).

6.2.2 Selection Bias

Selection bias is defined as an error that may underestimate or overestimate the measure of association (e.g., OR). It usually occurs as a result of using inappropriate methods for selecting subjects from the target population (33). In order to prevent this type of bias certain steps were taken in this study: 1) cases and controls were selected from the same base and time period at UMN; 2) NIDCR's TIRR examiners and participants were unaware about sNGF levels and putative confounders before the recruitment; and 3) the selection of participants was independent of pain intensity levels in order to have a homogeneous pTMD population.

Controls for this study were recruited from the dental clinic during the same time period as cases and they could not have any orofacial pain condition, which

may decrease selection bias. Enrollment at the dental clinic may increase the chance of introducing confounding due to some conditions (i.e., periodontal disease) related to sNGF. To be considered as a confounder, a determined variable must be not only related to sNGF, but also to pTMD without being in the pathway between sNGF and pTMD. Our results showed that self-reported periodontal disease was related neither to sNGF nor pTMD.

6.2.3 Information Bias

Information bias is a systematic error in the measurement or classification of participants in a study (35). In order to decrease chances of information bias in this study: 1) cases completed questionnaires just after the clinical examination (diagnosis of TMD and pain intensity), which is a standard approach to reduce information bias (121); 2) calibrated examiners performed the diagnosis of pTMD using a validated method (CMI) to select pTMD and controls; 3) participants also completed validated questionnaires to assess pain status (GCPS) on the same day of clinical examination and saliva sample collection; 4) saliva was collected on the same day as clinical examination; and 5) the laboratory expert who ran the assay for sNGF was blind to the outcome of the study (case and control groups).

6.2.3.1 *Recall Bias*

Recall bias is a type of information bias where participants who have the disease report more exposures than participants who are healthy (122). In this study, the levels of NGF *per se* could not be affected by this type of bias.

However, pain intensity and pain subgroups (persistent and recurrent) were measures that were considered more susceptible to the incurrence of recall bias since participants had to report the level of pain intensity, and persistence or recurrence of their pain in the past 6 months. Thus, in order to inhibit the chances of this bias: first, participants were unaware about their sNGF levels and its possible correlation with pain intensity; second, we investigate the impact of sNGF not only on the worse and average pain in the last 6 months, but also on current pain intensity. Our hypothesis was that current pain is less influenced by recall bias than worst and average pain.

6.2.4 Acquiescence Bias

To confirm whether participants with pTMD had a bias towards positive answers to the questionnaires, we investigate the frequency of other conditions, which were unrelated to TMD and sNGF: having a birthmark, dark moles, consuming soft drinks daily and/or tea daily. We hypothesized that if the participant with pTMD had the propensity to respond yes to the questions, they might also have the tendency to answer yes to those items.

We found similar frequencies for having birthmarks among cases (n = 30, 24%) and controls (n = 26, 26%; $P = 0.66$), dark moles among cases (n = 6, 4%) and controls (n = 6, 6%; $P = 0.66$), consuming soft drinks daily among cases (n = 39, 31%) and controls (n = 24, 24%; $P = 0.24$), and drinking tea daily among cases (n = 17, 13%) and controls (n = 14, 14%; $P = 0.90$).

6.2.5 Confounding

Confounders can lead to underestimation or overestimation of the true association between a covariate (e.g., biomarker) and a condition (e.g., pTMD) (34). It is always possible to minimize confounding variables by employing certain strategies:

1) Restricting the admission into the study to a group of subjects who have the same confounding factors; however, this strategy can considerably reduce the number of participants in the study, consequently decreasing the power of the study (123) and its external validity (34).

2) Matching two groups that are being compared by the possible existing confounders, such as age and gender, is also a method to control confounding (33). In order to perform matching, we have to be sure about the relationship between the confounder and exposure as well as the outcome. Moreover, we should only match for important confounders (33).

3) In the manuscript, multivariable analyses were applied instead of restricting or matching. This approach has the advantage of controlling confounders without excluding individuals. We also decided to adjust rather than match as we wanted to evaluate the relationship among sNGF, age and gender, which would not be possible if matching was used. In the model I presented in the manuscript, the analyses were adjusted by anti-inflammatory intake, grinding, clenching, periodontal treatment, alcohol intake, back pain, stress, gender, and age which were considered as putative confounders. Then, a parsimonious model

(model II) was obtained by including the primary dependent variable (pTMD or sNGF), age, gender, and the confounders that were associated with the dependent variable in the model I.

6.3 Strengths

This case-control study has a number of strengths. First, the database from NIDCR's TIRR is considered one of the most reliable databanks for pTMD worldwide.

Second, in this study controls were also recruited from the NIDCR's TIRR and from the same base and time period as cases. In fact, they attended the dentistry department of the University of Minnesota for any dental complaint other than pTMD, which may decrease the chance of diagnosis misclassification and selection bias, and help to ensure consistent assessment and confounder exposure (124).

Thirdly, calibrated examiners recruited all participants, which reduced the chance of information bias.

Fourth, all participants received a clinical examination performed by calibrated examiners, for the diagnosis of pTMD, using a validated method (CMI).

Fifth, saliva samples were collected on the same day of clinical examination and questionnaire assessments.

Sixth, participants also completed a validated questionnaire to assess pain intensity (GCPS) on the same day of clinical examination and questionnaire assessments, which shows that this study has a low chance of misclassification.

Seventh, saliva samples were collected by trained researchers who followed valid collection, storage and transportation protocols, and were not aware of the participants' sNGF levels before recruitment and collection. Participants were also unaware of their sNGF levels and its possible correlation with pain intensity, which considerably decreases the chances of recall bias.

Finally, sNGF assays were conducted by the same researcher at the Lady Davis Institute, Jewish General Hospital, who was blinded to the study group and saliva outcome. In addition, he performed the assays in the same run and day.

6.4 Limitations

It is important to take into account the limitations of this study. First of all, chances of misclassification of the subjects in a case-control study are possible, even though calibrated examiners conducted the clinical data collection based on the CMI protocol. However, this bias may be non-differential (toward underestimation) because TMD misclassification and pain status should not be related to the sNGF misclassification as: the examiners and participants were unaware about sNGF levels and putative confounders before the recruitment; and the assays were conducted by the same researcher who was blinded to the study group and saliva outcome and performed the assays in the same run.

Second, even if ELISA is often indicated as being a valid and reliable method to assess different biomarkers (37, 40, 41), measurement errors have to be considered.

Third, changes in the concentration of sNGF over time were not studied and we have a prolonged period during which the saliva samples were kept stored, which may interfere with the stability of this biomarker. However, the direction of this bias may again be toward underestimation since the researcher who performed the assays was blind to pTMD groups.

Finally, although several statistical adjustments were executed to control for confounders, unaccounted confounders still may have influenced the observations.

The identification of human salivary biomarkers associated with pTMD may advance our knowledge of the prognostic factors related to pTMD, may facilitate the understanding of the mechanisms involved in these conditions, thereby facilitating the identification of therapeutic targets for pain treatment.

CHAPTER 7. CONCLUSION

The present study indicates that:

1) High levels of sNGF did not modify the likelihood of having pTMD; except among older participants;

2) sNGF levels may contribute to worsening the pain intensity among participants reporting current moderate to severe pTMD, regardless of anti-inflammatory use, gender and age;

3) Indeed this study provides a basis to the use of sNGF to assess the severity of pTMD.

Table 1. Crude and adjusted **logistic regression analyses** of painful TMD (dependent variable) and log salivary NGF levels, and putative confounders (independent variables).

Variables	Crude (n = 219)			Model I (n = 213)			Model II (n = 213)		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Log sNGF	0.92	0.76 – 1.12	0.43	0.98	0.75 – 1.27	0.89	1.00	0.77 – 1.30	0.98
Anti-inflammatory	2.94	1.12 – 7.72	**0.03***	3.09	1.05 – 9.05	**0.04***	2.69	0.93 – 7.73	0.06**
Grinding	3.33	1.63 – 6.80	**0.001***	1.25	0.46 – 3.37	0.66	Not Included		
Clenching	9.60	4.56 – 20.21	**<0.0001***	11.30	4.45 – 28.70	**<0.0001***	11.90	4.99 – 28.35	**<0.0001***
Periodontal Treatment	1.43	0.54 – 3.78	0.47	0.38	0.09 – 1.52	0.17	Not Included		
Alcohol intake	2.80	0.75 – 10.46	0.12	1.84	0.30 – 11.33	0.51	Not Included		
Back Pain	9.14	4.21 – 19.83	**<0.0001***	6.69	2.58 – 17.32	**<0.0001***	6.61	2.68 – 16.28	**<0.0001***
Stress	1.68	0.93 – 3.02	0.08**	1.00	0.43 – 2.30	0.99	Not Included		
Gender	3.30	1.66 – 6.56	**0.0007***	1.59	0.64 – 3.97	0.31	1.56	0.64 – 3.77	0.32
Age	1.04	1.02 – 1.06	**<0.0001***	1.03	1.01 – 1.06	**0.007***	1.03	1.00 – 1.05	**0.009***

Notes: * *P*-Value ≤ 0.05; **Borderline association.
Model I: Adjusted by log sNGF, anti-inflammatory intake, grinding, clenching, periodontal treatment, alcohol intake, back pain, stress, gender and age.
Model II: Final model adjusted by log sNGF, anti-inflammatory, clenching, back pain, gender and age.

Table 2. Crude and adjusted **linear regression** assessing the association between **current pain** (dependent variable) and log salivary NGF levels and putative confounders (independent variables).

	Crude (n = 219)			**Model I (n = 213)**			**Model II (n = 213)**		
Variables	*β*	95% CI	*P*-Value	*β*	95% CI	*P*-Value	*β*	95% CI	*P*-Value
Log sNGF	-0.20	-0.50 – 0.11	0.18	-0.13	-0.42 – 0.16	0.37	-0.11	-0.40 – 0.17	0.43
Anti-inflammatory	1.30	0.38 – 2.22	**0.005***	1.14	0.24 – 2.03	**0.01***	0.99	0.17 – 1.86	**0.03***
Grinding	1.50	0.55 – 2.45	**0.002***	0.33	-0.67 – 1.33	0.51	Not Included		
Clenching	2.36	1.55 – 3.17	**<0.0001***	1.92	1.03 – 2.81	**<0.0001***	2.08	1.27 – 2.89	**<0.0001***
Periodontal Treatment	0.11	-1.36 – 1.58	0.88	-0.98	-2.36 – 0.41	0.16	Not Included		
Alcohol intake	1.37	-0.37 – 3.10	0.12	0.46	-1.22 – 2.15	0.58	Not Included		
Back Pain	2.10	1.25 – 2.92	**<0.0001***	1.18	0.25 – 2.12	**0.01***	1.25	0.36 – 2.15	**0.006***
Stress	0.64	-0.24 – 1.51	0.15	0.14	-0.73 – 1.01	0.75	Not Included		
Gender	-1.29	-2.29 – -0.30	**0.01***	-0.33	-1.30 – 0.65	0.51	-0.32	-1.28 – 0.63	0.50
Age	0.04	0.01 – 0.06	**0.005***	0.02	-0.003 – 0.05	0.08**	0.02	-0.006 – 0.05	0.13

Notes: **P*-Value ≤ 0.05; ***Borderline association.
Model I: Adjusted by log sNGF, anti-inflammatory intake, grinding, clenching, periodontal treatment, alcohol intake, back pain, stress, gender and age.
Model II: Final model adjusted by log sNGF, anti-inflammatory intake, clenching, back pain, gender and age.

Table 3. Crude and adjusted **linear regression** assessing the association between current pain (dependent variable) and log salivary NGF levels and putative confounders (independent variables) including only participants with current **moderate to severe pain** (>4, 0-10 NRS).

	Crude (n = 63)			**Model I (n = 59)**			**Model II (n = 59)**		
Variables	*β*	95% CI	*P*-Value	*β*	95% CI	*P*-Value	*β*	95% CI	*P*-Value
Log sNGF	0.38	0.10 – 0.65	**0.008***	0.56	0.26 – 0.87	**0.0005***	0.59	0.31 – 0.86	**<0.0001***
Anti-inflammatory	0.50	-0.23 – 1.23	0.18	0.79	0.05 – 1.53	**0.04***	0.71	0.003 – 1.41	**0.05***
Grinding	0.09	-0.79 – 0.98	0.83	0.24	-0.67 – 1.16	0.59	Not Included		
Clenching	-0.66	-1.49 – 0.17	0.12	-0.91	-1.79 – -0.04	**0.04***	-0.82	-1.61 – -0.03	**0.04***
Periodontal Treatment	-1.15	-2.53 – 0.24	0.10	-0.70	-2.07 – 0.66	0.30	Not Included		
Alcohol intake	0.16	-1.39 – 1.71	0.84	0.36	-1.31 – 2.03	0.66	Not Included		
Back Pain	0.08	-0.78 – 0.93	0.86	0.34	-0.62 – 1.31	0.48	0.47	-0.41 – 1.35	0.29
Stress	-0.16	-1.02 – 0.70	0.71	0.29	-0.60 – 1.19	0.51	Not Included		
Gender	0.18	-1.07 – 1.43	0.77	-0.01	-1.20 – 1.18	0.98	-0.05	-1.18 – 1.08	0.93
Age	-0.007	-0.04 – 0.02	0.59	-0.02	-0.06 – 0.009	0.15	-0.03	-0.06 – 0.001	0.06**

Notes: **P*-Value ≤ 0.05; ***Borderline association.
Model I: Adjusted by log sNGF, anti-inflammatory intake, grinding, clenching, periodontal treatment, alcohol intake, back pain, stress, gender and age.
Model II: Final model adjusted by log sNGF, anti-inflammatory intake, clenching, back pain, gender and age.

Table 4. Analysis of variance (ANOVA) of means **log salivary NGF levels** (dependent variable) between groups (independent variables).

Variables		Crude (n = 220)			Model I (n = 215)			Model II (n = 215)		
		Mean	95% CI	*P*-Value	Mean	95% CI	*P*-Value	Mean	95% CI	*P*-Value
Anti-inflammatory	Intake	-0.73†	-1.13 – -0.33	**0.0004***	-0.63†	-1.06 – -0.21	**0.003***	-0.68†	-1.09 – -0.26	**0.001***
Grinding	Yes	6.28	5.91 – 6.66	0.49	6.44	5.83 – 7.04	0.38	Not Included		
	No	6.43	6.22 – 6.64		6.45	6.10 – 7.20				
Clenching	Yes	6.43	6.12 – 6.74	0.80	6.67	6.08 – 7.25	0.29	6.57	6.17 – 6.97	0.36
	No	6.37	6.14 – 6.59		6.42	5.86 – 6.98		6.37	6.10 – 6.64	
Periodontal Treatment	Yes	5.88	5.27 – 6.50	0.09**	6.37	5.61 – 7.13	0.31	Not Included		
	No	6.44	6.25 – 6.63		6.71	6.26 – 7.16				
Alcohol intake	Yes	7.16	6.42 – 7.90	**0.03***	6.86	6.02 – 7.71	0.11	Not Included		
	No	6.34	6.15 – 6.53		6.22	5.83 – 6.62				
Back Pain	Yes	6.10	5.78 – 6.43	**0.05***	6.42	5.81 – 7.03	0.29	6.30	6.38 – 6.91	0.13
	No	6.50	6.28 – 6.72		6.67	6.13 – 7.21		6.64	5.88 – 6.71	
Stress	Yes	6.12	5.80 – 6.44	**0.04***	6.46	5.88 – 7.05	0.46	Not Included		
	No	6.52	6.30 – 6.74		6.62	6.07 – 7.17				
Gender	Female	6.30	6.10 – 6.50	0.06**	6.34	5.84 – 6.62	0.08**	6.24	6.01 – 6.47	**0.05***
	Male	6.73	6.34 – 7.13		6.75	6.11 – 7.39		6.70	6.27 – 7.14	
Age	Years	0.006	-0.005 – 0.01	0.25	0.007	-0.006 – 0.02	0.26	0.01	-0.002 – 0.02	0.11
Painful TMD	Cases	6.33	6.09 – 6.57	0.47	6.52	5.96 – 7.07	0.84	6.45	6.15 – 6.76	0.88
	Controls	6.47	6.20 – 6.74		6.57	5.97 – 7.16		6.49	6.10 – 6.88	

Notes: * *P*-Value ≤ 0.05; **Borderline association; †slope.
Model I: Adjusted by anti-inflammatory intake, grinding, clenching, periodontal treatment, alcohol intake, back pain, stress, gender, age, and painful TMD.
Model II: Final model adjusted by anti-inflammatory intake, clenching, back pain, gender, age, and painful TMD.

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CHAPTER 9. APPENDIX

A selection including the consent form, examination forms, medical questionnaire, and other relevant questionnaires that were used in this study will be following.

National Institute of Dental and Craniofacial Research
TMJ Implant Registry & Repository (NIDCR's TIRR)

CONSENT TO PARTICIPATE

You are invited to participate in a data and tissue registry and repository related to temporomandibular joint dysfunction (TMD). You were selected as a possible participant because you 1) have a past or current history of TMD, 2) have had or will have temporomandibular joint (TMJ) surgery, 3) have had or currently have a TMJ implant, or 4) may be a control subject for this project. We ask that you read this form and ask any questions you may have before agreeing to be a participant in NIDCR's TIRR.

This project is being conducted by James R. Fricton, DDS, MS; Sandra L. Myers, DMD; John O. Look, DDS, MPH, PhD; and Ana Velly, DDS, PhD in the Department of Diagnostic & Biological Sciences at the University of Minnesota School of Dentistry. It is funded by the National Institute of Dental & Craniofacial Research (NIDCR) at the National Institutes of Health (NIH).

Project Purpose:
Many different treatments have been recommended for people with TMD including medications, splints, physical therapy, dental treatment and surgery. Implants have sometimes been used to support or replace the moving parts of the joint. For some people, these implants have caused problems that have necessitated their removal. The disease process of TMD and causes of failure of TMJ implants are not well understood.

The purpose of NIDCR's TIRR is to create a national database to centralize medical information, biological tissues, and retrieved TMJ implants. Information and biological specimens will then be made available to researchers. Studies using these materials will lead to a better understanding of TMD and improved treatment outcomes.

Project Procedures:
If you agree to participate in this project, you will be asked to do the following:

1. Complete an initial registration, medical history and questionnaire. These should be completed before your appointment and requires approximately 1 hour.

2. Allow NIDCR's TIRR to contact you to complete follow-up questionnaires.

3. Give permission to NIDCR's TIRR to obtain and transfer information from your health records and/or data from previous studies.

4. Undergo a clinical examination to evaluate your temporomandibular joint.

5. Allow NIDCR's TIRR to collect saliva and approximately 3 -ml (6 teaspoons) of blood. This is done at the time of exam, which requires approximately 1 hour total.

If you have TMJ surgery, NIDCR's TIRR will obtain from your surgeon tissue or implant material that was removed as part of the procedure. If you had TMJ surgery in the past, you are asked to permit NIDCR's TIRR to obtain any tissue or implant materials that were removed and held at the place where your surgery was performed.

If you will be having oral surgery, while under local anesthetic, conscious sedation or general anesthesia, and are eligible to donate synovial (joint) fluid from your TMJ, this fluid may be collected at the time of your surgery. Using a needle, a sterile mixture of cyanocobalamin (Vitamin B12) and saline will be flushed through the joint space to collect this fluid. Saline is routinely used in surgical procedures, and Vitamin B12 will be used to measure the amount of synovial fluid obtained. Vitamin B12 is a necessary part of normal body function and is approved by the Food & Drug Administration (FDA) for treatment of medical conditions such as anemia. Before the synovial fluid collection is performed, you will be asked if you have ever had any unusual or allergic reaction to vitamin B12 or cobalt. More information about Vitamin B12 and the method used for synovial fluid collection may be found on NIDCR's TIRR website at http://tmjregistry.org.

Your blood, saliva, tissues and synovial fluid will be used to study genes, gene products and other measurable factors that may be related to TMD or pain.

If you are *not* having oral surgery and are eligible and consent to donate synovial (joint) fluid from your TMJ, you have the option of having it done with local anesthesia or conscious sedation.

Benefits of Participation:
There is no direct benefit to participation.

One benefit of participation in this project is that you will have access to a private, electronic record of your TMD health information.

The use of your medical information and specimens will enable researchers to learn more about factors involved in the success of TMJ treatments including implants and surgical or non-surgical therapy.

Risks of Participation:

- The risks of drawing blood include brief pain, slight bruising and, rarely, infection where the needle entered your skin. Project staff members will take every precaution to prevent an infection. Some people may feel dizzy when they have blood drawn, but this goes away when the person lies down.
- The risks associated with jaw joint synovial fluid extraction are:
    - Pain and/or slight bruising.
    - Infection.
    - Swelling.
    - Bleeding.
    - Arthritis, although rare.
- There is also a risk associated with the release of private information from your health records. NIDCR's TIRR follows all confidentiality guidelines to ensure the protection of your privacy. See the "Confidentiality" portion of this consent form for details on how your private information is protected.
- Your oral surgeon will discuss with you any risks associated with sedation.

Compensation:
You will receive compensation of $50 after completion of the initial questionnaires, clinical examination and collection of blood and saliva.

If you donate synovial fluid for this project, you will be compensated an additional $125.

Participation Related Injury:
In the event that your participation in this project results in an injury, treatment will be available including first-aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered an injury related to participation in this project, let the project staff know right away.

Confidentiality:
All records and private information obtained by NIDCR's TIRR will be kept private. Data is maintained on a secure website at the University of Minnesota. All identifying information will be removed from your data and specimens before they are released to researchers. A research code will be assigned to these materials so that the researcher cannot link them to you. You will be asked to sign a separate Patient Information Release form in order for NIDCR's TIRR to obtain information from your past health records. In any publications or presentations, no information will be used that would make it possible to identify you as a participant. Your record for this project may be reviewed by the NIDCR, the Food and Drug Administration, and departments at the University of Minnesota with appropriate regulatory oversight. Due to the necessity of gathering information from your doctor or past records, this data may be faxed or transmitted to or from NIDCR's TIRR via the Internet. Every attempt will be made to protect you and your information transmission via the secure Academic Health Center website. To these extents, confidentiality is not absolute.

Protected Health Information (PHI):
Your PHI created or received for the purposes of this project is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Project:
Participation in this project is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University of Minnesota or your doctor/surgeon. If you decide to participate, you are free to withdraw at any time without affecting those relationships. If you choose to withdraw from this project, you will not be contacted by NIDCR's TIRR any more, and all information identifying you will be destroyed. Your specimens will remain the property of NIDCR's TIRR and will not be returned to you, although we will destroy the identifying link to your specimen. You should contact the project staff person listed in this consent form to withdraw from NIDCR's TIRR.

Contacts and Questions:
The person describing this project to you is available to answer any questions you have now or in the future. Also, **you are encouraged to** contact the Program Director, Dr. James R. Fricton, at 612-626-4744 for any additional questions. You may contact NIDCR's TIRR in writing or in person at the University of Minnesota School of Dentistry, 7-546 Moos Tower, 515 Delaware St. SE, Minneapolis, MN 55455.

If you have any questions or concerns regarding the project and would like to talk to someone other than the researcher(s), **you are encouraged to** contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at the University of Minnesota Medical Center, Fairview-Riverside Campus, #815 Professional Building, 2450 Riverside Avenue, Minneapolis, MN 55454.

If you are interested in results from this project or publications by researchers involved in NIDCR's TIRR, this information will be listed on the project's website: http://tmjregistry.org.

Personnel from this project may contact you to invite you to participate in other studies. If you do not wish to be contacted, please inform the project staff at 612-626-4744.

You will be given a copy of this form to keep for your records.

Statement of Consent:
I have read the above information. I have asked questions and have received answers. I agree to participate in NIDCR's TIRR.

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Obtaining Consent Date

HIPAA[1] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

1. Purpose. As a research participant, I authorize **Dr. James Fricton** and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research project entitled National Institutes of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR'sTIRR). **Human Subjects' Code: 0210M33782**

2. Individual Health Information to be Used or Disclosed. My individual health information that may be used or disclosed to conduct this research includes: Demographic information, results of physical exams, x-rays diagnostic and medical procedures as well as medical history.

3. Parties Who May Disclose My Individual Health Information. The researcher and the researcher's staff may obtain my individual health information from:
Hospitals: _____
Clinics: _____
Other Providers: _____

4. Parties Who May Receive or Use My Individual Health Information. The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by Dr. James Fricton and the researcher staff, the National Institute of Health/NIDCR and the FDA.

5. Right to Refuse to Sign this Authorization. I do not have to sign this Authorization. If I decide not to sign the Authorization, I may not be allowed to participate in this study or receive any research related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke. I can change my mind and withdraw this authorization at any time by sending a written notice to Dr. James Fricton at the University of Minnesota School of Dentistry/Division of TMJ and Orofacial Pain, 6-320 Moos Tower, 515 Delaware St. S.E., Minneapolis, MN 55455 to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

7. Potential for Re-disclosure. Once my health information is disclosed under this authorization, there is a potential that it will be re-disclosed outside this study and no longer covered by this authorization. However, the research team and the University's Institutional Review Board (the committee that reviews studies to be sure that the rights and safety of study participants are protected) are very careful to protect your privacy and limit the disclosure of identifying information about you.

8. Also, there are other laws that may require my individual health information to be disclosed for public purposes. Examples include potential disclosures if required for mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

This authorization does not have an expiration date.
I am the research participant or personal representative authorized to act on behalf of the participant.
I have read this information, and I will receive a copy of this authorization form after it is signed.

signature of research participant or research participant's personal representative	date
printed name of research participant or research participant's personal representative	description of personal representative's authority to act on behalf of the research participant

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

NIDCR'S TIRR PATIENT REGISTRATION FORM

1. Patient Name: (Last, First, MI)	2. Social Security No.	3. Birth Date (MM/DD/YY)	4. Sex □ M □ F

5. Address (Street)	Apt No.	City	State	Country	Zip

6. Home Phone	7. E-mail	8. Spouse Name (Last, First, MI)

9. Employer's Name	City	State	Work Phone

10. Person to Notify in an Emergency	City	State	Phone

11. Name of Relative Not Living With You	City	State	Phone

12. Ethnicity: (please choose only one)	13. Racial Group: (you may choose more than one)	
□ Hispanic or Latino	□ American Indian or Alaska Native	□ Asian
□ Not Hispanic or Latino	□ Native Hawaiian or Other Pacific Islander	□ White
□ Unknown	□ Black or African American	□ Unknown or unlisted

14. Marital Status: □ Single/Never Married □ Single/Divorced □ Married □ Widowed □ Separated □ No Answer

15. Primary Occupation	16. Number of Children: Ages of Female Children: Ages of Male Children:

17. PRIMARY JOB STATUS In the Past Month (check only one)		18. EDUCATIONAL LEVEL (last year completed)
□ Employed fulltime	□ Employed part time	□ No formal education
□ Fulltime student and not employed	□ Fulltime homemaker	□ High school
□ Have a job but am on unpaid leave	□ Retired and not employed	□ Vocational technical school
□ Have a job but am on paid leave	□ Unemployed	□ College
□ Disabled due to health problems	□ Other _____	□ Graduate school
		□ Post graduate

19. Are you receiving or applying for any DISABILITY INCOME? □ Yes □ No

If so, what type (list all that apply)?

□ None	□ Social security disability	□ Worker compensation.
□ Long term assistance	□ General assistance	□ Private insurance
□ Veterans	□ Other_____	

20. Referring Doctor Name	Specialty	Address	Phone	E-Mail

21. Primary Physician Name	Specialty	Address	Phone	E-Mail

22. Primary Dentist Name	Address	Phone	E-Mail

23. Primary Pharmacy Name	Address	Phone	E-Mail

PATIENT INFORMATION

24. Primary Insurance Company Name	Address			Phone
	Member/Claim #	Group #	Subscriber	Relation to Patient
25. Secondary Insurance Company Name	Address			Phone
	Member/Claim #	Group #	Subscriber	Relation to Patient
26. Name of Work/Car insurance (if accident was involved)	Address			Phone
	Member/Claim #	Group #	Subscriber	Relation to Patient
27. Person Responsible for the Bill	Name	Address		Phone
28. Attorney Name (if you have one)	Address			Phone
	Claim Representative		Date of Injury	

While you are a patient here, you will be asked to give certain information about your dental problems, medical history, your response to care you have received, and related information that is needed to assist in identifying and treating your problem(s). The dentists or staff who work with you will also make notes on their observations of you, and all this information will be recorded in your chart. Other information regarding fees incurred, and payments of such fees shall also be maintained as part of your record. This information is intended for use in your examination, diagnosis, and treatment, but may also be reviewed by others for a variety of purposes. Your records may be reviewed as part of the educational or research purposes to identify new or better ways to treat problems of the head, neck, and related structures. They may also be reviewed as part of general survey of patient care to assure standards of high quality service and financial integrity. In all cases, other than those where you have specifically authorized the release of your records, your identity and personal health record will be maintained in the strictest confidence by those authorized to review records.

PATIENT AGREEMENT **Please seek assistance if you do not understand any terms of this agreement**

1. I hereby authorize the doctors and staff working under their supervision, to perform ordinary diagnostic procedures, including x-rays and photographs, to determine the general nature of my dental problems.
2. I understand that the benefits, alternatives, discomforts and risks relating to my treatment will be explained to me in terms that I understand and properly annotated in my chart using appropriate consent forms BEFORE treatment is initiated.
3. I permit the doctors or staff to review my dental record for possible participation in dental research. I understand that someone may contact me to request my participation and that appropriate consent will be obtained before I become involved in the study.
4. I permit the your clinic to photograph or record all or part of my treatment or clinical records for publication in scientific journals or for teaching purposes by the staff or students concerned, provided this material is not identified with me by name, recognition, or otherwise.
5. I authorize the your clinic to utilize all tissues, including teeth, removed during the course of treatment for educational and research purposes in accordance with current tissue policies and regulations concerning the use of human subjects in research.
6. I understand that I must authorize in writing, the copying and distribution of any portion of my health record to any person or agency outside the Clinic with the exception of third party payers. I understand there may be an additional fee for this service.

I have read and understand all of the above. I have crossed out and initialed any statement (1 through 7) to which I do not agree. I further understand that I may withdraw my consent to specific treatment of activities without prejudice to alternative treatment or continuing care.

Patient/Guarantor Signature _____ Date_____

AUTHORIZATION FOR RELEASE OF INFORMATION (All patients/guarantors must sign)

I certify that the above information is correct. I authorize the Clinic to use and release dental, medical or financial information to other parties who have an implicit "right to know" due to my use of their services. This includes insurance companies and state agencies. I understand that no other information related to my treatment or health status will be released without my written consent. I understand and agree to the terms and conditions of the payment policy described above. I agree to pay this account, when due, in accordance with Clinic and State/Federal Agency policies covering the payment of outstanding balances.

Patient/Guarantor Signature _____ Date_____

ASSIGNMENT OF INSURANCE BENEFITS

I authorize the payment of the group insurance benefits otherwise payable to my billing clinic.

Police Holder/Guarantor Signature_____ Date _____

MEDICARE – BENEFICIARY AGREEMENT

I have been notified by my physician/dentist that he or she believes that Medicare is likely to deny payment for the services identified, for the reasons stated. If Medicare denies payment, I agree to be personally and fully responsible for payment.

Police Holder/Guarantor Signature_____ Date _____

TIRR Examination

Patient Name:	Date:	Examiner:

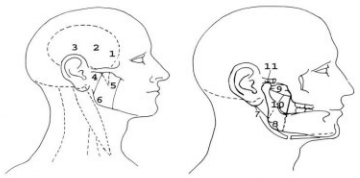
Mandibular Range of Motion

1. Incisal overlap and midline deviation of lower incisor	☐ Right (#8) or ☐ Left (#9) __ mm vertical __ mm horizontal __ mm deviation ☐To right ☐To left		
2. Incisal pattern on opening (deviation ≥ 5mm)	☐ Straight ☐ Uncorrected to right ☐ Uncorrected to left ☐ Corrected(S) ☐ Other:		
3. Unassisted opening without pain	__ mm		
4. Maximum unassisted opening (by patient)	__ mm		
Pain?	☐ no	☐ joint ☐ Rt ☐ Lt	☐ muscle ☐ Rt ☐ Lt
5. Maximum assisted opening (with stretch)	__ mm		
Pain?	☐ no	☐ joint ☐ Rt ☐ Lt	☐ muscle ☐ Rt ☐ Lt
6. Right lateral excursion	__ mm		
Pain?	☐ no	☐ joint ☐ Rt ☐ Lt	☐ muscle ☐ Rt ☐ Lt
7. Left lateral excursion	__ mm		
Pain?	☐ no	☐ joint ☐ Rt ☐ Lt	☐ muscle ☐ Rt ☐ Lt
8. Protrusion	__ mm		
Pain?	☐ no	☐ joint ☐ Rt ☐ Lt	☐ muscle ☐ Rt ☐ Lt

TMJ Examination

1. TMJ movement on opening	Right:	☐ normal	☐ limited ☐ closed lock	☐ locks open
	Left:	☐ normal	☐ limited ☐ closed lock	☐ locks open
2. TMJ lateral pole tenderness		☐ none	☐ on right ☐ on left	☐ both
3. TMJ sounds on right	opening click or pop:	☐ none	☐ reproducible	☐ non-reproducible
	closing click or pop:	☐ none	☐ reproducible	☐ non-reproducible
	crepitus:	☐ none	☐ fine	☐ coarse
	Is click eliminated on protrusive opening?	☐ no	☐ yes	
4. TMJ sounds on left	opening click:	☐ none	☐ reproducible	☐ non-reproducible
	closing click:	☐ none	☐ reproducible	☐ non-reproducible
	crepitus:	☐ none	☐ fine	☐ coarse
	Is click eliminated on protrusive opening?	☐ no	☐ yes	

Tenderness of Muscles



Right Side Yes	No	Dupl		Left Side Yes	No	Dupl
☐	☐	☐	1. Anterior Temporalis	☐	☐	☐
☐	☐	☐	2. Middle Temporalis	☐	☐	☐
☐	☐	☐	3. Posterior Temporalis	☐	☐	☐
☐	☐	☐	4. Origin of the Masseter	☐	☐	☐
☐	☐	☐	5. Body of the Masseter	☐	☐	☐
☐	☐	☐	6. Insertion of Masseter	☐	☐	☐
☐	☐	☐	7. Posterior Mandibular	☐	☐	☐
☐	☐	☐	8. Submandibular Area	☐	☐	☐

Occlusal Examination

1. Missing teeth and not permanently replaced	Right:	01 02 03 04 05 06 07 08		09 10 11 12 13 14 15 16	
	Left:	32 31 30 29 28 27 26 25		24 23 22 21 20 19 18 17	
2. Dentures	Maxillary:	☐ none	☐ complete	☐ partial	
	Mandibular:	☐ none	☐ complete	☐ partial	
	Edentulous:	☐ no dentures			
3. Angle classification	Right:	☐ I	☐ II.1	☐ II.2	☐ III
	Left:	☐ I	☐ II.1	☐ II.2	☐ III
4. Cross bite	Right:	☐ none	☐ both	☐ anterior only	☐ posterior only
	Left:	☐ none	☐ both	☐ anterior only	☐ posterior only
5. Open bite	Right:	☐ none	☐ both	☐ anterior only	☐ posterior only
	Left:	☐ none	☐ both	☐ anterior only	☐ posterior only
6. Additional items:					

Updated 2/22/06

Diagnosis (check all that apply)

R L Joint Disorders	Muscle Disorders	Neuropathic
☐ ☐ TMJ Ankylosis and Adhesions 524.61 ☐ ☐ TMJ Arthralgia and Inflammation 524.62 ☐ ☐ TMJ Disc Disorder (reducing) 524.63 ☐ ☐ TMJ Disc Disorder (non-reducing) 524.63 ☐ ☐ TMJ Dislocated Jaw, closed lock 830.00 ☐ ☐ TMJ Dislocated Jaw, open lock 830.10 ☐ ☐ TMJ Osteoarthritis, local & 1° 715.18 ☐ ☐ TMJ Rheumatoid Arthritis 715.00 ☐ ☐ TMJ Traumatic Arthropathy 716.18 ☐ ☐ TMJ Strain/Sprain from Overuse 848.1 ☐ ☐ TMJ Implant Failure 524.61 ☐ ☐ TMJ Tumor Benign 213.1 ☐ ☐ TMJ Tumor Other: _____	☐ Muscle Spasm 728.85 ☐ Myofascial Pain: Masticatory 729.1 ☐ Myofascial Pain: Cervical 729.1 ☐ Fibromyalgia/Chronic fatigue 729.1 Headache ☐ Migraine with Aura 346.0 ☐ Migraine without Aura 346.1 ☐ Cluster Headache 346.2 ☐ Tension-Type Headache 307.81 ☐ Rebound/Transformed 784.0	☐ Trigeminal Neuralgia 350.1 ☐ Atypical Face Pain 350.2 ☐ Glossodynia/ Burning Mouth 529.6 Other ☐ Orofacial Dyskinesia 333.82 ☐ Bruxism/Teeth Grinding 306.8 ☐ Psychological Factors 316.0 ☐ Anomalies of Jaw Size 524.00 ☐ List: _____

Recommendations

Imaging	☐ Bone Scan ☐ CT Scan ☐ Panorex ☐ MR Scan of Brain ☐ MR Scan of TMJ ☐ Tomograms ☐ Other:
Self Care	☐ Exercise ☐ Oral Habits ☐ Pain Diary ☐ Palliative ☐ Other:
Splint/Orthotic	☐ Mandibular Flat ☐ Maxillary Flat ☐ Repositioning ☐ Other:
Medication	☐ Anti-Inflammatory ☐ Muscle Relaxant ☐ Opioid ☐ Neuropathic ☐ Sedative ☐ Tricyclic ☐ Other:
Physical Therapy	☐ Post Surgical ☐ Evaluate and Treat ☐ Modality:_____ per wk for ____ wks ☐ Exercise: ☐ Postural ☐ 6 by 6 ☐ Stretching ☐ Relaxation ☐ Conditioning
Behavioral Health	☐ Chemical Dependency ☐ Depression/Anxiety ☐ Oral Habit Reversal ☐ Occupational ☐ Relaxation/Biofeedback ☐ Sleep Management ☐ Stress Management ☐ Team Synthesis ☐ Other:
Injections	☐ Botox ☐ Nerve Block ☐ TMJ Injections: ☐ Trigger Point Injection:
TMJ Surgery	☐ Arthrocentesis/Lysis/Lavage ☐ Athroplasty ☐ Arthroscopy ☐ Arthroscopy Lysis & Lavage ☐ Disc Repair ☐ Disc Repositioning ☐ Discectomy ☐ Implant Surgery ☐ Laser Repair ☐ Total Joint Implant ☐ Adv. TMJ Arthroscopy w/ ☐ Sup. Lat. Pterygoid Myotomy ☐ Exc. of Fibullated Cartilage ☐ Laser Synovectomy ☐ Arthroscopic Disc Suturing DATE OF FUTURE SURGERY: _____
Implant Surgery If Applicable	☐ Implant Removed ☐ Implant Placed ☐ Right ☐ Left Type of Implant: ☐ Endotec ☐ Proplast® ☐ Kent/Vitek® ☐ Silicone/Silastic® ☐ Christensen/TMJ: Stock ☐ Techmedica/TMJ Concepts ☐ Christensen/TMJ: Custom ☐ Other: ☐ Lorenz/Biomet
Other	

Dr:	Date:

MEDICAL HISTORY FORM			
1. Patient Name: (Last, First, MI)	2. Social Security No.	3. Birth Date (MM/DD/YY)	4. Sex ☐ M ☐ F

We appreciate the time you spend completing this questionnaire. The information you provide is confidential and will allow us to provide you the best care possible. Thank you. Sincerely, Clinic Staff

5. Please list all major HOSPITALIZATIONS OR SURGERIES for any surgical operation or illness in the past.

Date	Reason or Procedure	Name and Address of Hospital

6. Please list any MAJOR ILLNESSES OR SPECIAL MEDICAL OR PSYCHOLOGICAL PROBLEMS that you have now or have had in the past.

Date	Reason	Name and Address of Doctor Who Treated You

Version 1.1 Revised on 11/22/04

7. What MEDICATIONS are you CURRENTLY taking for any health problems?

Medication Name	Dossage Per Day (mg, cc, etc.)	Times Per Day	Reason	Length of Time Taken

8. What MEDICATIONS have you taken for the problem IN THE PAST but not now?

Medication Name	Dossage Per Day (mg,cc,etc)	Times Per Day	Reason	When and why Did You Stop?

HEALTH PROBLEMS: Please check all health problems that you currently have or had in the past.

9. Cardiovascular	Yes	No
Rheumatic fever/heart disease	☐	☐
Heart murmur	☐	☐
Mitral valve prolapse	☐	☐
Artificial heart valve	☐	☐
Infective endocarditis	☐	☐
High blood pressure	☐	☐
High cholesterol	☐	☐
Angina	☐	☐
Heart attack	☐	☐
Congenital heart defect or lesion	☐	☐
Heart surgery/angioplasty	☐	☐
Pacemaker/defibrillator	☐	☐
Stroke	☐	☐
Vascular disease or surgery	☐	☐
Aneurysm	☐	☐
Other heart problems	☐	☐

10. Respiratory	Yes	No
Asthma	☐	☐
Bronchitis/Pneumonia	☐	☐
Emphysema	☐	☐

11. Allergic/Immunologic	Yes	No
Hay fever	☐	☐
Anaphylactic shock reaction	☐	☐
Reaction to foods:	☐	☐
Type of food: _____		
Reaction to local anesthetic (novacaine)	☐	☐
Reaction to penicillin, other antibiotics	☐	☐
Reaction to sulfa drugs	☐	☐
Reaction to sedatives, or sleeping pills	☐	☐
Reaction to barbiturates	☐	☐
Reaction to aspirin or other pain medication	☐	☐
Reaction to iodine	☐	☐
Reaction to other medications	☐	☐
List:		

12. Gastrointestinal	Yes	No
Stomach/intestinal ulcers	☐	☐
Gastritis	☐	☐
Colitis	☐	☐
Liver disease/jaundice	☐	☐
Gall Bladder Stones	☐	☐

13. Oropharyngeal Disorders	Yes	No
Stomach reflux-heartburn	☐	☐
Bad breath (malodor)	☐	☐
Enlarged tonsils	☐	☐

14. Eyes	Yes	No
Glaucoma	☐	☐
Full or Partial Blindness	☐	☐
Wear glasses/contacts	☐	☐

15. Ear and Nose, and Throat	Yes	No
Sinusitis or sinus headache	☐	☐
Nasal rhinitis	☐	☐
Inner ear infections	☐	☐

16. Neurologic	Yes	No
Multiple sclerosis (MS)	☐	☐
Epilepsy, seizures or convulsions	☐	☐
Migraine	☐	☐
Muscular dystrophy	☐	☐
Cerebral Palsy	☐	☐
Parkinon's Disease	☐	☐

17. Infectious disease	Yes	No
Sexually transmitted disease(syphilis, gonorrhea, or genital herpes)	☐	☐
HIV positive	☐	☐
Hepatitis Type: _____.	☐	☐
Tuberculosis (TB)	☐	☐
Other current infectious disease	☐	☐

18. Skin/Integumentary	Yes	No
Allergy to latex (rubber)	☐	☐
Hives or allergic skin rash	☐	☐
Psoriasis (chronic skin rash)	☐	☐
Dark moles (recent change in appearance)	☐	☐
Birth marks	☐	☐

19. Endocrine	Yes	No
Diabetes	☐	☐
Thyroid disease	☐	☐
Pancreatic disease	☐	☐

20. Genito-Urinary	Yes	No
Bladder problem/ infections	☐	☐
Kidney disease	☐	☐
Women	**Yes**	**No**
Are you taking contraceptives	☐	☐
Are you pregnant	☐	☐
Are you nursing presently	☐	☐
Had a miscarriage or stillbirth	☐	☐
Had a hysterectomy or ovariectomy	☐	☐
Are you on hormone replacement therapy	☐	☐
Dysmenorrhea (painful menstrual periods)	☐	☐
Premenstrual syndrome (PMS)	☐	☐
Menopause	☐	☐
Breast cancer	☐	☐
Men	**Yes**	**No**
Testicular tumors or disorders	☐	☐
Prostatitis	☐	☐
Prostate cancer	☐	☐
Breast cancer	☐	☐

21. Hematologic/Lymphatics	Yes	No
Blood transfusion	☐	☐
Anemia	☐	☐
Hemophilia/other bleeding disorders	☐	☐
Leukemia	☐	☐
Sickle Cell Anemia Disease	☐	☐
Tumor or cancer	☐	☐
Chemotherapy	☐	☐
Radiation therapy	☐	☐

22. Musculoskeletal/Rheumatic	Yes	No
Fibromyalgia	☐	☐
Chronic fatigue syndrome	☐	☐
Osteoarthritis	☐	☐
Osteopoerosis	☐	☐
Rheumatoid arthritis	☐	☐
Artificial joint (knee/hip/other)	☐	☐
Sjogren's syndrome	☐	☐
Muscle pain/rheumatism	☐	☐

23. Mental Health	Yes	No
Depression	☐	☐
Anxiety disorder	☐	☐
Mental health treatment	☐	☐
Physical or sexual abuse	☐	☐
Eating disorder	☐	☐

COMMENTS:

Version 1.1 Revised on 11/22/04

REVIEW OF SYSTEMS: Please check all symptoms that you have had recently (in the past month).

24. Constitutional Symptoms	Yes	No
Frequent fever	☐	☐
Weight loss or gain recently	☐	☐
Unsteady when walking/standing	☐	☐
General weakness	☐	☐
Fatigue	☐	☐
Chills	☐	☐
Hot and cold spells	☐	☐
Change in appetite	☐	☐

25. Cardiovascular	Yes	No
Racing heart (palpitations)	☐	☐
Chest pain	☐	☐
Cold hands	☐	☐
Swollen feet/ankles	☐	☐

26. Respiratory	Yes	No
Chronic cough	☐	☐
Cough up blood	☐	☐
Shortness of breath	☐	☐
Breathing difficulties	☐	☐

27. Gastrointestinal	Yes	No
Stomach pain	☐	☐
Nausea	☐	☐
Vomiting	☐	☐
Persistent diarrhea	☐	☐
Persistent constipation	☐	☐
Heartburn /indigestion	☐	☐
Bloody or black stools	☐	☐
Pain with bowel movement	☐	☐
Bloating (gassy feeling)	☐	☐
Intolerance to a variety of foods	☐	☐

28. Eyes	Yes	No
Eye pain	☐	☐
Eye strain/ sensitivity to light	☐	☐
Double vision	☐	☐
Blind spots	☐	☐
Blurred vision	☐	☐
Seeing halo around lights	☐	☐

29. Ears, Nose, and Throat	Yes	No
Earaches	☐	☐
Frequent nasal congestion	☐	☐
Sneezing frequently	☐	☐
Change in sense of smell	☐	☐
Vertigo (head spinning)	☐	☐
Ringing or noises in the ears	☐	☐
Hearing difficulty/ loss	☐	☐
Plugged Ears	☐	☐
Frequent sore throat	☐	☐
Need to clear throat	☐	☐
Post-nasal drainage	☐	☐
Tight throat	☐	☐
Changes in voice or voice difficulties	☐	☐
Difficulty swallowing	☐	☐
Lump in the throat	☐	☐

30. Oropharyngeal Disorders	Yes	No
Stomach reflux-heartburn	☐	☐
Bad breath (malodor)	☐	☐
Bad taste in mouth	☐	☐
Coating on tongue	☐	☐
Enlarged tonsils	☐	☐
Sore throat with mouth sores	☐	☐

31. Skin/Integumentary	Yes	No
Night sweats	☐	☐
Itching/burning skin	☐	☐
Skin color change	☐	☐
Sweating change	☐	☐
Temperature change of skin	☐	☐

32. Genito-Urinary	Yes	No
Urinary retention or difficulty urinating	☐	☐
Urinate frequently	☐	☐
Pain during urination	☐	☐
Blood in urine	☐	☐

33. Hematologic/Lymphatics	Yes	No
Bleed for a long time	☐	☐
Bruise easily	☐	☐
Swollen glands	☐	☐

34. Musculoskeletal/Rheumatic	Yes	No
Stiff joints	☐	☐
Swollen joints	☐	☐
Aching painful joints	☐	☐
Arm pain/tingling	☐	☐
Hand/wrist pain/carpel tunnel	☐	☐
Low back pain	☐	☐
Neck pain	☐	☐
Shoulder and upper back pain	☐	☐
Leg pain/tingling	☐	☐
Painful feet/ankles	☐	☐
Knee pain	☐	☐

35. Neurologic	Yes	No
Severe headaches	☐	☐
Wake up from headache	☐	☐
Fainting, dizzy spells or black-outs	☐	☐
Speech difficulty/slurring	☐	☐
Facial weakness/drooping	☐	☐
Facial twitching	☐	☐
Tingling or numbness in face	☐	☐
Tingling or numbness in arms/fingers	☐	☐
Hands shake or tremble	☐	☐
Memory loss	☐	☐
Balance problem	☐	☐
Weakness in parts of body	☐	☐

36. Chemical Use	Yes	No
Coffee daily	☐	☐
beer or wine daily	☐	☐
tea daily	☐	☐
cocktails or other alcoholic beverages daily	☐	☐
soft drinks(pop) daily	☐	☐
marijuana or other recreational drugs	☐	☐
cigarettes/pipe/cigar daily	☐	☐
chewing tobacco	☐	☐
cocaine or other stimulants	☐	☐
Drug/alcohol dependency (current/recovering)	☐	☐
Take alcohol or recreational drugs to help with pain	☐	☐
Immediate family members chemically dependent	☐	☐

37. Psychiatric	Yes	No
Stressed out /overwhelmed	☐	☐
Low energy level	☐	☐
Crying spells	☐	☐
Sleep problems/insomnia	☐	☐
Poor concentration	☐	☐
Trouble relaxing	☐	☐
Felt like taking your own life in past 6 months	☐	☐

COMMENTS:

Version 1.1 Revised on 11/22/04

DENTAL AND OROFACIAL HISTORY

38. Have you had any of the following dental treatments?	Yes	No
Orthodontic braces	☐	☐
Orthognathic or bite surgery	☐	☐
Wisdom teeth extracted	☐	☐
Other teeth extracted	☐	☐
Periodontal or gum treatment	☐	☐
Bite adjusted	☐	☐
Splint or bite guard	☐	☐
Crowns or bridge	☐	☐
Dental fillings	☐	☐
Upper full denture	☐	☐
Lower full denture	☐	☐
Upper partial denture	☐	☐
Lower partial denture	☐	☐
Mouth biopsy	☐	☐

39. Dental Problems	Yes	No
Missing teeth need replacement	☐	☐
Need new crown(s) or filling(s)	☐	☐
Problem with dentures	☐	☐
Tooth fracture(s)	☐	☐
Broken filling(s)	☐	☐
Tooth decay	☐	☐
Tooth wear	☐	☐
Persistent tooth pain	☐	☐
Tooth or teeth sensitive to hot/cold	☐	☐
Painful tooth when biting on it	☐	☐

40. TMJ and Orofacial Pain	Yes	No
Jaw pain	☐	☐
Facial pain	☐	☐
Cheek pain	☐	☐
TMJ (jaw joint) pain	☐	☐
Jaw joint clicking or popping noise	☐	☐
Jaw joint grating or crepitus noise	☐	☐
Jaw locking or getting stuck open	☐	☐
Jaw locking closed/cannot open all the way	☐	☐
Temple headache	☐	☐
Ear pain	☐	☐
Mouth pain	☐	☐
Jaw stiffness when moving it	☐	☐
Jaw pain on movement	☐	☐
Jaw pain on opening wide	☐	☐
Jaw stiffness upon wakening	☐	☐

41. Mouth Lesions or Disease	Yes	No
Burning or painful tongue	☐	☐
Dry mouth	☐	☐
Mouth sores	☐	☐
Tongue sores	☐	☐
Lips cracking or sore	☐	☐
Fever Blisters/Cold sores on lips	☐	☐
Lumps or bumps in mouth	☐	☐
Swelling in mouth	☐	☐
Mouth ulcers or canker sores	☐	☐
Colored or discolored areas in mouth	☐	☐

42. Dental Occlusion	Yes	No
Difficulty chewing due to bite	☐	☐
Malocclusion (bad bite)	☐	☐
Bite that is changing	☐	☐
Cross bite	☐	☐
Open bite	☐	☐

43. Oral Habits

Have you or others noticed yourself doing any of the following oral habits regularly (more than once a week)?	Yes	No
Chewing on one side	☐	☐
Leaning on the jaw	☐	☐
Grinding the teeth at night	☐	☐
Grinding your teeth when awake	☐	☐
Waking up with sore jaws	☐	☐
Clenching your teeth when awake	☐	☐
Clenching your teeth at night	☐	☐
Holding your jaw forward	☐	☐
Chewing gum	☐	☐
Playing a musical instrument with the mouth	☐	☐
Sleeping on stomach	☐	☐
Touching or holding your teeth together	☐	☐
Holding or pressing the tongue against your teeth	☐	☐
Holding your jaw in a rigid or tense position	☐	☐
Biting objects (pens, tooth picks, etc.)	☐	☐
Biting your cheeks	☐	☐
Biting your nails or cuticles	☐	☐
Biting your lips	☐	☐
Biting tongue	☐	☐
Bracing the phone with shoulder or jaw	☐	☐

44. Periodontal (Gums)	Yes	No
Periodontal disease	☐	☐
Gingivitis or bleeding gums	☐	☐
Loose teeth	☐	☐
Deep pockets in gums	☐	☐
Sore gums	☐	☐
Difficulty in cleaning teeth	☐	☐
Calculus (tartar build-up)	☐	☐
Impacted or unerupted teeth	☐	☐

45. Oral Obstructive Sleep/Breathing Problems	Yes	No
Snore loudly	☐	☐
Stop breathing while sleeping	☐	☐
Choke or struggle for breath while sleeping	☐	☐
Wake up at night frequently	☐	☐
Move around a lot while sleeping	☐	☐
Doze off or fall asleep during day	☐	☐
Have difficulty breathing through nose	☐	☐
Wake up feeling tired	☐	☐

46. Mouth or Facial Injury	Yes	No
Have you had trauma or injury to your jaw, head, or neck?	☐	☐

Describe:_____

_____

Have you or will you consult an attorney about this condition?	☐	☐

COMMENTS:

Version 1.1 Revised on 11/22/04

GENERAL HEALTH STATUS FORM

1. Patient Name: (Last, First, MI)	2. Social Security No.	3. Birth Date (MM/DD/YY)	4. Sex □ M □ F

This questionnaire is a description of you from YOUR point of view and, thus, there are no right or wrong answers. Please respond with your first thought to each question as accurately as possible. If a question does not seem to apply to you, please answer to the best of your ability. There are three types of questions;

1) Multiple choice questions 2) Yes/No questions 3) Placement on line questions. Although the multiple choice questions and yes/no questions are probably familiar to you, the placement on line questions may not be. Here is an example of this type of question. You need to fill in the dot for both where you feel you are NOW (in the past month) as well as where you feel you SHOULD BE.

Sample: How often have you received emotional support from your family and friends?

Now ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ● ○ ○ ○ ○ ○ ○ ○ ○

Should ○ ● ○ ○ ○ ○ ○

Never Sometimes Half of the the time Usually Always

5. What is your MAIN problem or complaint? (Choose only one)

○ None	○ Jaw Pain	○ Facial Pain	○ Earaches
○ Headache	○ Pain in Jaw Joint	○ Locking of Jaw	○ Inability to Open Jaw
○ Tooth Pain	○ Noises in Jaw Joint	○ Fatigue in Jaws	○ Neck Pain
○ Bite is off	○ Other_____		

6. Choose one answer for each question to describe this MAIN problem:

What side is it on?	○ Right only	○ Left only	○ Both sides		
What is the pattern?	○ Persistent	○ Recurrent	○ One-time		
Quality of the pain?	○ Throbbing	○ Dull	○ Sharp	○ Burning	○ N/A

How many days (0-30) in the past month has it occurred? _____

7. In the past 6 months, how OFTEN has the MAIN problem occurred?

○ ○

Never Once a Month Once a week Once a day Once an hour Constantly

8. When the MAIN problem occurs, how LONG does it last?

○ ○

Does not occur 1 minute 1 hour 1 day 1 week Continuous

9. How would you rate the WORST pain on a 0 to 10 scale at the PRESENT time, that is right now, where 0 is "no pain" and 10 is "pain as bad as could be"?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No pain Pain as bad as it could be

10. In the past six months, how intense was your worst pain, rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No pain — Pain as bad as it could be

11. In the past six months, ON THE AVERAGE, how intense was your pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"? [That is, your usual pain at times you were experiencing pain].

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No pain — Pain as bad as it could be

12. How UNPLEASANT OR DISTURBING is your usual level of this MAIN problem?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

Least Imaginable — Worst Imaginable

13. What is your SECOND WORST problem or complaint? (Choose only one)

○ None	○ Jaw Pain	○ Facial Pain	○ Earaches
○ Headache	○ Pain in Jaw Joint	○ Locking of Jaw	○ Inability to Open Jaw
○ Tooth Pain	○ Noises in Jaw Joint	○ Fatigue in Jaws	○ Neck Pain
○ Bite is off	○ Other_____		

14. If present, choose one answer for each question to describe your 2nd worst problem:

What side is it on?	○Right only	○ Left only	○Both sides		
What is the pattern?	○Persistent	○ Recurrent	○One-time		
Quality of the pain?	○Throbbing	○ Dull	○ Sharp	○ Burning	○ N/A
How long does it last?	○It's gone	○ Minutes	○ Hours	○ Days	○ Constant

How many days (0-30) in the past month has it occurred? _____

How intense is it usually on a 0 to 10 scale (10 is the worst)? _____

15. What is your THIRD WORST problem or complaint? (Choose only one)

○ None	○ Jaw Pain	○ Facial Pain	○ Earaches
○ Headache	○ Pain in Jaw Joint	○ Locking of Jaw	○ Inability to Open Jaw
○ Tooth Pain	○ Noises in Jaw Joint	○ Fatigue in Jaws	○ Neck Pain
○ Bite is off	○ Other_____		

16. If present, choose one answer for each question to describe your 3rd worst problem:

What side is it on?	○Right only	○ Left only	○Both sides		
What is the pattern?	○Persistent	○ Recurrent	○One-time		
Quality of the pain?	○Throbbing	○ Dull	○ Sharp	○ Burning	○ N/A
How long does it last?	○It's gone	○ Minutes	○ Hours	○ Days	○ Constant

How many days (0-30) in the past month has it occurred? _____

How intense is it usually on a 0 to 10 scale (10 is the worst)? _____

17. If you have HEADACHES, please answer the following questions about them:

Where does it occur? ○ Temple ○ Forehead ○ Top of head ○ Side of head ○ Base of head

What side is it on? ○ Right only ○ Left only ○ Both sides

What is the pattern? ○ Persistent ○ Recurrent ○ One-time

Quality of the headache? ○Throbbing ○ Dull ○ Sharp ○ Burning ○ N/A How long does it last? ○It's gone ○ Minutes ○ Hours ○ Days ○ Constant

How many days (0-30) in the past month has it occurred? _____

How intense is it usually on a 0 to 10 scale (10 is the worst)? _____

When it occurs, do you have any: ○ Nausea ○ Vomiting ○ Sensitivity to light ○ Sensitivity to noise

Right before it occurs, do you have any: ○ Speech changes ○ Vision changes ○ Weakness ○ Other sensations:_____

Please answer the following questions about all of the above problems.

18. How difficult is it to ENDURE OR TOLERATE the problem(s) over time?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

Least imaginable — Worst imaginable

19. In the past six months, how much has the problem interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No interference — Unable to carry on any activities

20. In the past six months, how much has the problem(s) changed your ability to take part in RECREATIONAL, SOCIAL AND FAMILY ACTIVITIES where 0 is "no change" and 10 is "extreme change"?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No change — Extreme change

21. In the past six months, how much has the problem(s) changed your ABILITY TO WORK (including housework) where 0 is "no change" and 10 is "extreme change"?

⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩

No change — Extreme change

22. About how many days in the LAST SIX MONTHS (180 days) have you been kept from your usual activities (work, school or housework) because of the problem(s)?

_____ (0-180) Days

23. What activities does the problem(s) prevent or limit you from doing?

	Yes	No		Yes	No
swallowing	☐	☐	chewing	☐	☐
eating hard food	☐	☐	drinking	☐	☐
eating soft foods	☐	☐	exercising	☐	☐
maintaining normal weight	☐	☐	cleaning teeth or face	☐	☐
yawning	☐	☐	having your usual facial appearance	☐	☐
talking	☐	☐	sexual activity	☐	☐
smiling/laughing	☐	☐			

24. What other activities do all health problems prevent or limit you from doing?

	Yes	No		Yes	No
Working	☐	☐	Riding in the car or bus	☐	☐
Driving	☐	☐	Fixing meals	☐	☐
Household chores	☐	☐	Yard work	☐	☐
Walking long distances	☐	☐	Active sports	☐	☐
Hard exercise	☐	☐	Mild exercise	☐	☐
Active hobbies	☐	☐	Reading	☐	☐
Sitting for hours	☐	☐	Standing for hours	☐	☐
Socializing with friends or family	☐	☐	Discussing personal problems	☐	☐
Sleeping	☐	☐			

25. When was the problem first noticed? ____/____/_____ (mm/dd/yy)

26. The problem began with (check all that apply):

○ Jaw surgery	○ Blow to jaw/head/neck	○ Motor vehicle accident
○ Dental work	○ Chewing	○ Tooth extraction
○ Orthodontics (braces)	○ Stressful situation	○ Nothing, pain just came on
○ Work accident	○ Athletic injury	○ Other_____

27. Please describe the onset of your problem:

28. Which TESTS have you had for the problem? (check all that apply)

○ None	○ TMJ x-ray	○ Panoramic xrays
○ Other xrays	○ EMG (electromyography)	○ Urine studies
○ Venogram/arteriogram	○ MR scan (magnetic resonance)	○ Blood studies
○ Arthrogram in the joint	○ Nerve block (injection)	○ CT scan (CAT)
○ Myelogram	○ Diet analysis	○ Thermogram
○ Jaw tracking	○ Bone scan	○ Tooth pulp test
○ Other_____		

29. Which of these HEALTH/HELPING PROFESSIONALS have you seen for the problem? (check all that apply)

○ None	○ Acupuncturist	○ 'insurance' Physician/Dentist
○ Orthodontist	○ Anesthesiologist	○ Internist
○ Ear/Nose/Throat	○ Ophthalmologist	○ TMJ specialist
○ Neurologist	○ Dentist	○ Psychologist
○ Orthopedic Surgeon	○ Rheumatologist	○ Neurosurgeon
○ Oral Surgeon	○ Psychiatrist	○ Physical Therapist
○ Physical Medicine Specialist	○ Occupational Therapist	○ Chiropractor
○ General Practitioner (M.D.)	○ Other_____	

30. Which TREATMENTS have you had for the problem? (check all that apply)

○ No treatment	○ Traction	○ Splints or bite planes
○ Electrical stimulation (TENS)	○ Injections/nerve blocks	○ Counseling
○ Ultrasound or iontophoresis	○ Acupuncture	○ Medications
○ Root canal/dental treatment	○ Massage/acupressure	○ Heat/cold applications
○ Exercise	○ Biofeedback	○ Stress management
○ Neurosurgery	○ TMJ surgery without implants	○ TMJ implant surgery
○ Orthodontic/braces	○ Pain program	○ Hypnosis
○ Chiropractic treatment	○ Botox injections	○ Other_____

31. How many EMERGENCY ROOM VISITS (for any reason) have you had in the past year?

O 0 O 1 O 2 or 3 O 4 or 5 O 6 or more

32. What is the total number of DIFFERENT KINDS OF PILLS or MEDICINES (any type, except vitamins) that you take daily?

O 0 O1 to 2 O 3 to 4 O 5 to 6 O 7 or more

33. How many days did you spend IN THE HOSPITAL during the past year?

O 0 O 1 to 3 O 4 to 6 O 7 to 14 O 15 or more

34. How often have you been seen by HEALTH PROFESSIONALS (for any reason) in the last year?

O O O O O O O O O O O O O O O O O O O O O O O O O O O O

Daily — Once a Week — Once a month — Once every 3 months — Not at all

35. How many SURGERIES have you had for a jaw joint (TMJ) problem? Right: ____Left: ____

36. If you have had TMJ surgery, please check the type of surgeries you have had.

O No surgery

	right	left		right	left
Arthroscopic surgery…………….....	O	O	TMJ disk removal………………….....	O	O
Orthognathic surgery……………...	O	O	TMJ disk implant removal…………….	O	O
TMJ disk implant placed………….	O	O	Arthroplasty…………………………….	O	O
Total synthetic joint placement…...	O	O	Arthrocentesis/lysis and lavage……..	O	O
TMJ disk repair………………...…..	O	O	Arthrotomy……………………………..	O	O
Other____________________	O	O			

37. If you have had a TMJ implant, please check the type of implant(s) that you have had.

O No Implants

	right	left		right	left
Silicone/Silastic® disk (permanent)	O	O	Lorenz/Biomet………………….…...	O	O
Silicone/Silastic® disk (temporary)	O	O	Proplast/teflon® disk…………………	O	O
Christensen (TMJ, Inc) joint……...	O	O	Techmedica/TMJ Concepts joint…....	O	O
Hoffman-Pappas/Endotec joint…..	O	O	Kent/Vitek joint……………………….	O	O
Other:____________________	O	O			

38. Please check any side effects you have had from TMJ treatment or TMJ surgery;

O No Side Effects

	right	left		right	left
Facial or jaw swelling……………	O	O	Asymmetry of the face…………….	O	O
Facial muscle weakness………..	O	O	Objectionable scarring…………….	O	O
Allergic reaction to drugs……….	O	O	Bruising or discoloration…………..	O	O
Numbness to skin……………….	O	O	Change in bite………………………	O	O
Worsening of pain……………..…	O	O	Difficulty opening jaw……………...	O	O
Ear ringing………………………..	O	O	Difficulty chewing…………………...	O	O
Ear plugged…………………….	O	O	Infection……………………………...	O	O
Ear pain…………………………..	O	O	TMJ noise or crepitus………..…...	O	O
Dental problems…………………	O	O	Eye brow weakness…………….….	O	O

39. How many years has this problem or other health problems affected your life?

O less than 1 O 1 to 2 O 3 to 4 O 5 to 10 O 11 to 19 O 20 or more

40. How many members of your household (not including you) have a pain problem, a physical handicap, or a chronic disease?

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 or more

41. a. Have any of your LIVING blood related family members had the following illnesses or conditions?

	Father	Mother	Any Brother	Any Sister	Any Grandfather	Any Grandmother	Any Child
TMJ disorders………	○	○	○	○	○	○	○
Arthritis………………	○	○	○	○	○	○	○
Heart disease……….	○	○	○	○	○	○	○
Cancer……………….	○	○	○	○	○	○	○
Headaches…………..	○	○	○	○	○	○	○
Hip joint implant…….	○	○	○	○	○	○	○
Knee joint implant….	○	○	○	○	○	○	○
Joint implant failure…	○	○	○	○	○	○	○
None of the above….	○	○	○	○	○	○	○

b. Have any of your DECEASED blood related family members had the following illnesses or conditions?

	Father	Mother	Any Brother	Any Sister	Any Grandfather	Any Grandmother	Any Child
TMJ disorders………	○	○	○	○	○	○	○
Arthritis………………	○	○	○	○	○	○	○
Heart disease……….	○	○	○	○	○	○	○
Cancer……………….	○	○	○	○	○	○	○
Headaches…………..	○	○	○	○	○	○	○
Hip joint implant…….	○	○	○	○	○	○	○
Knee joint implant….	○	○	○	○	○	○	○
Joint implant failure…	○	○	○	○	○	○	○
None of the above….	○	○	○	○	○	○	○

Please fill in the bubble on the: 1) first line where you feel you are NOW (in the past month)
2) second line for where you feel you SHOULD be.

42. What has been your usual activity level in the past month?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

Lay in bed all day	Lay down half the day	Sit and rest half the day	Sit and rest a few times a day	Up and busy all day without any rest

43. What has been your usual exercise level in the past month?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

No exercise	Pleasure drives, go outside	Short walks fishing, etc.	Long walks golf, bowling, etc.	Regular running tennis, etc.

44. What has your usual sleep been like in the past month?

Now

Should

No sleep	Sleep poorly 3-5 hrs.	Difficulty falling asleep, wake early	Wake on occasion during night	Sleep soundly all night

45. What have your usual eating habits been like in the past month?

Now

Should

Do not eat	No appetite, eat lightly	Snack most of the day, occasional regular meal	Eat one regular meal and snack for the rest	Eat three good regular meals

46. How often are you tense in a typical day?

Now

Should

Always	Usually	Half the time	Twice a day	Never

47. How often do you hurry in a typical day?

Now

Should

I hurry all day and night	I usually hurry	I hurry half the time	I occasionally hurry when necessary	I never hurry

48. How much do you take responsibility for your health?

Now

Should

Not at all	Somewhat	Moderately	A lot	Completely

49. How often is the problem used as a reason to others that keeps you from doing something?

Now

Should

Always	Usually	Half the	Sometimes	Never

50. How regular has your lifestyle (eat, sleep, work, etc.) been in the past month?

Now

Should

Irregular, always miss eating, sleeping, and work	One-two regular days per week	Regular for half the week	Five-six regular days per week	Eat, sleep, and work regularly every day

51. How often do you feel you have had financial problems?

Now

Should

Always	Usually	Half the time	Sometimes	Never

52. How often do you enjoy your work (or if not working your usual daily activities)?

Now

Should

Never	Sometimes	Half the time	Usually	Always

53. How often have you received emotional support from your family and friends?

Now

Should

Never	Sometimes	Half the time	Usually	Always

54. How often are you dependent on family or friends to fulfill your daily needs?

Now ○

Should ○

Always | Usually | Half the Time | Sometimes | Never

55. When you are in pain, how have others reacted in the past month?

Now ○

Should ○

They attend to all of my needs | They do some things for me | They ask me how I am | They complain about me | Nobody knows when I am in pain

56. How are your relationships with your co-workers, or if not working, your companions at your usual daily activities?

Now ○

Should ○

Worst Possible | Poor | Moderate | Good | Best Possible

57. How is your relationship with the most important person in your life (spouse, significant other, best friend)?

Now ○

Should ○

Worst Possible | Poor | Moderate | Good | Best Possible

58. How well do you understand the problem?

Now ○

Should ○

Not at all | Poor | Moderate | Good | Completely

59. How motivated are you to reduce the problem?

Now ○

Should ○

No motivation | Low | Moderate | High | Complete motivation

60. How much do you expect the problem to be reduced in the future?

Now ○

Should ○

No change | Lessened slightly | Half of it gone | Most of it gone | Completely gone

61. How long do you feel it will take to reduce the problem when treated?

Now ○

Should ○

Never be reduced | Months to years | Weeks to months | Days to weeks | Immediate reduction

62. How often do you feel depressed?

Now ○

Should ○

Always | Usually | Half the time | Sometimes | Never

63. How often do you feel anxious or worried?

Now ○

Should ○

Always | Usually | Half the time | Sometimes | Never

64. How often do you feel angry?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

Always | Usually | Half the Time | Sometimes | Never

65. How often do you feel confused about life?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

Always | Usually | Half the time | Sometimes | Never

66. How often do you feel bad about yourself?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

Always | Usually | Half the time | Sometimes | Never

67. How is your energy level?

Now ○○○○○○○○○○○○○○○○○○○○○○○○○○○○
Should ○○○○○○○○○○○○○○○○○○○○○○○○○○○○

Always low | Usually low | Low Half the time | Sometimes low | Never low

68. In general, would you say your health is:

○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

The following questions are about activities you might do during a typical day. Does your health *now* limit you in these activities? If so, how much?

	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
69. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
70. Climbing **several** flights of stairs	☐	☐	☐

During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	**No**
71 Accomplished less than you would like	☐	☐
72. Were limited in the **kind** of work or other activities	☐	☐

During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

	Yes	**No**
73. Accomplished less than you would like	☐	☐
74. Didn't do work or other activities as **carefully** as usual	☐	☐

75. During the *past 4 weeks*, how much did pain **interfere with your normal work** (including both work outside the home and housework)?

○Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the *past 4 weeks*

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
76. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
77. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
78. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

79. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

○ All of the time ○ Most of the time ○ Some of the time ○ A little of the time ○ None of the time

.....ADDITIONAL QUESTIONS CONTINUED ON THE NEXT PAGE.....

80. In the last month, how much have you been distressed by

	Not at all	A little bit	Moderately	Quite a bit	Extremely
Headaches	⓪	①	②	③	④
Loss of sexual interest or pleasure	⓪	①	②	③	④
Faintness or dizziness	⓪	①	②	③	④
Pains in the heart or chest	⓪	①	②	③	④
Feeling low in energy or slowed down	⓪	①	②	③	④
Thoughts of death or dying	⓪	①	②	③	④
Poor appetite	⓪	①	②	③	④
Crying easily	⓪	①	②	③	④
Blaming yourself for things	⓪	①	②	③	④
Pains in the lower back	⓪	①	②	③	④
Feeling lonely	⓪	①	②	③	④
Feeling blue	⓪	①	②	③	④
Worrying too much about things	⓪	①	②	③	④
Feeling no interest in things	⓪	①	②	③	④
Nausea or upset stomach	⓪	①	②	③	④
Soreness of your muscles	⓪	①	②	③	④
Trouble falling asleep	⓪	①	②	③	④
Trouble getting your breath	⓪	①	②	③	④
Hot or cold spells	⓪	①	②	③	④
Numbness or tingling in parts of your body	⓪	①	②	③	④
A lump in your throat	⓪	①	②	③	④
Feeling hopeless about the future	⓪	①	②	③	④
Feeling weak in parts of your body	⓪	①	②	③	④
Heavy feelings in your arms or legs	⓪	①	②	③	④
Thoughts of ending your life	⓪	①	②	③	④
Overeating	⓪	①	②	③	④
Awakening in the early morning	⓪	①	②	③	④
Sleep that is restless or disturbed	⓪	①	②	③	④
Feeling everything is an effort	⓪	①	②	③	④
Feelings of worthlessness	⓪	①	②	③	④
Feeling of being caught or trapped	⓪	①	②	③	④
Feelings of guilt	⓪	①	②	③	④

Thank you for your time and effort.

HISTORY QUESTIONNAIRE

ID# _____

Date: ___ ___ / ___ ___ / ___ ___

Please read each question and respond accordingly. For each of the questions below circle only one response.

1. Would you say your health in general is excellent, very good, good, fair or poor?

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Would you say your oral health in general is excellent, very good, good, fair or poor?

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

3. Have you had pain in the face, jaw, temple, in front of the ear or in the ear in the past month?

No	0
Yes	1

[If no pain in the past month, SKIP to question 14]

If Yes,

4.a. How many years ago did your facial pain begin for the first time?

___ ___ years

[If one year ago or more SKIP to question 5] **[If less than one year ago, code 00]**

4.b. How many months ago did your facial pain begin for the first time?

____ ____ months

5. Is your facial pain persistent, recurrent or was it only a one-time problem?

Persistent	1
Recurrent	2
One-Time	3

6. Have you ever gone to a physician, dentist, chiropractor or other health professional for facial ache or pain?

No	1
Yes, in the last six months	2
Yes, more than six months ago	3

7. How would you rate your facial pain on a 0 to 10 scale at the present time, that is right now, where 0 is "no pain" and 10 is "pain as bad as could be"?

No pain										**Pain as bad as could be**
0	1	2	3	4	5	6	7	8	9	10

8. In the past six months, how intense was your worst pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"?

No pain										**Pain as bad as could be**
0	1	2	3	4	5	6	7	8	9	10

9. In the past six months, on the average, how intense was your pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"? [That is, your usual pain at times you were experiencing pain].

No pain										**Pain as bad as could be**
0	1	2	3	4	5	6	7	8	9	10

10. About how many days in the last six months have you been kept from your usual activities (work, school or housework) because of facial pain?

_____ _____ _____
DAYS

11. In the past six months, how much has facial pain interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"?

No Interference										**Unable To Carry On Any Activities**
0	1	2	3	4	5	6	7	8	9	10

12. In the past six months, how much has facial pain changed your ability to take part in recreational, social and family activities where 0 is "no interference " and 10 is "extreme change"?

No **Interference**										**Unable To Carry On Any Activities**
0	1	2	3	4	5	6	7	8	9	10

13. In the past six months, how much has facial pain changed your ability to work including housework) where 0 is "no interference " and 10 is "extreme change"?

No Interference										**Unable To Carry On Any Activities**
0	1	2	3	4	5	6	7	8	9	10

14.a. Have you ever had your jaw lock or catch so that it won't open all the way? No 0 Yes 1

[If no problem opening all the way, SKIP to question 15]

If Yes,

14.b. Was this limitation in jaw opening severe enough to interfere with your ability to eat? No 0 Yes 1

15.

a. Does your jaw click or pop when you open or close your mouth or when chewing? No 0 Yes 1

b. Does your jaw make a grating or grinding noise when it opens and closes or when chewing? No 0 Yes 1

c. Have you been told, or do you notice that you grind your teeth or clench your jaw while sleeping at night? No 0 Yes 1

d. During the day, do you grind your teeth or clench your jaw? No 0 Yes 1

e. Does your jaw ache or feel stiff when you wake up in the morning? No 0 Yes 1

f. Do you have noises or ringing in your ears? No 0 Yes 1

g. Does your bite feel uncomfortable or unusual? No 0 Yes 1

16.a. Do you have rheumatoid arthritis, lupus, or other systemic arthritic disease? No 0 Yes 1

16.b. Do you know of anyone in your family who has had any of these diseases? No 0 Yes 1

16.c. Have you had or do you have any swollen or painful joint(s) other than the joints close to your ears (TMJ)? No 0 Yes 1

[If no swollen or painful joints, SKIP to question 17.a.]

If Yes,

16.d. Is this a persistent pain which you have had for at least one year? No 0 Yes 1

17.a. Have you had a recent injury to your face or jaw? No 0 Yes 1

[If no recent injuries, SKIP to question 18]

If Yes,

17.b. Did you have jaw pain before the injury? No 0 Yes 1

18. During the last six months have you had a problem with headaches or migraines? No 0 Yes 1

19. What activities does your present jaw problem prevent or limit you from doing?

a.	Chewing	No	0	g.	Sexual activity	No	0
		Yes	1			Yes	1
b.	Drinking	No	0	h.	Cleaning teeth or face	No	0
		Yes	1			Yes	1
c.	Exercising	No	0	i.	Yawning	No	0
		Yes	1			Yes	1
d.	Eating hard foods	No	0	j.	Swallowing	No	0
		Yes	1			Yes	1
e.	Eating soft foods	No	0	k.	Talking	No	0
		Yes	1			Yes	1
f.	Smiling/laughing	No	0	l.	Having your usual facial appearance	No	0
		Yes	1			Yes	1

20. In the last month, how much have you been distressed by. . .

		Not At All	A Little Bit	Moder-ately	Quite A Bit	Ex-tremely
a.	Headaches	0	1	2	3	4
b.	Loss of sexual interest or pleasure	0	1	2	3	4
c.	Faintness or dizziness	0	1	2	3	4
d.	Pains in the heart or chest	0	1	2	3	4
e.	Feeling low in energy or slowed down	0	1	2	3	4
f.	Thoughts of death or dying	0	1	2	3	4
g.	Poor appetite	0	1	2	3	4
h.	Crying easily	0	1	2	3	4
i.	Blaming yourself for things	0	1	2	3	4
j.	Pains in the lower back	0	1	2	3	4
k.	Feeling lonely	0	1	2	3	4
l.	Feeling blue	0	1	2	3	4
m.	Worrying too much about things	0	1	2	3	4
n.	Feeling no interest in things	0	1	2	3	4
o.	Nausea or upset stomach	0	1	2	3	4
p.	Soreness of your muscles	0	1	2	3	4
q.	Trouble falling asleep	0	1	2	3	4
r.	Trouble getting your breath	0	1	2	3	4
s.	Hot or cold spells	0	1	2	3	4
t.	Numbness or tingling in parts of your body	0	1	2	3	4
u.	A lump in your throat	0	1	2	3	4
v.	Feeling hopeless about the future	0	1	2	3	4
w.	Feeling weak in parts of your body	0	1	2	3	4
x.	Heavy feelings in your arms or legs	0	1	2	3	4
y.	Thoughts of ending your life	0	1	2	3	4
z.	Overeating	0	1	2	3	4
aa.	Awakening in the early morning	0	1	2	3	4

		Not At All	A Little Bit	Moder-ately	Quite A Bit	Ex-tremely
bb.	Sleep that is restless or disturbed	0	1	2	3	4
cc.	Feeling everything is an effort	0	1	2	3	4
dd.	Feelings of worthlessness	0	1	2	3	4
ee.	Feeling of being caught or trapped	0	1	2	3	4
ff.	Feelings of guilt	0	1	2	3	4

21. How good a job do you feel you are doing in taking care of your health overall?

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

22. How good a job do you feel you are doing in taking care of your oral health?

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

23. When were you born? Month __ __ Day __ __ Year __ __

24. Are you male or female?

Male	1
Female	2

25. Which of the following groups best represent your race?

Aleut, Eskimo or American Indian	1
Asian or Pacific Islander	2
Black	3
White	4
Other	5
(please specify) _____	

26. Are any of these groups your national origin or ancestry?

Puerto Rican	1	Chicano	5
Cuban	2	Other Latin American	6
Mexican/Mexicano	3	Other Spanish	7
Mexican American	4	None of the above	8

27. What is the highest grade or year of regular school that you have completed?

Never attended or Kindergarten:	00							
Elementary School:	1	2	3	4	5	6	7	8
High School:	9	10	11	12				
College:	13	14	15	16	17	18+		

28. During the past 2 weeks, did you work at a job or business not counting work around the house (include unpaid work in the family farm/business)?

Yes	1
No	2

29. Are you married, widowed, divorced, separated or never been married?

Married-spouse in household	1
Married-spouse not in household	2
Widowed	3
Divorced	4
Separated	5
Never Married	6

30. Which of the following best represents your total combined household income during the past 12 months?

___ $0-$14,999 ___ $25,000-$34,999 ___ $50,000 or more
___ $15,000-$24,999 ___ $35,000-$49,999

31. What is your USA 5 digit zip code or your International Area Code? _ _ _ _ _

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RESEARCH DIAGNOSTIC CRITERIA
TMD CLINICAL EXAMINATION FORM

ID# _____

Date: ___ ___ / ___ ___ / ___ ___

1. Do you have pain on the right side of your face, the left side or both sides?

None	0
Right	1
Left	2
Both	3

2. Could you point to the areas where you feel pain?

[Examiner feels area subject points to, if it is unclear whether it is joint or muscle pain]

Right		Left	
None	0	None	0
Jaw Joint	1	Jaw Joint	1
Muscles	2	Muscles	2
Both	3	Both	3

3. Opening Pattern

Straight	0
Right Lateral Deviation (uncorrected)	1
Right Corrected ("S") Deviation	2
Left Lateral Deviation (uncorrected)	3
Left Corrected ("S") Deviation	4
Other	5
Type_____ (specify)	

4. Vertical Range of Motion

Maxillary incisor used	8
	9

		MUSCLE PAIN				JOINT PAIN			
		None	Right	Left	Both	None	Right	Left	Both
a. Unassisted opening without pain	___ ___mm								
b. Maximum unassisted opening	___ ___mm	0	1	2	3	0	1	2	3
c. Maximum assisted opening	___ ___mm	0	1	2	3	0	1	2	3
d. Vertical incisal overlap	___ ___mm								

5. Joint Sounds (palpation)

			RIGHT	LEFT
a.	Opening	None	0	0
		Click	1	1
		Coarse Crepitus	2	2
		Fine Crepitus	3	3
	Measurement of Opening Click		___ ___mm	___ ___mm
b.	Closing	None	0	0
		Click	1	1
		Coarse Crepitus	2	2
		Fine Crepitus	3	3
	Measurement of Closing Click		___ ___mm	___ ___mm
c.	Reciprocal click eliminated on protrusive opening	No	0	0
		Yes	1	1
		NA	8	8

6. Excursions

		MUSCLE PAIN				JOINT PAIN			
		None	Right	Left	Both	None	Right	Left	Both
a. Right Lateral Excursion	___ ___mm	0	1	2	3	0	1	2	3
b. Left Lateral Excursion	___ ___mm	0	1	2	3	0	1	2	3
c. Protrusion	___ ___mm	0	1	2	3	0	1	2	3

		RIGHT	LEFT	NA
d. Midline Deviation	___ ___mm	1	2	8

7. Joint Sounds on Excursions

Right Sounds:

	None	Click	Coarse Crepitus	Fine Crepitus
Excursion Right	0	1	2	3
Excursion Left	0	1	2	3
Protrusion	0	1	2	3

Left Sounds:

	None	Coarse Click	Fine Crepitus	Crepitus
Excursion Right	0	1	2	3
Excursion Left	0	1	2	3
Protrusion	0	1	2	3

DIRECTIONS, ITEMS 8-10

The examiner will be palpating (touching) different areas of your face, head and neck. We would like you to indicate if you do not feel pain or just feel pressure (0), or pain (1-3). Please rate how much pain you feel for each of the palpations according to the scale below. Circle the number that corresponds to the amount of pain you feel. We would like you to make a separate rating for both the right and left palpations.

0 = No Pain/Pressure Only

1 = Mild Pain

2 = Moderate Pain

3 = Severe Pain

8. Extraoral muscle pain with palpation:

		RIGHT	LEFT
a.	Temporalis (posterior) "Back of temple"	0 1 2 3	0 1 2 3
b.	Temporalis (middle) "Middle of temple"	0 1 2 3	0 1 2 3
c.	Temporalis (anterior) "Front of temple"	0 1 2 3	0 1 2 3
d.	Masseter (superior) "Cheek/under cheekbone"	0 1 2 3	0 1 2 3
e.	Masseter (middle) "Cheek/side of face"	0 1 2 3	0 1 2 3
f.	Masseter (inferior) "Cheek/jawline"	0 1 2 3	0 1 2 3
g.	Posterior mandibular region (Stylohyoid/posterior digastric region) "Jaw/throat region"	0 1 2 3	0 1 2 3
h.	Submandibular region (Medial pterygoid/Suprahyoid/anterior digastric region) "Under chin"	0 1 2 3	0 1 2 3

9. Joint pain with palpation:

		RIGHT	LEFT
a.	Lateral pole "outside"	0 1 2 3	0 1 2 3
b.	Posterior attachment "inside ear"	0 1 2 3	0 1 2 3

10. Intraoral muscle pain with palpation:

		RIGHT	LEFT
a.	Lateral pterygoid area "Behind upper molars"	0 1 2 3	0 1 2 3
b.	Tendon of temporalis "Tendon"	0 1 2 3	0 1 2 3

Questions Used to Grade Chronic Pain Status

Pain intensity items

1. How would you rate your back/headache/facial pain on a 0–10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

No pain										Pain as bad could be
0	1	2	3	4	5	6	7	8	9	10

2. In the past 6 months, how intense was your worst pain rated on a 0–10 scale where 0 is 'no pain' and 10 is 'pain as bad as could be'?

No pain										Pain as bad could be
0	1	2	3	4	5	6	7	8	9	10

3. In the past 6 months, on the average, how intense was your pain rated on a 0–10 scale where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.)

No pain										Pain as bad could be
0	1	2	3	4	5	6	7	8	9	10

Disability items

4. About how many days in the last 6 months have you been kept from your usual activities (work, school or housework) because of back/headache/facial pain?

Disability days

5. In the past 6 months, how much has back/headache/facial pain interfered with your daily activities rated on a 0–10 scale where 0 is 'no interference' and 10 is 'unable to carry on any activities'?

No interference										Unable to Carry on any activities
0	1	2	3	4	5	6	7	8	9	10

6. In the past 6 months, how much has back/headache/facial pain pain changed your ability to take part in recreational, social and family activities where 0 is 'no change' and 10 is 'extreme change'?

No change										Extreme change
0	1	2	3	4	5	6	7	8	9	10

7. In the past 6 months, how much has back/headache/facial pain changed your ability to work (including housework) where 0 is 'no change' and 10 is 'extreme change'?

No change										Extreme change
0	1	2	3	4	5	6	7	8	9	10

Methods of Grading Chronic Pain Severity

Scoring

Characteristic Pain Intensity is a 0–100 score derived from questions 1–3:
Mean (Pain Right Now, Worst Pain, Average Pain) × 10
Disability Score is a 0–100 score derived from questions 5–7:
Mean (Daily Activities, Social Activities, Work Activities) × 10
Disability Points: add the indicated points for disability days (question 4) and for Disability Score.

Disability points			
Disability days (0–180)		Disability score (0–100)	
0–6 Days	0 Points	0–29	0 Points
7–14 Days	1 Point	30–49	1 Point
15–30 Days	2 Points	50–69	2 Points
31 + Days	3 points	70 +	3 points