Effects of Obesity, Physical Activity, and Nutrient Intake on Knee Osteoarthritis

by

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Abstract

In all stages of knee osteoarthritis (OA), identifying and addressing modifiable risk factors is essential in managing OA, including the recovery trajectory following total knee arthroplasty (TKA). Obesity is the greatest modifiable risk factor for both the development and progression of knee OA, and it is one of the most important predictors for the risk of TKA. Along with obesity management, diet and physical activity are also repeatedly recommended by the guidelines as modifiable risk factors. Therefore, the assessments and monitoring of modifiable risk factors in patients with knee OA is warranted. In the first study of this thesis, data from the Alberta Bone and Joint Health Institute (ABJHI) repository in patients who underwent TKA (N=15151) between 2012 and 2016 has been used. The association between obesity (defined by the World Health Organization (WHO) classification of Body Mass Index (BMI) to normal weight (BMI≤24.99 kg/m^2), overweight (25≤BMI≤29.99 kg/m^2), obese class I (30≤BMI≤34.99 kg/m^2), obese class II (35≤BMI≤39.99 kg/m^2), or obese class III (BMI≥40 kg/m^2) and comorbidities with complication rates in patients was examined. Results showed that patients in obese class I and II groups were more likely to have pulmonary embolism (p<.001; OR:2.73 and 2.77, respectively), whereas the patients in obese class III group were more likely to have pulmonary embolism (p<.001; OR:3.62), deep wound infection (*P*=.04; OR:2.25) compared to patients in the normal BMI group. Patients with diabetes, cardiac disease, and circulatory/blood clotting disorders were more likely to undergone postoperative blood transfusion (p<.001; OR:1.76, 3.07, and 7.02, respectively), compared to patients without comorbidities. Patients with diabetes and poor mental health were more likely to be readmitted (p<.001; OR:1.6 and 2.12, respectively), compared to patients without comorbidities. In the second study, we used ABJHI data to investigate the impact of the degree of obesity on patient-reported outcome measures following TKA. Patients who completed the

Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (N=7714), as well as the EuroQol-5D (EQ-5D; N=3848) quality of life questionnaire were included. By 12 months postoperatively, there were no differences among BMI groups in terms of WOMAC subscales as well as EQ-5D-5L, and all patients, regardless of BMI group, received similar benefits from surgery ($p<.001$). In the third study, we used a cross-sectional study design to compare nutrient intake, including the amount of fat and saturated fatty acids (SFA) intakes, and daily physical activity between patients with knee OA (N=57) and healthy controls (N=49). We also examined the association between nutrient intake as well as the amount of daily physical activity with self-reported and performance-based measures. Results revealed that patients had less steps/day compared to the control ($p=.04$; 5319±432 versus 6839±483 steps/day) after adjusting for sex, age, and BMI. Compared to the control group, patients with OA had significantly higher energy-adjusted SFA ($p=.04$; 250±13.1 and 204±14.8 gr/day, respectively) and trans fatty acids (TFA) intake ($p=.05$; 1.43±0.15 and 0.91±0.20 gr/day, respectively). Increased SFA intake was associated with greater pain and worse physical function measured using both self-reported WOMAC (pain and function subscales) and Lower Extremity Function Score (LEFS), as well as a performance-based 6-minute walk test (6MWT) distance. Increased TFA intake was associated with worse WOMAC pain and function, total, and shorter 6MWT distance. However, increased steps/day was associated with better scores in all WOMAC subscales, LEFS, 6MWT, and stair test. Overall, findings from this dissertation support the following: 1) obesity appears to be an independent risk factor for adverse events following TKA; 2) patients with higher BMI reported similar benefits from TKA compared to the normal BMI group in terms of OA symptoms and quality of life measures; 3) patients with knee OA walked significantly fewer steps than healthy controls. In terms of nutrient intake, patients also had significantly higher levels of energy, SFA, and TFA

intake compared to the healthy control group. More walking was associated with better performance in WOMAC subscales, stair test, LEFS, and 6MWT. Higher consumption of SFA and TFA were associated with worse WOMAC subscales, LEFS, and 6MWT. These findings may be used by patients and care providers to inform the risks and benefits of an elective TKA procedure, and by care providers to emphasize the importance of dietary intake and daily physical activity to manage symptoms in patients with OA.

Preface

This thesis is the original work by Fatemeh Baghbaninaghadehi and consists of three studies. The first two studies were retrospective studies using data from patients undergoing TKA acquired from Alberta Bone and Joint Health Institute (ABJHI), and the third study was an cross-sectional study.

The first project (first and second study) received ethics approval from the University of Alberta Health Research Ethics Board, Project Name "IMPACTS OF OBESITY ON QUALITY OF LIFE, FUNCTION, AND PAIN AFTER TOTAL KNEE ARTHROPLASTY", No. Pro00053754, June 9, 2015. The second project (third study) received ethics approval from the University of Alberta Health Research Ethics Board, Project Name "DIETARY INTAKE AND PHYSICAL ACTIVITY OF PATIENTS WITH OSTEOARTHRITIS (OA) COMPARED TO HEALTHY NON-OA PARTICIPANTS", No. Pro00083386, February 20, 2019, and from Edmonton Bone and Joint Centre Research Approval Committee, February 20, 2019.

The introduction in chapter 1 and the literature review in chapter 2 are my original work.

Chapter 3 of this thesis will be submitted for publication as Baghbaninaghadehi, F., Armijo Olivo, S., Forhan, M., Prado, C. M., Gramlich, L., Manns, P. J., and Woodhouse, L. Obesity, comorbidities and the associated risk among patients who underwent Total Knee Arthroplasty in Alberta.

For Chapter 3, I was responsible for concept formation, data acquisition, data analysis, and ethics submission, as well as the manuscript composition, and revision. Armijo Olivo, S. provided the statistical expertise and manuscript edits. Prado, C. M., Forhan, M., Gramlich, L., and Manns,

P. J., contributed manuscript edits. Woodhouse, L. was the supervisory author and was involved with concept formation, data acquisition, and manuscript edits.

Chapter 4 of this thesis will be submitted for publication as Baghbaninaghadehi, F., Armijo Olivo, S., Prado, C. M., Gramlich, L., Manns, P. J., and Woodhouse, L. Does obesity affect patient-reported outcomes following Total Knee Arthroplasty?

For Chapter 4, Baghbaninaghadhei F was responsible for concept formation, data acquisition, data analysis, and ethics submission, as well as the manuscript composition and revision. Armijo Olivo, S. provided the statistical expertise and manuscript edits. Prado, C. M., Gramlich, L., and Manns, P. J., contributed to manuscript edits. Woodhouse, L. was the supervisory author and was involved with concept formation, data acquisition, and manuscript edits.

Chapter 5 of this thesis will be submitted for publication as Baghbaninaghadehi, F., Armijo Olivo, S., Prado, C. M., Manns, P. J., and Woodhouse. L. Dietary fat intake, physical activity, and their relationship with osteoarthritis symptoms.

For Chapter 5, I was responsible for concept formation, participant recruitment, data collection, data analysis, as well as the manuscript composition and revision. Armijo Olivo, S. provided the statistical expertise and involved in manuscript edits. Prado, C. M. contributed to training on dietary analysis and manuscript edits. Woodhouse, L., and Manns, P.J. were the supervisory authors and were involved with concept formation and manuscript edits.

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Glossary of Terms

Osteoarthritis: Osteoarthritis (OA) is a chronic musculoskeletal disorder characterised by loss of cartilage in synovial joints, osteophyte formation, synovitis, and subchondral bone changes.

Primary knee OA: It is the most common type of OA and is the result of articular cartilage degeneration which appears insidiously without apparent cause.

Secondary Knee OA: It is often the result of articular cartilage degeneration secondary to a known reason such as injury/trauma, occupation, obesity, or metabolic diseases, such as diabetes and hormonal disorders.

Obesity: A chronic disease characterized by excessive or abnormal body fat that impairs health. Different measures of body fat and distribution are available including Body Mass Index (BMI).

World Health Organization (WHO) obesity criteria: The WHO classifies BMI to normal weight (BMI≤24.99 kg/m^2), overweight (25≤BMI≤29.99 kg/m^2), obese class I (30≤BMI≤34.99 kg/m^2), obese class II (35≤BMI≤39.99 kg/m^2), or obese class III (BMI≥40 kg/m^2).

Physical activity: Any bodily movement produced by skeletal muscles that results in energy expenditure.

Exercise: Physical activity that is planned, structured, and repetitive and is designed to improve or maintain physical capacity.

Dietary Records: Dietary record (also called food diary) is a self-reported description of the type and amount of all foods and beverages consumed at the time of eating.

List of abbreviations

TKA: Total knee arthroplasty

OA: Osteoarthritis

BMI: Body Mass Index

WHO: World Health Organization

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

EQ5D: EuroQol-5D

SFA: Saturated fatty acids

TFA: Trans fatty acids

LEFS: Lower Extremity Function Score

6MWT: 6-minute walk test distance

ABJHI: Alberta Bone and Joint Health Institute

ACL: Anterior cruciate ligament

MUFAs: Monounsaturated fatty acids

PUFAs: polyunsaturated fatty acids

AA: Arachidonic acid

FFQs: Food frequency questionnaires

DAD: Discharge Abstract Database

OR: Odds ratios

CI: Confidence intervals

HRQoL: Health-related quality of life

PROMS: Patients Reported Outcome Measures

AHS: Alberta Health Services

MCID: Minimal clinically important difference

WC: Waist girth circumference

OARSI: Osteoarthritis Research Society International

VIF: Variance-inflation factor

Chapter 1

Introduction

1.1. Introduction and Purpose

Osteoarthritis (OA) is a chronic musculoskeletal disorder, characterized pathologically by loss of cartilage in synovial joints, osteophytic formation, synovitis, and subchondral bone changes that result in pain and impaired mobility [1, 2]. It is a degenerative chronic disease that affects 10–15% of adults in Canada [3], with the highest proportion of the OA burden occurring in the knee joint [4]. The overall treatment goal of OA is to relieve pain, restore loss of function, and preserve health-related quality of life [5, 6]. Numerous studies have highlighted the importance of modifiable risk factors in treating osteoarthritis symptoms [7-9]. Modifiable risk factors related to lifestyle, such as obesity, dietary imbalance, and physical inactivity, might accelerate disease onset and progression through a combination of mechanical and systemic mechanisms [10].

Obesity is the greatest modifiable risk factor for both the development and progression of knee OA [11, 12]. Longitudinal studies have shown that the risk of developing knee OA increases by 30% for every 5 kg increase in weight [13]. The pathophysiology of obesity-related OA is multi-factorial. Structural joint damage could be the result of both mechanical factors [14, 15] and metabolic factors [16]. Having obesity increases joint loading, decreases muscle strength, and alters biomechanics during everyday activities [17]. Leung et al. [18] found that Body Mass Index (BMI), as a measure of obesity, is one of the primary predictors of increased risk for Total Knee Arthroplasty (TKA). BMI also increases the risk of perioperative and postoperative TKA complications. However, the benefits versus the risks of TKA for patients with obesity remain controversial [19]. While some studies suggest that BMI has no impact on perioperative risk or

postoperative recovery [20, 21], others suggest it has a negative impact [19, 22-24]. Whether an association exists between BMI and clinical outcomes, following TKA remains unclear. Identifying and addressing obesity in patients with knee OA to alter disease progression, and to delay, avoid or reduce complications after TKA has both downstream economic and health benefits to individuals, healthcare systems, and society as a whole.

Nutritional imbalance plays an important role in the initiation and progression of many chronic diseases, including type II diabetes and OA [25]. The hypothesis that nutritional factors may influence the course of OA through a wide variety of mechanisms is supported by preliminary results from both laboratory and observational studies [26, 27]. The majority of current data examining the association between nutrition and OA has been gathered using observational and epidemiological studies on serum levels of nutrients and on the role of certain nutrients, mostly vitamins, including vitamins A, E, C [28], and D [26]. The association between a high-fat diet and early onset of OA in an animal model has been recognized since 1950 [29]. Increased dietary fat has been shown to alter systemic levels of pro-inflammatory cytokines and trigger cartilage degradation in animal models [30, 31]. For example, in mice, consuming a high-fat diet increased the levels of serum leptin, adiponectin, interleukin-8 (IL-8), and IL-1α, and also induced symptomatic characteristics of OA [32]. Whether the same relationship between diet and OA symptoms exists in humans remains unknown. Evidence on the impact of diet on OA onset and progression is largely absent due to a paucity of observational studies and well-designed randomized clinical trials.

The benefits of regular exercise regimen in reducing pain and improving physical function for patients with knee OA have been documented in previous literature [33, 34]. However, patients with knee OA do not often comply with exercise [33], due to pain and limited function [33, 34].

Walking is the most common type of physical activity among patients with knee OA [35]. The assessment of physical activity in patients with knee OA is traditionally conducted via self-reported questionnaires, but they can lead to overestimation of physical activity and may not reflect actual every day physical activity patterns due to subjectivity [35, 36]. The literature on objective measures of physical activity (steps/day) in patients with knee OA is sparse, [35, 37, 38] and from the available literature, we cannot determine the actual level of physical activity in terms of steps/day in patients with knee OA. There is also a lack of studies on the association between steps/day and health outcomes; hence objective assessment and monitoring level of physical activity (steps/day) during routine daily life may be helpful to understand the association between physical activity and OA [39, 40].

The assessment of physical activity is traditionally conducted via self-report questionnaires. These questionnaires are easy to use in clinical practice settings and inexpensive, but they can lead to overestimation of physical activity and may not reflect actual every day physical activity patterns due to subjectivity and validity [35, 36]. Based on the gaps in the literature described above, we designed three studies (Chapters 3, 4, and 5) to investigate the following hypotheses and objectives.

1.2. Objectives and Hypotheses

Chapter 3: Obesity, comorbidities and the associated risk among patients who underwent Total Knee Arthroplasty in Alberta

Objectives:

1) To examine whether obesity, according to the WHO classification based on BMI, was associated with other comorbidities or perioperative/postoperative complications in patients who underwent primary unilateral TKA.
2) To examine the association between major comorbidities and complications in patients who underwent primary unilateral TKA.

Hypotheses:

a) Patients who undergo TKA in higher BMI groups categorized using the WHO classification (Overweight, Obese I, Obese II, and Obese III) will be more likely to have peri/postoperative complications compared to a normal BMI group after controlling for age, sex, discharge date, zone of service, and comorbidities.
b) Patients who undergo TKA with comorbidities will be more likely to have perioperative/postoperative complications compared to patients without comorbidities after controlling for age, sex, discharge date, zone of service, and comorbidities.

Chapter 4: Does Obesity Affect Patient-Reported Outcomes Following Total Knee Arthroplasty?

Objectives:

1) To evaluate the extent to which BMI, categorized according to the WHO classification, affects self-reported pain, function and stiffness (measured using WOMAC subscales) preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months following TKA.
2) To evaluate the extent to which BMI, categorized according to the WHO classification, affects quality of life (measured using EQ5D index) preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months following TKA.

Hypotheses:

a) Patients who undergo TKA in higher BMI groups classified using the WHO (Overweight, Obese I, Obese II, and Obese III), will have the similar WOMAC (pain, function and stiffness) scores preoperatively, as well as similar mean change from pre to 3 and 3 to 12 months following TKA compared to the normal BMI group.
b) Patients who undergo TKA in higher BMI groups classified using the WHO (Overweight, Obese I, Obese II, and Obese III) will have the similar EQ5D index preoperatively, as well as similar mean change from pre to 3 and 3 to 12 months following TKA compared to the normal BMI.

Chapter 5: Dietary Fat Intake, Physical Activity, and Their Relationship with Osteoarthritis Symptoms

Objectives:

1) To examine the dietary intake, specifically saturated fatty acids (SFA) and trans fatty acids (TFA) as well as the level of physical activity (steps/day) in patients with and without osteoarthritis
2) To investigate the association between nutrient intake (including SFA and TFA) and physical activity (steps/day) with both of the performance-based and self-reported measures of function and pain in adults with and without knee OA.

Hypotheses:

a) Patients with moderate to severe unilateral knee OA will have lower steps/day compared to healthy control after adjusting for age, sex, and BMI.
b) Patients with moderate to severe unilateral knee OA will have higher fat intake (SFA and TFA) compared to healthy control after adjusting for age, sex, and BMI.
c) There will be a significant association between steps/day with all WOMAC subscales, LEFS, 6MWT, and stair test; slope of the regression of steps/day to WOMAC subscales, LEFS, 6MWT, and stair test is not equal to zero.
d) There will be a significant association between SFA and TFA with all WOMAC subscales, LEFS, 6MWT, and stair test; slope of the regression of SFA or TFA to WOMAC subscales, LEFS, 6MWT, and stair test is not equal to zero.

Chapter 2

Literature Review

2.1. Osteoarthritis and Its Etiology

Osteoarthritis (OA) is a chronic musculoskeletal disorder, which is characterised by loss of cartilage in synovial joints, osteophyte formation, synovitis, and subchondral bone changes [41]. OA is a progressive disease, which may eventually lead to disability [42]. Knee OA is broadly categorized as primary or secondary, depending on its cause. Primary knee OA, the most common type of OA, is the result of articular cartilage degeneration which appears insidiously without apparent cause, as an aging phenomenon. Secondary knee OA is often the result of articular cartilage degeneration due to a known reason such as injury/trauma, occupation, obesity, or metabolic diseases, such as diabetes and hormonal disorders [43]. Secondary OA is more likely to occur at a younger age than primary OA [44].

2.2. Risk Factors Associated with Knee Osteoarthritis

OA is a heterogeneous disease that is a collection of different subtypes or OA phenotypes [45], which may explain the complex nature and heterogeneity of OA. Clear definition of the existing OA subtypes is yet to be fully delineated; however, epidemiologic studies have shown that the distinct subtypes would suggest distinct underlying causes or risk factors [46]. Along with genetics, sex, age, joint injury, and obesity, different systemic etiological factors, such as adipose tissue inflammation, dyslipidemia, and inflammation are recognizable risk factors for OA. Those risk factors can further be categorized into non-modifiable and modifiable risk factors.

2.2.1. Non-modifiable Risk Factors

Classic twin and family aggregation studies have investigated the influence of genetic factors on the development of knee OA [47, 48]. A recent systematic review concluded that there is a

gene-environment interaction in the etiology of knee OA [49]. OA has a complex polygenetic nature, and different genes that have been identified to increase the susceptibility for OA were linked to different ethnic groups (Asian vs. European), sex, and joint sites. Overall, these estimates suggest inheritability of almost 50% for OA, suggesting that genetic factors account for half of the variation in susceptibility to disease [12].

Age is one of the strongest non-modifiable risk factors for OA. Half of the world's population aged 65 and older suffers from OA [50]. Many studies have shown that increased age is the most prominent risk factor for the initiation and progression of OA in the typically affected joints including the hands, hips, knees, and intervertebral joints [51]. Osteoarthritis development can be separated into aging-dependent and aging-independent processes [52, 53]. Age-related changes in chondrocytes are induced by increased production of matrix metalloproteinases, cytokines, production of reactive oxygen species, and reduced levels of collagen type II synthesis, and estrogen [53, 54]. These changes alter cartilage function, and sarcopenia during the aging process which further leads to decreased joint stability [52]. Cellular senescence, impaired regeneration, and repair are recognized factors contributing to cartilage damage with aging. It has been observed that aging and OA may be inter-dependent. Studies suggest that chondrocytes exposed to the "osteoarthritic environment" are characterized by oxidative stress and production of cytokines, and this induces the so-called stress-induced senescent state. There are also hormonal changes that occur at menopause in women (reduced estrogen) and andropause in men that are associated with the loss of muscle mass and shift in muscle fiber type along with deterioration in muscle performance and functional capacity [55-57]. Since the reduction in strength of the quadriceps muscles is one of the predictors for OA in women, a better understanding of the mechanisms responsible for these changes is warranted [54].

Sex is also a significant contributor to the onset and progression of OA. Differences in the incidence and severity of OA between men and women have been identified in epidemiological study conducted by the Centers for Disease Control and Prevention and the National Institutes of Health [55, 58, 59]. Women tend to develop knee and hand OA more than men [55]. Early onset of post-traumatic OA in women, more so among those who lead a physically active lifestyle, is higher [60]. Although little is known about the mechanisms that underlie disparities between men and women in OA disease development and progression, research indicates that mechanical, hormonal, and neural events are involved [55].

2.2.2. Modifiable Risk Factors

2.2.2.1. Obesity

Obesity Definition and Measurement. Fat is a normal component of the human body that is stored in adipose tissue throughout the human body, in specific patterns that are influenced by non-modifiable factors such as sex, hormonal status, age, and genetics as well as modifiable factors such as exercise training and physical activity level. However, an excess amount of fat in the body that impairs health is defined as obesity. Besides fat mass, body fat distribution is also a strong metabolic risk factor [61, 62]. The accumulation of adipose tissue in the trunk region (abdomen) has been associated with the development of obesity-related comorbidities such as diabetes and all-cause mortality [63]. Scientists have tried to measure body fat and distribution in different ways. A wide range of different physical principles, devices, models and assumptions have been used to provide a more useful evaluation of how likely a person's weight will contribute to chronic health risks [63]. Different measures of body fat and distribution include underwater weighing, ultrasound, bioelectrical impedance, computed tomography (CT), magnetic resonance imaging (MRI), and dual x-ray absorptiometry (DEXA) [64]. It has been shown that fat distribution

(specifically visceral fat) is a more important predictor of mortality risk than total fat levels [65]. Despite the overall accuracy of these methods, they are relatively expensive, cumbersome, less acceptable for routine use, and have no standardized threshold to define high-risk people. Anthropometric measures of body fat such as BMI are therefore most commonly used.

BMI is an anthropometric measure of obesity and is defined as weight divided by height squared (kg/m^2) [66]. BMI is a relatively simple, low-cost indirect measure which is widely used for screening, diagnosis, and classification of overweight and obesity in population studies [67]. BMI is a useful measure for initial screening to detect excess body fat [68] however, it has several drawbacks. BMI cannot distinguish between lean and fat mass and provides no indication of body fat distribution [69], and it also does not take into account the changes in body composition that occur with age. Several studies have recommended that, compared with BMI, measures of central obesity including waist circumference, waist to hip ratio, and waist to height ratio are better predictors of visceral fat, cardiometabolic disease, and mortality [70]. However, these measures are strongly correlated with BMI and have a comparable strength of association with the risk of cardiovascular disease, and so add little further information [71]. Among the central obesity measures, waist to hip and waist to height ratios are perhaps better predictors of obesity than waist circumference, though more difficult to measure. Although these measures can be used for clinical assessment of central obesity mostly in people with lower BMI index, they lack standardized measurement protocols, reference data, and accuracy in people with severe obesity (BMI>35) [64]. Overall, BMI remains the most commonly used, widely accepted, and practical measure of obesity, mainly for surveillance. Besides, at the individual level, alternative approaches are needed to measure the obesity. Measures of central adiposity, in addition to BMI, is valuable for assessing health risk associated with obesity [62].

Obesity and Knee Osteoarthritis. Obesity is a well-recognized risk factor for knee OA. The biomechanical effect of increased body weight is one explanation for this association, especially in weight-bearing joints, such as the knee [72], which is subjected to a force of 3 to 6 times the body weight during normal walking. Obesity-related changes in knee biomechanics impair joint stability, shift loads to less frequently loaded regions, and increase loading magnitude in the joints that eventually develop OA [73]. Emerging evidence suggests that the mechanism by which obesity increases the risk of OA is more than just an effect of load on the joint [72]. Obesity is also characterized by an abnormal lipid profile or dyslipidemia. A study on obesity and cardio-metabolic risk factor clustering (including HDL-c, LDL-c, triglycerides, blood pressure, waist to hip ratio, glucose, and hsC-RP) demonstrated that middle-aged women who had obesity and two or more cardiovascular risk factors were six times more likely to have knee OA compared to women without obesity and cardio-metabolic clustering factors [74]. Adipose tissue, once considered a passive storage portal of energy, is now acknowledged as a highly metabolic endocrine organ, which has the capability of releasing active agents including adipokines, such as leptin, resistin, and adiponectin [75]. The changes in distribution and amount of these adipokines in synovial fluid of patients with obesity initiate a proinflammatory cytokines, such as tumor necrosis factor (TNF)-α which is related to local joint degradation and systemic effects associated with obesity [74, 75].

2.2.2.2. Activity Related Risk Factors

A sedentary lifestyle (defined as activities, such as sitting and inactivity, that do not increase energy expenditure above resting level) [76], increases the susceptibility to obesity and inflammation and results in worse symptoms of OA, including pain, stiffness, and reduced physical function [77-79]. Conversely, it is also believed that excessive amounts/types of physical activity

may be associated with knee OA. These activities involve repetitive movements and high-impact joint loadings [80]. OA occurs more in people who work in jobs that require repetitive movements, and the risk of localized OA (OA in specific joint and the surrounding tissue) is doubled in these occupations compared with people whose jobs do not require repetition of the same movement and physical activity [81]. Another activity related risk factor associated with the onset of OA is the increased acute and direct joint impact or torsional loading that occurs during work or especially competitive sports (such as soccer, hockey, or skiing). In these types of activities, the knee is the most repeatedly injured joint with the rupture of anterior cruciate ligament (ACL) or an intra-articular fracture, which often leads to the development of secondary or posttraumatic OA [81]. However, recent systematic reviews concluded that, in the general population, the type of sports or daily recreational activities is not considered a consistent risk factor for clinical or radiographic knee OA as long it has been performed moderately [80]. Therefore, to sustain a healthy joint, normal mechanical joint-loading and moderate physical activity are considered extremely important.

2.2.2.3. Dietary Intake

Westernized diet is characterized by an overconsumption of saturated fat, refined sugars, and salt and lack of nutritional factors such as vitamins and minerals essential to our body. Westernized diet and many of the dietary choices we make in today's modern society appear to have a harmful influence on our immune system and have been gaining attention as a potential contributor to the increase in systemic chronic diseases such as diabetes, cardiac disease, or osteoarthritis [46]. Unhealthy dietary behaviors may lead to obesity, which is responsible for both inflammatory response related to the metabolic disorders in the cartilage as well as overload of the joints, especially knees [46, 81]. Therefore, manipulating dietary choices is a feasible approach in

preventing OA onset and progression. Recent findings suggest a potential role for dietary intake of fat and saturated fatty acids (SFA) as well as dietary antioxidant deficiency in the onset and progression of OA, making diet a potential target to influence the natural history of OA.

Dietary Lipids. The underlying mechanisms behind the effect of a high-fat diet on onset and progression of OA could be related to both localized (joint) and systemic inflammation. Articular cartilage and synovial fluid contain lipids such as phospholipids, cholesterol, and fatty acids. Although chondrocytes can synthesize these lipids, dietary lipids may reach the cartilage and synovial fluid as a source of energy, and they also contribute as a structural component and signaling molecules [82]. Lipids may be incorporated in chondrocyte metabolism or change its composition and eventually may contribute towards inflammation and degradation of the cartilage and impaired chondrocyte structure [82]. Studies have shown that cholesterol and fatty acids accumulate in the superficial area of OA cartilage. OA joints also accumulate high levels of omega-6 (n-6) fatty acids, precursors of pro-inflammatory eicosanoids [82]. A prospective study in patients with OA found that higher intakes of total and saturated fatty acids were associated with increased loss of knee joint space [83], while higher intakes of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) were linked to reduced radiographic progression of OA [83]. In individuals with, or at high risk of, knee OA a positive association was noted between the n-6 PUFA arachidonic acid (AA) and synovitis but an inverse relationship between total plasma n-3 PUFA, docosahexaenoic acid (DHA) and patellofemoral cartilage loss, as measured by MRI [84].

The metabolic changes and systemic inflammation brought about by a high-fat diet also appear to be key mediators in the onset and progression of OA. A high-fat diet elevates FFAs and cytokines in the circulatory system, which triggers inflammatory pathways in the central nervous

system [85]. In addition, when eating a high-fat diet on a regular basis, the adipose tissue fails to store the excess amount of fat. As a result, excess fat is deposited in other tissues, including skeletal muscle, blood vessels, the pancreas, and the liver [86]. This ectopic fat deposition leads to the release of proinflammatory mediators and the recruitment of activated inflammatory macrophages (M1), provoking systemic inflammation [87]. Since diet influences the composition and metabolism of chondrocytes [36] and systemic lipid levels, identifying the most influential nutrient intake in individuals with knee OA is warranted.

Antioxidant Vitamins. Chondrocytes are extremely sensitive to the effects of reactive oxygen species (ROS), especially in the growth plate [88]. ROS and reactive nitrogen species may be involved in the pathophysiology of OA [89]. Thus, to protect the chondrocytes from the oxidative stress, enzymatic and nonenzymatic antioxidant defense systems are needed. The antioxidant vitamins E, C, A, and D have received the most attention in this context [89].

Vitamin E is a fat-soluble, water-insoluble nutrient found in many foods including vegetable oils, nuts, and seeds. It plays a variety of important roles as an antioxidant in lipid environments [89]. Vitamin E helps to reduce inflammation and to protect cells from the damage caused by free radicals [89]. Regarding vitamin E supplementation beyond a healthy diet that includes an adequate amount, some studies suggest that Vitamin E supplementation does not alter cartilage volume loss, symptoms of osteoarthritis, and the management of symptomatic relief of knee OA [90]. However, a study on vitamin E supplementation (200 mg/day) in knee OA found a significant reduction of pain and significant improvement in circulating antioxidant enzyme levels [91]. Available evidence is inconclusive about the benefits of vitamin E supplementation and thus is not recommended beyond a healthy diet that includes an adequate amount of this vitamin [92].

Vitamin C (Ascorbate) is a highly effective soluble antioxidant and is the only antioxidant that can completely protect lipids from detectable peroxidative damage [93]. Vitamin C reacts with free radicals and acts as a cofactor for hydroxylase enzymes in the synthesis of collagen in cartilage, intervertebral discs, tendons, ligaments, skin, and blood vessels. Data on the association between dietary intake of vitamin C and knee structural outcomes remains inconclusive [93]. A cohort study reported that higher dietary intake of vitamin C was associated with reduced risk of OA progression, measured as joint space narrowing, but not with the incidence of knee OA [94]. Two studies examining the effect of vitamin C supplementation on OA management reported that higher dietary intake of vitamin C was associated with reduced risk of the development of knee pain, but it was not associated with knee pain severity [93, 95].

Vitamin A is a group of related compounds (carotenoids and retinoids) and is a type of lipid antioxidant. It plays an important role in maintaining bone growth, cell division, reproduction, cell differentiation, and vision. Vitamin A and its related compounds not only help in the regulation of the immune system, but they also have an important effect on preventing cardiovascular disease and cancer. Although vitamin A can behave as a radical-trapping antioxidant at oxygen pressures significantly less than 150 torr, the pressure of oxygen in normal air, they lose their antioxidant characteristic and act as a pro-oxidant at elevated oxygen pressure [93]. While the effect of vitamin A alone on osteoarthritis has not been investigated, when combined with other antioxidant vitamins no effect was seen [93]. A systematic review of randomized clinical trials reported no convincing evidence that combinations of vitamin A, vitamin C, vitamin E are effective in the treatment of any type of arthritis [89]. To date, there is no clear evidence of association between dietary intake of vitamin A, in combination with other vitamins, and knee symptoms or structural progression of OA.

Vitamin D is a fat-soluble vitamin that is naturally made in the body when exposed to sunlight. It is present in very few foods but can be obtained through the ingestion of fatty fish and mushrooms. Vitamin D-fortified products are also available as a form of dietary supplements [96]. Normal bone and cartilage metabolism rely on the availability of vitamin D. Vitamin D deficiency adversely affects calcium metabolism, osteoblastic activity, matrix ossification, and bone density as well as the articular cartilage turnover [97]. A systematic review concluded that serum 25-hydroxy vitamin D was negatively associated with knee OA in regards to structural changes rather than symptoms, with limited evidence for other joints [97]. However, a recent study showed that consistent maintenance of sufficient plasma vitamin D (>50 nmol/l) levels had beneficial effects on preserving knee cartilage and physical function in people with knee OA [98]. Hence, the literature regarding the effect of vitamin D on osteoarthritis onset and progression is mixed.

2.3. Management of Knee Osteoarthritis

The goals of osteoarthritis treatments include alleviation of pain and improvement of functional status and quality of life [99, 100]. Treatment options include non-pharmacologic, pharmacologic and/or surgical options, including total joint arthroplasty [100].

2.3.1. Pharmacological Treatments

Traditional medications to alleviate pain in patients with OA can be categorized into acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, serotonin-norepinephrine reuptake inhibitors (SNRIs), intra-articular (IA) injections of corticosteroids, and dietary supplements. These medications are included in evidence-based management guidelines [101] and are commonly used in the clinical management of OA [102]. Although these medications alleviate pain, they should be used with caution as they also carry a risk of adverse effects due to their known side effects [99].

2.3.2. Non-Pharmacological Management

2.3.2.1. Educational and Self-management

Guidelines on treatments indicate that education and self-management should be an important component of knee OA management [103]. These should include details of the disease, its investigations, and management [103]. Educational techniques that have been shown to be effective for managing OA include individualized education packages, regular telephone calls, group education, patient coping skills, and spouse assisted coping skills training [104]. The benefits of different educational techniques in reducing pain and increasing coping skills have been demonstrated by several large randomized control trials (RCTs) and a meta-analysis [103]. Education has also been shown to result in fewer visits to primary care and therefore has a cost-saving implication. [105]. The results showed that 80% of the costs of delivering effective self-care education were offset within a year by the reduced frequency and costs of primary care visits [105].

2.3.2.2. Weight Loss

Obesity is one of the main risk factors for the onset and progression of OA, and the biomechanical effect of increased body weight on knee OA is recognized. Symptoms, including pain, in patients with OA who also have obesity can be relieved by weight loss [106]. The importance of weight loss is supported by the result from a cohort of 1,410 individuals with symptomatic knee OA that reported a significant dose-response relationship between changes in body weight and changes in self-reported pain [107]. Studies have shown that loss of approximately 5% of body weight provides some relief in pain [108], however, in order to see a significant reduction in pain an initial decrease of 10% in body weight should be an ultimate goal in patients with OA and obesity [108]. Pain reduction following weight loss increases mobility,

physical function, quality of life, and satisfaction with body function and appearance of patients with OA [107, 109]. Successful approaches to lose weight are lifestyle factors including calorie restriction, increased physical activity, and behavioral therapies [110]. Although these approaches are considered as the cornerstone of weight loss management, they are less effective in the long term since individuals must battle with strong biological and environmental influences that promote weight gain [110]. To attain long-term weight loss, medications which has been approved by Food and Drug Administration (FDA) can be combined with lifestyle factors. However, guidelines suggest that patients implement lifestyle factors for at least 6 months before using drug therapy. Currently, bariatric surgery is considered the most sustainable weight loss strategy in patients with a BMI greater than 40 kg/m^2 or BMI greater than 35 kg/m^2 with significant comorbidities [111]. However, besides the gastrointestinal complications associated with bariatric surgery, patients may have nutritional problems such as protein-calorie malnutrition and/or micronutrient deficiencies, which requires long term monitoring and supplementation [112].

In summary, weight loss management is a promising modality for the treatment of knee OA. It is a safe and effective way to improve knee pain and function without adverse side effects. There are several options to lose weight, however, the "right choice" of the treatment should be tailored depending on the severity of obesity and/or OA to meet an individual's needs. However, it should be noted that weight cycling (repeated gain and loss of body weight) may lead to skeletal muscle loss, increase adiposity and contributes the development of sarcopenic obesity, then coupling exercise training with weight loss has been recommended to prevent sarcopenia and the associated risk [52].

2.3.2.3. Physical Activity and Exercise

Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” [113]. Many activities contribute to physical activity and its related energy expenditure. The broad components of physical activity are home and household-related, occupational, and leisure time (which consists of exercise, recreational or competitive sport) activities. Exercise, however, is not synonymous with physical activity; it is a type of physical activity that is planned, structured, and repetitive and is designed to improve or maintain physical fitness [113].

In terms of clinical care, exercise is considered an important non-pharmacological behavioral intervention for OA management, particularly knee OA [103]. A few available well-designed clinical trials [109, 114] and a recent umbrella review [33] with a total of 240 studies involving 24,583 participants confirmed that there is no clear benefit of one form of exercise type over another for improving pain and function in patients with OA. For the majority of people with OA, a combination of aerobic fitness training, strength- training exercise, and neuromuscular exercise is optimal to address the spectrum of impairments associated with OA [115]. It is important to individualize exercise regimen for the patients with OA, and the choice of one type over another will be based on an assessment of the individual patient considering factors such as patients' age, mobility, comorbidities, and preferences.

In patients with OA, exercise prevents or even reverses sarcopenia (skeletal muscle loss), a condition which is associated with more physical disability and falls in patients with OA [52]. Besides, it strengthens the muscles around the affected joints and decreases bone loss. Regular activity boosts the circulation of synovial fluid, blunts inflammatory responses, replenishes the lubrication of the joints, and reduces stiffness and pain [116]. Exercise also helps to enhance

energy and stamina by decreasing fatigue and improving sleep. Exercise can lead to weight loss and help sustain long-term weight management in patients with arthritis and obesity [33]. Evidence on the effects of exercise for patients with OA suggests that the pain reduction and improvement in physical function are comparable to those reported for non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics [33].

Guidelines recommend that patients with disability, who are able, should obtain at least 150 minutes per week of moderate or 75 per week minutes of vigorous-intensity [117] aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic activity [118]. However, for people with knee OA, even 10- min bouts of exercise can be challenging, and greater knee pain can contribute to poorer compliance with exercise [33]. Thus, individuals with OA may benefit from practicing a more physically active lifestyle, typically by increasing ambulatory activity throughout the day [119]. Walking is one of the most common types of unstructured PA that older adults with knee OA engage in daily, and that has the potential to improve health [119].

Step count is gaining widespread attention since it can be easily communicated to the public and directly translated to the clinical setting. Thus, quantifying and examining steps/day may be an important measure to monitor physical activity in patients with knee OA. Previous studies used self-reported physical activity measures such as Godin Leisure-Time questionnaire in patients with knee OA to examine the association between physical activity and OA symptoms. Although an association between a high level of physical activity and improvement in OA symptoms has been reported [120, 121], self-reported measures have been shown to overestimate physical activity, especially in the older population [122, 123], and lack adequate measurement properties [124]**.** Few studies [125-127] have examined the association between physical activity and OA symptoms

using objectively measured physical activity such as pedometers and accelerometers [34, 37, 38, 128]. Results are contradictory with findings ranging from no association [37] to a positive association with physical function [125-127] and pain [127]. There are several reasons related to this controversy, such as the inclusion of patients who varied extensively with respect to the severity of disease (including patients at risk and from early-stage knee OA up to pre-TKA) and the use of different objective measures of physical activity. Given the scarcity of evidence on objective measures of physical activity (steps/day) and understanding the relationship between steps/day and health outcomes, further investigation is warranted [119].

2.3.2.4. Total Knee Arthroplasty (TKA)

Surgical treatment of OA should be considered only after the failure of nonsurgical treatments, when damage to the articular cartilage reaches such a level that there is bone-to-bone contact in the knee joint, which causes pain and impairs the normal functioning of the knee joint[129]. The overall treatment goal of TKA for patients is to improve quality of life, enhance function, reduce pain, and correct the patient's deformity [129]. However, joint replacements do not last forever, with prosthetic wear and loosening occurring after about 15-20 years, necessitating revision surgery [8]. There are many patients for whom TKA is inappropriate, because of medical comorbidities such as obesity, age, or other circumstances [8]. There is a higher prevalence of obesity among patients who undergo TKA, and studies have raised concerns regarding the outcomes of TKA, including complications, in patients with obesity. These studies have consistently demonstrated increased rates of wound healing complications, superficial and deep infections, early revisions, and poor functional outcomes following TKA in patients with obesity. It has been shown that patients with a BMI of >30 kg/m^2 had more infections and a higher revision rate compared with patients with a BMI of <30 kg/m^2. However, defining obesity simply based on

BMI below or above 30 leaves out critical information related to the degree of obesity. Overall, the risk and effectiveness of TKA in individuals with obesity remains unclear.

2.4. Physical Activity Assessment

There are a variety of methods to assess physical activity, from sophisticated measurement that requires very highly specialized personnel and high cost (e.g. breath-by-breath oxygen consumption or doubly-labeled water (DLW) to measure energy metabolism at rest or during exercise), to questionnaires that are easy, inexpensive, and practical. These tools can be categorized into three main groups of criterion (gold standard), subjective, and objective methods [130]. The ideal instrument is one that is valid, reliable, and sensitive to change (responsive) and a practical tool that does not influence the daily physical activity behavior of subjects.

2.4.1. Criterion Methods

The level of physical activity is highly linked to the energy expenditure, and direct measuring of energy expenditure through heat production (calorimetry) is considered the gold standard. Indirect calorimetry using the doubly labeled water (DLW) method, which is based on the amount of oxygen consumption and carbon dioxide production, is used as a criterion measurement. The method estimates energy expenditure based on the elimination of 2H (deuterium) from the body in the form of water and 18O (Oxygen-18) in the form of water and carbon dioxide over 5-14 days[131]. DLW is accurate within 3-10% of calorimetry in adults [132]. DLW is an accurate method and does not interfere with physical activity patterns, however, it is an expensive method and not applicable for large-scale studies. Nevertheless, DLW remains a gold standard against which to validate other methods until other less expensive and portable methods of measuring energy expenditure become available [130].

2.4.2. Subjective Methods

There are three main types of subjective measures of physical activity: records, logbooks, and questionnaires. Researchers can obtain detailed information using the records and logbooks, but this information is prone to memory errors and patient's motivation may alter the habitual pattern of daily activities. Global, recall, and quantitative histories are the three main types of questionnaires. Global questionnaires can be completed in less than 1 minute and provide information on general physical activity levels. Recall questionnaires provide more detailed information about daily physical activities such as frequency, duration, and types of physical activity during the past day, weeks, or months. Quantitative historical data provide information on the frequency and duration of physical activity over the past year, or even lifetime. Although questionnaires are an inexpensive method to measure physical activity, especially in a larger population trial, they are prone to recall bias. In general, questionnaires are limited in their objectivity, and factors such as age, and social desirability, among other variables, could cause over- or under-estimation of physical activity [133]. Results from a systematic review of 23 self-report physical activity questionnaires, deemed suitable for patients with OA, demonstrated that none had adequate measurement properties across all domains of reliability, validity, and responsiveness [124].

2.4.3. Objective Methods

Pedometers and accelerometers are the most commonly available devices to monitor physical activity. Pedometers are small devices to measure movement in one (vertical) direction, and they are usually worn on the waistband, laterally along the midline of the thigh. They measure steps/day over a period of time and, in certain devices, convert to the distance walked using average stride length. Since running and walking are part of most of the physical activity patterns, pedometers

are considered valuable devices to estimate the steps taken during walking. The disadvantage of using pedometers is that they do not measure upper body physical activity movements such as cycling or carrying a load. They are less accurate in people who walk more slowly, on measuring distance, and even less accurate for calories burned [134-136].

Accelerometers monitor movement in more than one dimension and rely on quantifying the magnitude and direction of the acceleration. Triaxial accelerometers are considered the best accelerometers as they monitor motion in three planes [137]. Accelerometers are valid estimators of overall physical activity [137], but even these devices are partially restricted due to limitations on measuring static activity, upper body movements, and energy expenditure estimation. There are a variety of research-grade accelerometers available on the market such as Actigraph (Actigraph LLC, Pensacola, FL, USA) and commercially available devices such as Fitbit (Fitbit Inc., San Francisco, CA, USA).

Actigraph is a valid and reliable tool for measuring physical activity; it is usually worn on the non-dominant arm/wrist. The Actigraph detects acceleration in the selected planes and converts data into activity "count" [138]. There are different algorithms available within the Actigraph software to classify activity from count information. These algorithms use cut-points to classify physical activity behaviors into sedentary, light, or moderate-to-vigorous levels, with sedentary behavior being less than 100 counts per minute. The limitation of using the Actigraph is that this device does not distinguish sitting versus standing [76].

Recently, consumer-based activity trackers (e.g. Fitbit, Jawbone UP, etc.) have become increasingly popular [139]. Fitbit (San Francisco, CA, USA) is one of the most commonly used brands amongst the consumer-based activity trackers. Fitbit Inc. offers a wide range of devices to

measure energy expenditure, track PA, and cover different activities such as walking, running, cycling, etc. The Fitbit Zip is a low-cost wearable device regarded as convenient and comfortable to wear, and has an expanded battery life for almost 4 to 6 months. Fitbit Zip was previously validated among older adults for measuring step count and physical activity and has been shown to be a valid and reliable method to measure steps and distance [140, 141]. The device is held by a silicon clip that can be attached essentially anywhere on the body. Participants could clip the device to their belt, pocket, or bra for consecutive days without altering their daily routine activities. It should be noted that this device does not provide information on the type of physical activity, but it provides the level of physical activity. Considering the validity and reliability of the Fitbit Zip to measure step counts, this device was selected to measure steps/day in this project [140].

2.5. Dietary Intake Measurement

In this section, the major and most important dietary assessment methods are discussed briefly.

2.5.1. Dietary Records

A food record (also called food diary) is a self-reported description of the type and amount of all foods and beverages consumed at the time of eating. Recording periods of 3 or 4 consecutive days are optimal, and more than 4 consecutive days of report are usually unsatisfactory due to a decrease in subjects' reporting of intake [142]. To avoid relying on memory, it is preferable that the recording be done at the time of the eating occasion throughout the recording day. The amounts consumed may be measured, using a scale or household measures (e.g., cups or tablespoons), or estimated using models, pictures, or without aid. Subjects must describe the foods and the amounts consumed including the name, brand-name, preparation methods, recipes, and portion size [142]. At the end of the recording period, a trained interviewer reviews the completed food diaries with

the subject to clarify food records and to probe for any forgotten foods [143]. Quantitatively accurate information on foods consumed during the recording period can be provided using a dietary record method [144]. Furthermore, this method provides more accurate information on portion size than the recall method, since the food intake has been reported as they are consumed [142].

2.5.2. The 24-hour Dietary Recall

In the 24-hour dietary recall, the subject will be asked to remember and report the foods and beverages in the past 24-hours. The diet recall is conducted by a trained interviewer, by phone, or in-person. The interviewer should know foods available in the marketplace and about the different ethnic foods. The method consists of precisely recalling, describing, and quantifying the foods and beverages consumed in the past 24 hours before the interview [145]. A minimum of 2 to 5 24-hour dietary recalls are needed (2-3 are usually collected) to establish the usual food intake. The information should describe the type of food and its characteristics (fresh, pre-cooked, frozen, canned, preserved), the net quantity consumed, method of preparation, commercial brands, sauces, dressings (type of fats and oils used), condiments, liquids, multivitamin supplements, and food supplements, as well as the time and place of consumption (at home, away from home), etc. [145]. Typically, the interview requires 20-60 minutes to complete. One of the advantages of this method is that the literacy of the respondent is not required. However, the disadvantage of this method is that respondents may not recall the food that has been consumed due to several reasons related to the memory, interview time, and interviewer knowledge. However, the 24-hour dietary recall is considered the least biased self-report instrument, and thus is useful for most research purposes. To calculate the actual intake, all foods and mixed dishes consumed according to the detailed

reports from the respondents should be matched and coded with the food listed in the food composition database, which is a highly expensive, laborious, and time-consuming process [142].

2.5.3. Food Frequency Questionnaires

The food frequency questionnaires (FFQs) are designed to assess the dietary patterns by collecting information regarding the frequency at which the respondent consumed food items based on a predefined food list over a specified reference period (Nutrition epidemiology [146]. FFQs are the most commonly used methods in large epidemiological studies. In this method, information is collected regarding the frequency of food consumption rather than the characteristics such as the amount, combination of food, or preparation method. When FFQs include a questionnaire about the quantity of the food that is consumed it is usually based on standard portion size, rather than direct weight or measuring based on utensils. Typically, FFQs have been used to obtain a crude estimate of usual daily intake over a designated recall period which may vary from 7 to 30 days or even as long as a year. The disadvantage of using FFQs is that they are subject to bias including selection bias and completion of the numbers of days recorded. Another disadvantage is that, unless the dietary intake is collected electronically, the data can be burdensome to code.

FFQs are relatively low cost, and they provide a rapid estimate of usual food intake [147]. However, the nutritional values derived from FFQ data are subject to both random and systematic errors [148]. Validation correlations between reported intakes from the FFQ and other methods [149-151] vary with the nutrient, but typically range from 0.40 to 0.70 [150, 152, 153].

In summary, there are three major dietary assessment methods (dietary records, 24-hour dietary recall, and food frequency questionnaire), and each method has its own strength and

limitation. In this thesis, a 3-day food record was used since it is feasible and cost effective. It has also been reported that 3-day food record compared to other methods is the best overall choice based on agreement between observed and reported intakes [142].

Chapter 3

Obesity, Comorbidities and the Associated Risk among Patients Who Underwent Total knee arthroplasty in Alberta

3.1. Background

Obesity impacts over 600 million adults around the world [154]. It is associated with an elevated risk of adverse health outcomes, including cardiovascular disease, diabetes, cancer, and osteoarthritis (OA) [155]. The rising prevalence of obesity and its associated health risks makes it a major public health issue worldwide [155, 156]. Obesity, a common risk factor for the onset and progression of OA [157], accelerates joint deterioration in patients with knee OA resulting in the need for early total knee arthroplasty (TKA). Thus, the management of OA requires an understanding of the role that obesity plays in the development and progression of end-stage knee OA [158]. With the rise in demand for TKA, orthopedic surgeons are concerned about whether patients with higher BMI, notably BMI class III, are at an increased risk for perioperative or post-operative complications compared to other BMI groups [157].

There has been an abundance of literature over the past decade that has raised concerns regarding the outcomes of TKA, including complications, in patients with obesity [159-163]. These studies have consistently demonstrated increased rates of wound healing complications, superficial and deep infections, early revisions, and poor functional outcomes following TKA in patients with obesity [164-166]. However, the role and importance that obesity plays in the decision to perform TKA remains under debate [157, 167]. This reflects a lack of general consensus about performing TKA surgery on patients with obesity [157].

A literature review conducted by a workgroup of the American Association of Hip and Knee Surgeons on obesity and total joint arthroplasty concluded that most studies examining TKA in

patients with obesity used different surgical procedures and post-operative care protocols, small sample sizes, and different definitions of obesity [157]. The majority of previous studies did not use the World Health Organization (WHO) classification of obesity to stratify patients into sub-classes of obesity; instead, they classified patients as either with obesity (Body Mass Index (BMI) $\geq 30 kg/m^2$) or without obesity (BMI$< 30 kg/m^2$)[157]. Moreover, patients with OA and obesity often have multiple medical comorbidities, such as diabetes and cardiopulmonary diseases [154]. Many of these comorbidities have been shown to be independent risk factors for the development of joint infection and also perioperative complications [157]. If the risks associated with these comorbidities have not been taken into account in the statistical analysis, they may act as confounders and affect the results of the study. Methodological approaches to adjust for comorbidities in the statistical analysis have been suggested, but they have not been consistently taken into consideration in previous studies of the association between obesity with complication [157, 168]. Therefore, the primary purpose of our study was to examine whether obesity using the WHO classification of BMI is associated with other comorbidities as well as with perioperative/postoperative complications in patients who underwent TKA adjusting for putative confounders. We also examined the association between major comorbidities and complications in people who underwent primary unilateral TKA over a 5-year period (2012 to 2016) in Alberta, Canada.

3.2. Methods

3.2.1. Data Acquisition

For this study, we extracted data for a retrospective cohort of patients who underwent primary unilateral TKA between January 2012 and March 2016, from a provincial database managed by the Alberta Bone and Joint Health Institute (ABJHI). Standardized care processes and consistent

data collection commenced in 2009 and remain ongoing for the province. Data have been collected under the authority of the provincial Privacy Impact Analysis (PIA) agreement in place (OIPC File # H2801) for all private clinics and public hospitals where TKAs are performed. Knee surgeries are performed at twelve hospitals across Alberta, Canada, and all data are sent to ABJHI for quality assurance purposes. The Discharge Abstract Database (DAD) is a national database that contains data captured in acute care hospitals and includes administrative, clinical, and demographic information for hospital discharges. Data from DAD were linked to the database managed by ABJHI to identify comorbidities and complications in patients. Diagnosis for morbidity and mortality and procedure coding were based on the 10th version of the International Classification of Diseases combined with the Canadian Classification of Health Intervention (ICD-10-CA/CCI).

3.2.2. Study Sample

We were able to identify 26,962 patients who underwent primary unilateral TKA between 2012 and 2016. Weight and height records were available for 15,151 (56.2%) patients to calculate BMI as weight in kilograms (kg) divided by height in meter squared (m^2). Only those patients with BMI records who underwent primary unilateral TKA were included in the analysis. There were no differences in participant characteristics (i.e. mean age and sex), the rate of major comorbidities, or complications (Supplementary Materials Table 3.1.S) between the included and excluded cohorts. Patients in the included cohort were classified into one of five groups according to the WHO classification of normal weight (BMI≤24.99 kg/m^2), overweight (25≤BMI≤29.99 kg/m^2), obese class I (30≤BMI≤34.99 kg/m^2), obese class II (35≤BMI≤39.99 kg/m^2), or obese class III (BMI≥40 kg/m^2) [1]. A total of 17 patients with a BMI lower than 18.5 (underweight) were included in the normal BMI group. Patients' demographic information including age, discharge date, and sex were available. Age was categorized into five groups of <50, 50-59, 60-69, 70-79,

and >80 years old. The discharge date was categorized by year into six groups: 2012, 2013, 2014, 2015, and 2016. Comorbidities included diabetes, moderate or severe mental health issues, cardiac disease, pulmonary disease, circulatory/clotting disorder, dementia, renal failure, cerebrovascular disease, and moderate or severe liver disease as recorded in the database.

3.2.3. Outcomes

Perioperative and postoperative complications, which were also recorded and used in the analysis were blood transfusion, pulmonary embolism, deep wound infection, myocardial infarction, ileus, pneumonia, deep vein thrombosis, gastrointestinal bleeding, readmission within 30 days, and cerebrovascular accident.

3.2.4. Statistical Analysis

The prevalence of obesity among patients who underwent primary unilateral TKA and the incidence rate of comorbidities and complications within each of the BMI groups were determined and compared using Chi-squared testing. The association between each of the main dependent variables (a complication or a comorbidity) with each of the nominal/categorical independent variables (year of surgery, age, sex, length of surgery, and BMI groups) was examined in a univariate fashion using Chi-squared test of independence. Independent variables with $p<0.15$ were included in the full model. Model selection was performed using backward and forward stepwise regression analysis, and competing models were compared using the Akaike Information Criterion. Both stepwise forward and backward methods confirmed that the full logistic regression model was the best model (the model with all variables). Binomial logistic regression was used to determine whether the dependent variable (a complication or comorbidity: yes/no) was associated with the independent variables (year of surgery, age, sex, length of surgery, and BMI groups). When complication was considered as a dependent variable, comorbidities were included as

independent variables. Results for each dependent variable are reported as odds ratios (OR) with 95% confidence intervals (CI) calculated to compare the likelihood between each of the BMI groups and the normal BMI group, considering all covariates of interest in the model [16]. An OR of one (i.e. OR=1) means the likelihood of the event is the same for the group of interest (high BMI) when compared with the reference group (normal BMI group). An OR>1 or OR<1 suggests an increased or reduced likelihood of the event in each group of interest occurring compared to the reference group. If a 95% CI for the OR includes the value of 1, then there is insufficient evidence to conclude that there is a statistically significant difference in likelihoods for the groups. All statistical analyses were performed using R software package version 0.99.902.

3.3. Results

Patients' characteristics are presented in Table 3.1. Between January 2012 and March 2016, a total of 15,151 patients who underwent TKA and had BMI records were identified, including 1,240 (8.2%) individuals with normal BMI, 4,189 (27.6%) overweight, 4,541 (30.0%) obese class I, 2,839 (18.7%) class II, and 2,342 (15.5%) in the class III BMI groups. Overall, the mean age ± standard deviation of the cohort was 66±9.2 years. As BMI increased, patients were more frequently younger in age and female. In total 23.7% (N=3,590) of patients who underwent TKA with BMI records had comorbidities. The most frequent comorbidities among patients were diabetes (58.1%, N=2,086), moderate or severe mental health issues (37%, N=1,329), and cardiac disease (3.3%, N=118). The remaining comorbidities were pulmonary disease (0.8%, N=29), and circulatory/clotting disorder (0.6%, N=21). As BMI increased, the proportion of people with diabetes increased, with obese class III group having the highest proportion, and differences in proportions among the groups were significant ($p<.001$). There were also significant differences

in the proportion of people with mental health issues (p<.001), circulatory/clotting disorders (p<.03), smoking (p<.002), and alcohol abuse (p<.001) between the different BMI groups.

Results of multiple regression analysis (Table 3.2; ORs and their 95%CI) showed that obese class I, II, and III were more likely (p<.001) to have diabetes compared to the normal BMI group. Although subjects with obese class III compared to the normal BMI group were more likely to have cardiac disease, these results did not reach statistical significance (p=0.14). Obese class I, II, and III groups compared to normal BMI group were more likely to experience pulmonary embolism (Obese class I: p=.004; class II: p=.006; class III: p<.001). Besides pulmonary embolism, patients with obese class III compared to the patients in normal BMI group were more likely to have deep wound infection (P=04), and a trend (p=.10) of increased likelihood of readmission (Table 3.2).

Results of the association between comorbidities and complications (Table 3.3; ORs and their 95%CI) showed that patients with a history of diabetes (p<.001), cardiac disease (p<.001), circulatory/clotting disorder (p<.001), mental health (p<.001), alcohol abuse (p=.04), and smoking (p=.002) were more likely to also receive a blood transfusion compared to the patients without those comorbidities. Patients with a history of diabetes (p<.001), mental health (p<.001), alcohol abuse (p<.001), and smoking (p<.001) were more likely to be readmitted to the hospital. Patients with cardiac (p<.001) and pulmonary (p<.001) diseases were more likely to have pulmonary embolism compared to patients without a history of cardiac and pulmonary disease. There was no association between deep wound infections and any of the comorbidities listed. The model did not generate odd ratios for some of the comorbidities due to the lower frequency of occurrence.

3.4. Discussion

The results of this study indicate that the obese class III group had a higher proportion of younger patients (<50 yrs. old) and a lower proportion of older patients (≥ 80 yrs. old) compared to the normal BMI group. This suggests that patients with obesity generally receive TKA at a younger age. Patients with obesity class III were on average 7.5 years younger than the group with normal BMI. Other studies have similarly reported that patients with obesity and severe OA were younger [165, 169, 170]. For example, Dowsey and colleagues [169], found that patients with severe obesity who had undergone TKA were 6 years younger than patients without obesity. Taken together, these results may suggest that obesity accelerates the progression of OA [162], resulting in patients with obesity reaching end-stage knee OA earlier. Consequently, patients with obesity seek surgical solutions at a younger age compared to patients with normal BMIs. It is well known that females require TKA more frequently than males [165]. In our cohort of patients who underwent TKA, there was also a higher proportion of females than males across all BMI groups, with obese class III group having the highest proportion. It is noteworthy that females tend to delay joint replacement and only consider TKA when they are in extreme need because they are more concerned about the surgical risk and being a burden on the family [171]. Delaying surgery may result in decreased physical activity (because of pain) and resultant weight gain, which may explain why there is an even higher proportion of females in the obese class III group [171].

Previous studies have shown that obesity increases the risk of adverse events after TKA [164, 165, 172]. However, defining obesity simply based on BMI below or above 30 kg/m^2 leaves out critical information because the degree of obesity also plays an important role in determining the risk of perioperative/postoperative complications. However, there is limited information about the

association between different grades of obesity, categorized according to WHO classification, and TKA complications in the literature. In our study, we categorized patients based on BMI using WHO classification to evaluate the effect of different BMI levels on complications following TKA. Results of the current study show that patients with higher BMI were more likely to have a pulmonary embolism, deep wound infection, and be readmitted to the hospital within 30 days of discharge. Besides obesity, other comorbidities were also associated with TKA complications. Patients with comorbidities were more likely to have a blood transfusion, infection, pulmonary embolism, and readmission.

Previous studies have similarly reported increased probability of pulmonary embolism in patients with higher BMI (obese class I, II, and III) [173-175]; while others did not find obesity to be an independent risk factor for pulmonary embolism [176, 177]. The variability of research findings in this area may be due to different cut-offs used to define obesity as well as inadequate adjustments for the possible confounding factors. Other studies similarly reported that the obese class III group compared to BMI normal group was more likely to have wound-related complications [174, 175, 178]. The higher amount of fat deposition around the knee may be related to delay in wound closure and healing, longer operative times, poor vascularization of fatty tissues, and a weakened immune response [174]. Other studies report that the higher risk of wound-related complications in the obese class III group may be related to the presence of diabetes [175]. However, we did not find any association between diabetes and wound-related complications.

Of note, further detailed analysis (data not shown) revealed that the normal BMI and obese class III groups were significantly more likely ($p<0.001$) to be readmitted to the hospital within 30 days of discharge compared to the other BMI groups (class I, II, and overweight). Previous studies have also suggested that readmission has a U-shaped relationship with BMI, and those with

very low or very high BMI had a higher risk of readmission [174, 179]. The higher risk of readmission in BMI class III could be due to higher rates of comorbidities and wound-related infections associated with obesity [174, 180, 181]. Whereas the higher risk of readmission in the normal BMI group could be related to higher rates of blood transfusion, mental health issues, and lower length of hospital stays [174, 180, 181]. We also found that the likelihood of blood transfusion was lower in patients with higher BMI, which is in line with other studies [174, 182]. In patients with higher BMIs, the actual percentage of blood volume lost following TKA might be lower due to the higher blood volume in these patients, which eventually leads to lower rates of blood transfusion compared to patients with normal BMI quality of life following TKA.

Besides obesity, other comorbidities are also independent predictors for postoperative complications. We found a higher likelihood of pulmonary embolism in patients with cardiac and pulmonary disease. A higher likelihood of readmission was detected in patients with diabetes, mental health problems, alcohol abuse, or current smokers. The higher likelihood of blood transfusion was observed in all of the comorbidities except pulmonary disease. These results are similar to previous research [180, 183-187]. However, some studies did not find an association between complications and comorbidities including diabetes [188, 189], cardiac disease, mental health [190], and smoking [191, 192]. The discrepancy in results could be due to sample size, severity of the disease, and lack of analysis of other potential confounding variables including age, sex, number of medical comorbidities. Altogether, our results support the finding that obesity, along with other comorbidities, is an independent risk factor for adverse events following TKA.

3.5. Strength and Limitations

Our study included a large data set routinely checked by ABJHI for quality assurance. These data were collected from the whole province, which makes our results more generalizable. We

categorized patients into five groups based on BMI according to WHO classification, which allowed us to demonstrate a clear relationship between BMI group with complications and comorbidities. Certain aspects of our study methodology should be emphasized. We only examined perioperative and postoperative events within 30 days of TKA. Some of the potential postoperative complications may occur after this time period, and our study did not capture those events. We were not able to report odd ratios for some of the parameters due to very low or zero event rates. There was a lack of information on the number of deaths in the dataset. Incomplete data collection for some variables such as weight and height records, length of stay in hospital, and lack of detailed clinical information including pre-surgical OA severity diagnosis, and the number of deaths that occurred in the cohort are all valid concerns. Moreover, we used BMI as a measure of obesity, however, BMI does not provide information about body composition and fat distribution [193]. Further studies are needed to elucidate the association between body composition and fat distribution using sophisticated methods such as dual-energy X-ray absorptiometry (DEXA) with complications in patients with TKA. It is also noteworthy that obesity definition has been changed in the newly released obesity guideline to "a chronic disease characterized by excessive or abnormal body fat that impairs health" [62]. The new guideline recommended the use of Edmonton Obesity Staging System [194] as a complementary measure for BMI. Future studies can explore the association between obesity staging and surgery outcomes. These recognized limitations are inherent to retrospective studies of administrative databases and could potentially be improved through prospective data collection.

3.6. Conclusion

This study adds to the literature on the association between obesity and other major comorbidities on short-term complications in patients who underwent TKA. Overall, we

demonstrated that the patients in the obese cohort was younger, included more females, and had a higher incidence of major comorbidities. With increase in BMI, the likelihood of having pulmonary embolism and deep wound infection were increased. The normal BMI group had the highest likelihood of blood transfusion. There was also a high association between major comorbidities with peri/post-operative complications Obesity, along with other comorbidities, places patients at increased risk of adverse events after TKA, though the level of risk depends on the severity of obesity. These findings may be used by patients and care providers to educate patients in higher BMI groups about the risks and benefits of an elective procedure and optimize comorbidities prior to the surgery.

Table 3.1. Patients characteristics by body mass index (BMI) group; N total = 15151

	Body mass index groups (kg/m^2)*					
	Normal	**Overweight**	**Obese Class I**	**Obese Class II**	**Obese Class III**	**p-value**
Total Number	**1240**	**4189**	**4541**	**2839**	**2342**	
Age group						
<50	2.0%	1.3%	2.0%	2.6%	4.1%	<.001
50-59	16.4%	15.8%	19.7%	23.0%	32.2%	<.001
60-69	29.4%	36.0%	38.5%	44.4%	45.4%	<.001
70-79	31.3%	33.4%	30.5%	25.4%	16.2%	<.001
≥80	21.0%	13.6%	9.4%	4.6%	2.1%	<.001
Sex						
Male	30.5%	44.6%	43.7%	35.4%	28.6%	<.001
Female	69.5%	55.4%	56.3%	64.6%	71.4%	<.001
Comorbidities						
Diabetes	10.1%	10.0%	13.4%	15.7%	20.9%	<.001
Mental health	11.1%	8.3%	8.4%	8.0%	10.1%	<.001
Cardiac disease	0.7%	0.8%	0.8%	0.7%	0.8%	.871
Pulmonary disease	0.2%	0.1%	0.2%	0.2%	0.3%	.242
Blood circulatory/clotting	0.2%	0.2%	0.2%	0.1%	0.1%	.030
Smoker	7.2%	7.4%	8.6%	7.8%	8.2%	.002
Alcohol abuse	2.8%	2.5%	2.2%	1.9%	2.2%	<.001
Complications						
Readmission/30 days	4.5%	3.7%	3.6%	3.3%	4.3%	<.001
Pulmonary embolism	0.7%	1.3%	1.7%	1.7%	1.9%	<.001
Deep wound infection	0.7%	0.5%	0.6%	0.8%	1.5%	<.001
Myocardial infarction	0.3%	0.4%	0.3%	0.3%	0.1%	<.001
Ileus	0.2%	0.2%	0.3%	0.4%	0.3%	.070
Pneumonia	0.2%	0.2%	0.3%	0.3%	0.1%	.020
Deep vein thrombosis	0.1%	0.2%	0.1%	0.1%	0.0%	.060
Gastrointestinal bleed	0.1%	0.0%	0.2%	0.2%	0.1%	.030
Cerebrovascular accident	0.1%	0.0%	0.0%	0.0%	0.0%	.040

*Normal weight (BMI ≤ 24.99 kg/m^2), overweight (BMI of 25 to 29.99 kg/m^2), obese class I (BMI of 30 to 34.99 kg/m^2), obese class II (BMI of 35 to 39.99 kg/m^2), and obese class III (BMI of ≥ 40 kg/m^2).
$^{\Phi}$ p-values are comparing the percentage of each row among different BMI groups

Table 3.2. Odds ratio for different BMI groups versus normal BMI group for comorbidities and complications

	Overweight Vs. Normal BMI		Obese Class l Vs. Normal BMI		Obese Class II Vs. Normal BMI		Obese Class III Vs. Normal BMI	
	OR[#] (95%CI)[¥]	p-Valu	OR (95%CI)	p-Valu	OR (95%CI)	p-Value	OR (95%CI)	p-Value
Comorbidities[£]								
Diabetes	0.96(0.77-1.19)	0.68	1.44(1.17-1.78)	<.001	1.99(1.60-2.48)	<.001	3.38(2.70-4.10)	<.001
Mental health	0.83(0.67-1.02)	0.08	0.85(0.69-1.05)	0.13	0.81(0.64-1.02)	0.07	0.94(0.74-1.19)	0.72
Cardiac disease	1.18(0.58-2.48)	0.66	1.22(0.58-2.57)	0.60	1.33(0.59-2.99)	0.48	1.95(0.84-4.29)	0.14
Complications[§]								
Blood transfusion	0.77(0.64-0.93)	<.001	0.61(0.50-0.74)	.006	0.53(0.42-0.66)	<.001	0.38(0.29-0.49)	<.001
Pulmonary embolism	1.95(0.96-3.97)	0.07	2.73(1.37-5.51)	<.001	2.77(1.34-5.71)	<.001	3.62(1. 37-7.56)	<.001
Deep wound infection	0.58(0.26-1.29)	0.18	0.74(0.34-1.59)	0.44	1.15(0.53-2.52)	0.73	2.25(1.07-4.85)	0.04
Readmission/30 days	0.89(0.65-1.23)	0.51	0.90(0.66-1.24)	0.53	0.93(0.65-1.31)	0.67	1.27(0.89-1.99)	0.12

[*]Normal weight (BMI ≤ 24.99 kg/m^2), overweight (BMI of 25 to 29.99 kg/m^2), obese class I (BMI of 30 to 34.99 kg/m^2), obese class II (BMI of 35 to 39.99 kg/m^2), and obese class III (BMI of ≥ 40 kg/m^2).
[#]OR= Odd ratio
[¥]CI=Confidence intervals
[£]Odd ratios for blood clots, pulmonary disease, and dementia were not generated due to lower or zero frequency for some BMI groups.
[£]Odd ratios for myocardial infarction, Ileus, pneumonia, deep vein thrombosis, gastrointestinal bleed, and cerebrovascular accident were not generated due to lower or zero frequency for some BMI groups

Table 3.3. Odds ratio of having peri/post operative complications given a certain comorbidity

	Complications							
	Blood transfusion		Readmission/ 30 days		Pulmonary embolism		Deep wound infection	
Comorbidities	**OR[#] (95% CI)[¥]**	**P[†]**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Diabetes	1.76(1.52-2.05)	<.001	1.60(1.30-1.98)	<.001	0.78(0.53-1.16)	.23	0.72(0.41-1.26)	.25
Cardiac disease	3.07(1.98-4.76)	<.001	1.78(0.92-3.47)	.09	4.89(2.47-9.70)	<.001	NC↟	NC
Pulmonary disease	2.20(0.89-5.44)	.08	0.43(0.06-3.30)	.42	7.51(2.46-2.29)	<.001	NC	NC
Circulatory/ clotting	7.02(2.88-17.08)	<.001	2.85(0.81-9.99)	.10	NC	NC	NC	NC
Mental health	1.62(1.36-1.93)	<.001	2.12(1.69-2.67)	<.001	1.15(0.74-1.78)	.52	1.34(0.74-2.44)	.33
Alcohol abuse	1.47(1.02-2.11)	.04	2.07(1.39-3.09)	<.001	0.41(0.10-1.70)	.22	1.66(0.70-3.94)	.25
Smoker	1.37(1.12-1.67)	.002	1.65(1.28-2.14)	<.001	1.31(0.84-2.04)	.23	1.54(0.88-2.69)	.13

[£]Results are from multivariate logistic regression to find the association between each of the complications and comorbidities adjusting for demographic information.
↟NC= Not converged. Logistic regression to find out the association between dementia, myocardial infarction, Ileus, pneumonia, deep vein thrombosis did not converge due to lower or zero frequency.
[#]OR= Odd ratio
[¥]CI=Confidence intervals
[†]P=Significance level

3.7. Supplementary Materials

Table 3.1.S. Patients' characteristics and proportion of comorbidities and complication between included (BMI data available) vs. excluded (no BMI data available) cohorts

Variable	Cohort (with weight and height record)	Excluded (without weight and height record)	P†
N	15151(56.2%)	11811(43.8%)	
Age, mean ± SD years	66.6±9.2	66.8±9.2	0.14
Female sex	61.03%)	59.61%	0.19
Comorbidities			
Diabetes	13.77%	14.03%	0.62
Mental health	8.79%	9.80%	0.46
Cardiac disease	0.77%	0.75%	0.87
pulmonary disease	0.20%	0.18%	0.75
Blood clot	0.15%	0.09%	0.22
Dementia	0.02%	0.06%	0.30
Smoking	7.95%	9.19%	0.35
Alcohol abuse	2.26%	1.95%	0.13
Complications			
Blood transfusion	8.82%	10.0%	0.38
Readmission/30 days	3.7%	4.74%	0.27
Pulmonary embolism	1.55%	1.01%	0.32
Deep wound infection	0.77%	0.60%	0.15
Myocardial infarction	0.30%	0.23%	0.34
Ileus	0.30%	0.16%	0.04
Pneumonia	0.27%	0.15%	0.06
Deep vein thrombosis	0.12%	0.16%	0.44
Gastrointestinal bleed	0.11%	0.15%	0.44
Cerebrovascular accident	0.03%	0.06%	0.32

Student's t-test was used to determine whether there was a significant difference between the mean age between the two groups. Chi-square test was used to compare comorbidities and complication rates between two groups.
†P=Significance level

Table 3.2.S. Patients characteristics by body mass index (BMI) group; N total = 15151

	Body mass index groups (kg/m^2)*					
	Normal	**Overweight**	**Obese Class I**	**Obese Class II**	**Obese Class III**	**p-value**
Total Number	**1240**	**4189**	**4541**	**2839**	**2342**	
Age group						
<50	25	54	91	74	96	<.001
50-59	203	662	895	653	754	<.001
60-69	365	1508	1748	1261	1063	<.001
70-79	388	1399	1385	721	379	<.001
≥80	260	570	427	131	49	<.001
Sex						
Male	378	1868	1984	1005	670	<.001
Female	862	2321	2557	1834	1672	<.001
Comorbidities						
Diabetes	125	419	608	446	489	<.001
Mental health	138	348	381	227	237	<.001
Cardiac disease	9	34	36	20	19	.871
pulmonary disease	2	4	9	6	7	.242
Blood circulatory/clotting	2	8	9	3	2	.030
Smoker	89	310	391	221	192	.002
Alcohol abuse	35	105	100	54	52	<.001
Complications						
Readmission/30 days	56	155	163	94	101	<.001
Pulmonary embolism	9	54	77	48	44	<.001
Deep wound infection	9	21	27	23	35	<.001
Myocardial infarction	4	17	14	9	2	<.001
Ileus	2	8	14	11	7	.070
Pneumonia	2	8	14	9	2	.020
Deep vein thrombosis	1	8	5	3	0	.060
Gastrointestinal bleed	1	0	9	6	2	.030
Cerebrovascular accident	1	0	0	0	0	.040

*Normal weight (BMI ≤ 24.99 kg/m^2), overweight (BMI of 25 to 29.99 kg/m^2), obese class I (BMI of 30 to 34.99 kg/m^2), obese class II (BMI of 35 to 39.99 kg/m^2), and obese class III (BMI of ≥ 40 kg/m^2).
$^{\Phi}$ p-values are comparing the percentage of each row among different BMI groups

Chapter 4

Does Obesity Affect Patient Reported Outcomes Following Total Knee Arthroplasty?

4.1. Background

Osteoarthritis (OA) is a degenerative chronic disease that affects 10–15% of adults in Canada and results in pain, disability, and reduced quality of life [3]. The knee is the most commonly affected joint [4]. When conservative treatments fail, patients are typically offered total knee arthroplasty (TKA), which is a well-established and effective intervention for end-stage OA [195]. The overall treatment goal of TKA is to relieve pain, restore loss of function, and improve the health-related quality of life (HRQoL) [5, 6]. Despite the known benefits of TKA on health-related outcomes, some patients experience complications [4, 196] and may receive less benefit than expected. Patients in the higher spectrum of body mass index (BMI) may be at greater risk of poor outcomes after TKA, and surgeons are left unsure as to whether TKA is beneficial for patients with higher BMI, especially class III [197].

While some studies suggest that BMI has no impact on postoperative recovery and subsequent pain and function [19, 198], others suggest it has a negative impact [19-24, 199-201]. The association, if any, between BMI and TKA outcomes following surgery remains unclear [19, 202]. A recently published meta-analyses [203] reported that the discrepancy in the results is related to the fact that most studies did not control for confounding factors such as age and sex, and they used different definitions of obesity. A Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee suggested that future studies sub classify BMI using the World Health Organization Classification (WHO) to examine the value of TKA in this population [157].

The purpose of the current study was to evaluate the extent to which BMI, categorized according to the WHO classification, affects Patient Reported Outcome Measures (PROMS) preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months after TKA adjusting for putative confounders of age, sex, and commodities. We used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and EuroQol-5D (EQ5D) as PROMS that have been widely used to evaluate the effectiveness of TKA [204-206]. The WOMAC questionnaire was used to measure self-reported pain, stiffness, and function, while the EQ5D questionnaire was used to assess the HRQoL, preoperatively, and again 3 and 12 months following TKA.

4.2. Method

4.2.1. Data Source and Sample

This study was a retrospective secondary data analysis using a provincial database in Alberta managed by the Alberta Bone and Joint Health Institute (ABJHI). We also used the discharge abstract database, which is a hospital administrative database that is collected as part of the standardized care process and not part of a clinical study. Diagnosis and procedure coding were based on the 10th version of the International Classification of Diseases combined with the Canadian Classification of Health Intervention (ICD-10-CA/CCI). Standardized care processes and consistent data collection for total joint arthroplasty in the province commenced in 2009 and are ongoing. Knee surgeries are performed at twelve public hospitals (Alberta Health Services: AHS) in Alberta, Canada, and all data were captured under the authority of the provincial Privacy Impact Analysis (PIA) agreement in place for quality assurance monitoring and reporting on Bone and Joint Health in Alberta (OIPC File # H2801).

Between 2012 and 2016, we identified 26,962 patients who underwent primary unilateral TKA from Alberta Bone and Joint Health Repository collected information. A subset of 15,151 patients had height and weight records. Within that group, two separate datasets (7,714 patients with WOMAC and 3,848 patients with EQ5D questionnaire) were prepared (Figure 4.1). BMI was calculated based on weight and height records (captured in each clinic) by dividing weight in kilograms (kg) by height in meter squared (m^2). Patients were then classified into one of five BMI groups according to the World Health Organization (WHO) classification of BMI: normal (BMI≤24.99 kg/m^2), overweight (25≤BMI≤29.99 kg/m^2), BMI class I (30≤BMI≤34.99 kg/m^2), BMI class II (35≤BMI≤39.99 kg/m^2), and BMI class III (BMI≥40 kg/m^2) [207]. In addition to WOMAC and EQ5D, information on age, sex, number of comorbidities, and the geographical zone of service were also available. Ethics approval (Appendix A) for this study was obtained from the University of Alberta Health Research Ethics Board. Permission to extract the data was obtained from, and done by, ABJHI.

4.2.2. Patient-reported Outcomes

ABJHI uses the WOMAC and EQ5D (described in more detail below) to determine the effectiveness of the TKA surgery. These two outcomes are widely used PROMS and are the primary outcomes in the present study.

4.2.2.1. WOMAC

The WOMAC Index, developed by Bellamy et al. [205] uses a 5-point Likert scale and contains 24 items covering three dimensions of pain (5 items), stiffness (2 items), and function (17 items). A total score combining the three dimensions may be used. Scores range from 0-20 for pain, 0-8 for stiffness, 0-68 for physical function, and 0-96 for the total aggregated score. A recent systematic review by Copsey et al. (2019) pointed out that a clear reporting of standardized

WOMAC scoring system should be implemented and all subscales should be converted to a 0-100 scale [208]. Using the transformed data has also been recommended in the WOMAC user guide and previous studies [209]. Each of the WOMAC subscales (i.e. pain, stiffness, function) and total score were converted to a scale of 0 to 100 (with 100 being the worst pain, stiffness, or function) by dividing the subscale score by the total possible score and multiplying by 100 [205, 208, 210]. The WOMAC questionnaire is reliable, valid, feasible, and responsive to change over time in people with knee osteoarthritis [205, 211, 212]. The minimal clinically important difference (MCID) values after rehabilitation programs for WOMAC pain, stiffness, and physical function (on the scale of 0-100) were reported as 7.09, 16.2, and 11.25, respectively [213, 214].

4.2.2.2. EQ5D

The quality of life of patients before and after surgery was measured using the EQ5D-5L index, a standardized self-report instrument for measuring generic health status. The EQ5D is widely used in the orthopedic field and medical research to collect HRQoL scores as a basis for determining health status. It has been routinely applied in TKA programs in Alberta, Canada [215]. EQ5D-5L has good reliability and validity [204, 216, 217], and consists of 5 dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Items are rated from 1 (no problems) to 5 (extreme problems). From these five dimensions, a health utility (EQ5D index) is calculated ranging from -0.59 to 1.00, with 1.00 indicating full health and 0 representing death. Negative EQ5D scores are possible, and they indicate health status valued worse than death [218]. The MCID for the EQ5D index is reported to be 0.20 [219].

4.2.2.3. Statistical Analyses

Sample characteristics were presented as mean and standard deviation for continuous variables, and frequencies for categorical variables. Repeated measurement analyses using mixed

effects models were performed to investigate the association between each of the patient reported outcome scores (WOMAC and EQ5D) and BMI groups. Separate models were used to analyze each of the dependent variables of pain, stiffness, physical function, total WOMAC scores, and EQ5D index. Since linear mixed effects models consider all available data and thus allow for missing values, any participants who had baseline in addition to 3 and/or 12 months data were included in the analysis. All models were adjusted for age, sex, number of comorbidities, length of surgery, and geographic zone of service. The patient effect was considered as a random effect in the model. The interaction of time by BMI in the models was considered to adjust for the within subject variation overtime, and the interaction term provides the adjusted mean changes for each group at different time intervals. All statistical analyses were performed using R software package version 0.99.902.

4.3. Results

4.3.1. Patient Characteristics

The mean±SD BMI of patients who were included in the study was 33.3±6.9 kg/m^2. Mean age of patients was 65.5±8.7 years old, and 61% of the sample was female. Among all patients 21.7 % had comorbidities, and 13% had preoperative/postoperative complications.

Patient demographic and baseline characteristics for each of the five BMI groups are also given in Table 4.1. On the basis of BMI, 572 (7.4%) of the participants had BMI normal; 2122 (27.5%) were overweight; 2314 (29.9%), BMI class I; 1460 (19.0%), BMI class II; and 1246 (16.2%), BMI class III. A total of 9 patients with a BMI lower than 18.5 kg/m^2 (underweight) were included in the BMI normal group.

Patients in higher BMI groups were younger ($p < .0001$) compared to patients with normal BMI. The mean age at surgery ranged from 70.1±10.3 in the BMI normal group to 62.2±7.8 years in the BMI class III group. Patients in higher BMI groups were also more likely to be female, have a higher number of comorbidities, and, on average, have higher 30-day readmission. Patients' self-reported preoperative measures of WOMAC total score, pain, stiffness, function, as well as EQ5D, on average (unadjusted), were 54.2, 53.4, 56.8, 54.1, and 0.51, respectively.

4.3.2. BMI Groups and WOMAC Subscales

At baseline, the adjusted means for WOMAC total score, pain, physical function, and stiffness were similar across different BMI groups (Figure 4.2 and Supplementary Table 4.3.S). The adjusted mean at baseline for WOMAC total scores, pain, physical function, and stiffness were 56.3, 55.3, 56.6, and 57.2, respectively.

Adjusted mean changes (baseline to 3 months, 3 to 12 months, and baseline to 12 months) by BMI group for each of the WOMAC subscales are presented in Table 4.2. From baseline to 3 months, the adjusted mean change (improvement) in all WOMAC subscales were significant (adjusted $p<.0001$) for all BMI groups. From baseline to 3 months, all BMI groups experienced similar improvement (mean change) in WOMAC total, function, and stiffness. However, patients in the BMI class II and class III groups compared to BMI normal experienced significantly ($p<0.01$) greater improvement (reduction) in pain from baseline to 3 months postoperatively.

Patients in all BMI groups continued to experience significant (adjusted $p<.0001$) improvement in all WOMAC subscales in the time interval of 3 to 12 months, though the magnitudes were smaller compared to the improvement from baseline to 3 months. From 3 to 12

months, all BMI groups experienced similar improvement (mean change) in all WOMAC subscales.

From baseline to 12 months, the adjusted mean changes (improvement) in all WOMAC subscales were significant ($p<.0001$) for all BMI groups, and all groups experienced similar magnitude of improvement. On average, the improvement for WOMAC total score as well as pain, function, and stiffness were -30.4, -31.5, -30.4, and -28.4 points, respectively (Table 4.2).

4.3.3. BMI Groups and EQ5D

At baseline, the adjusted mean for the EQ5D index was not significantly different across BMI groups (Supplementary Table 4.3.S). The adjusted mean for the EQ5D index was 0.44 across all BMI groups. The adjusted mean changes (baseline to 3 months, 3 to 12 months, and baseline to 12 months) by BMI group for the EQ5D index are presented in Table 4.2. From baseline to 3 months, the adjusted mean change (improvement) in the EQ5D index was significant (adjusted $p<.0001$) in all BMI groups, and all groups experienced similar improvement. In the time interval of 3 to 12 months, the improvement in the EQ5D index almost plateaued. From baseline to 12 months, the adjusted mean changes (improvement) in EQ5D were significant ($p<.0001$) for all BMI groups, and all groups experienced similar improvement. On average, the improvement for EQ5D was 0.27.

4.4. Discussion

In the present study, we evaluated the association between BMI groups, categorized according to WHO classification, with WOMAC and EQ5D preoperatively (baseline) and at different time intervals. There were no significant differences in self-reported preoperative pain, function, stiffness, or quality of life measures across all BMI groups. Our results indicate that by the end of

12 months all patients, regardless of their BMI, had improvement in pain, stiffness, physical function, and quality of life, and the magnitude of improvement was similar across all BMI groups.

The evidence of the impact of BMI on TKA surgical outcomes is conflicting. Some studies suggest there is an association between obesity and pain, functional recovery, and quality of life following TKA [19, 21, 23, 24, 199], while others suggest no association [20, 22, 201, 220]. The variation in findings may be related to differences in the overall health status of the cohorts, use of different cut-offs for BMI, lack of control for confounding factors such as age and sex, and the small sample size [157, 203].

Recently, a study in the U.S. population by Collins and colleagues [221] examined the association between BMI groups, using the recommended WHO classification, and WOMAC subscale of function. They demonstrated that subjects with higher BMI had worse preoperative WOMAC pain and function than patients with normal BMI. Studies by Baker et al. in the U.K. demonstrated that patients in higher BMI groups (assessed in groups of BMI of <25, 25 to 39.9, and ≥40 kg/m^2) also had significantly ($p<.01$) worse preoperative WOMAC total and EQ5D scores ($p<.001$) [220] than patients with normal BMI. We also observed that patients with higher BMI had poorer function, pain, and total scores at baseline, but these differences between BMI groups were not significant. The average baseline scores in our study compared to the U.S. population [221] were higher for pain (53.4 vs. 40.8) and function (54.1 vs. 42.5); whereas, the average baseline WOMAC total score was lower in our study compared to the U.K. population (54.2 vs. 63.2) [220]. Indeed, our patients had worse preoperative pain and function compared to U.S. patients, but better preoperative health status compared to the U.K patients. This discrepancy may be due to different health care systems in the U.S. and U.K. where different indication criteria and algorithms/cut-offs are used to guide the appropriateness of TKA [222-224].

Collins and colleagues [221] reported that patients in higher BMI groups experienced greater ($p<.001$) improvement in pain and function from baseline to 3 months after TKA compared to the lower BMI groups, but all groups had similar levels of pain and function at 24 months. We observed a greater improvement in pain from baseline to 3 months postoperatively in patients with higher BMI. However, all BMI groups attained similar level of pain reduction at 12 months. Baker et al. [220] reported that the average change for WOMAC total score from baseline to 12-month following TKA was similar across different BMI groups. Giesinger et al. [225] used WHO classification to categorize patients, with the Oxford Knee Score (OKS) used to measure self-reported pain and function, and the EQ-5D-3L used to measure general health status. They found no influence of BMI on postoperative self-reported pain, function, or general health scores. Our results were in line with the previous studies demonstrating that all patients received the same benefit from TKA regardless of their BMI [201, 220, 221, 226], and most of the improvement occurred by 3 months postoperatively [221].

Similar to other studies [201, 220, 221, 226], at the end of the study period, all BMI groups experienced statistically significant and clinically meaningful improvement in pain, function, stiffness, and total WOMAC score as well as EQ5D index. Despite substantial improvement in pain and function after TKA across all BMI groups, at the end of 12 months, our patients experienced worse pain and function than patients in Collins et al. study [221]. This may be explained by the worse baseline pain and function of our participants compared to Collins et al. study, as preoperative health status affects the postoperative outcomes [227].

We examined the PROMS preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months after TKA, and the findings of our study offer insight into the association between obesity

and TKA outcomes in Albertans following TKA. In this study, we were able to examine the impact of different levels of BMI groups on PROMS using the WHO classification of BMI.

4.5. Strengths and Limitations

The strength of this study includes a large sample of patients (N=7,714) with WOMAC total score and 3 subscales recorded at baseline and 3 and/or 12 months postoperatively. We have also categorized patients into 5 groups based on the WHO classification of BMI, which helped us to evaluate a clear relationship between each of the BMI groups with TKA outcomes. BMI records in our dataset were not self-reported, which provide more reliable results. Our analysis also had limitations inherent to retrospective studies. WOMAC was used to measure lower extremity physical function, which has been reported to have limited ability to accurately predict change in function [228]. Individuals who did not have weight and height records were excluded from the study, though there were no significant differences in patient-reported outcomes between the cohort that was excluded and those included in the cohort studied (Supplementary: Table 4.1.S and Table 4.2.S). In this study, BMI has been used as a measure of obesity, however, BMI does not provide us with information about the body's fat distribution as well as body composition [193]. Further studies using methods such waist to hip ratios or sophisticated methods such as dual-energy X-ray absorptiometry (DEXA) are recommended to evaluate the association between fat distribution and body composition with TKA outcomes in patients who have undergone surgery. Patients who had baseline and at least 1 follow-up visit (postoperative month 3 or 12) for WOMAC and EQ5D questionnaires were included in the study. Patients with missing follow up questionnaires were also included in the analysis as linear mixed effect models allow for missing data and are robust to determining estimates in presence of missing data [229].

4.6. Conclusions

Overall, we found that participants across all BMI groups achieved a similar benefit with respect to patients' self-reported outcomes of WOMAC scores (pain, function, stiffness, and total score) and EQ5D by the end of 12 months following TKA. Patients in the obese class II and III groups achieved more benefits (although not clinically meaningful in terms of pain outcome compared to normal groups by 3 months), but all BMI groups were able to attain the same benefit by the end of 12 months after surgery. The majority of improvement for all WOMAC subscales and the EQ5D occurred by 3 months after surgery. These results may help health care providers to discuss expectations regarding the TKA recovery in terms of pain, function, and quality of life improvements with their TKA candidates.

Figure 4.1. Flowchart for patients' enrollment and inclusion/exclusion

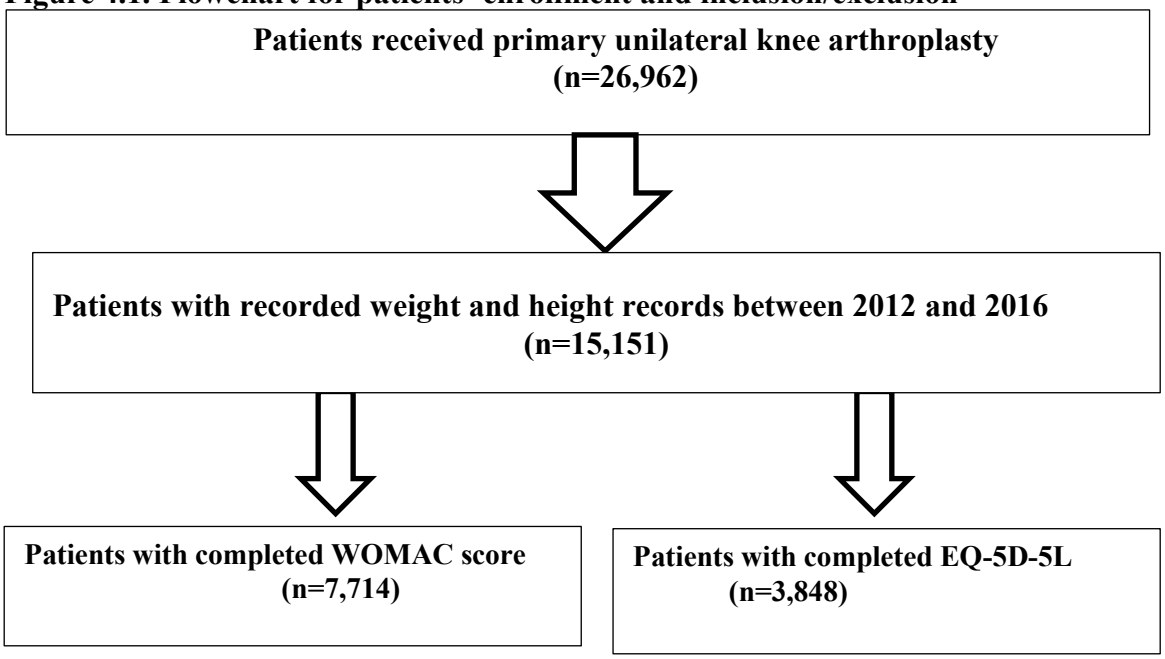

Table 4.1. Baseline characteristics[£]

	BMI groups according to baseline values (kg/m^2)					
	Overall	**<25**	**25-29.9**	**30-34.9**	**35-39.9**	**≥40**
	N=7714	**Normal N=572 (7.4%)**	**Overweight N=2122 (27.5%)**	**Obese class I N= 2314 (29.9%)**	**Obese class II N=1460 (19.0%)**	**Obese class III N=1246 (16.2%)**
BMI (kg/m^2)	33.3±6.9	23.0±1.6	27.7±1.4	32.3±1.4	37.2±1.44	45.0±4.7
Age (yrs)	65.5±8.7	70.1±10.3	68.7±9.2	66.7±8.9	65.0±8.3	62.2±7.8
Sex						
Female N (%)	4732(61.1%)	402 (69.8%)	1178 (55.3%)	1313(56.6%)	948(64.5%)	891(71.1%)
Male N (%)	3016(38.9%)	174(30.2%)	952(44.7%)	1006(43.4%)	522(35.5%)	362(28.9%)
# of Comorbidities N (%)						
0	6141(79.3%)	460(79.9%)	1762(82.7%)	1848(79.7%)	1152(78.4%)	919(73.3%)
1	1439(18.6%)	101(17.5%)	338(15.9%)	419(18.1%)	286(19.4%)	295(23.5%)
2	163(2.1%)	15(2.6%)	29(1.3%)	48(2.1%)	32(2.2%)	39(3.2%)
3	5(0.1%)	0(0.0%)	1(0.1%)	4(0.2%)	0(0.0%)	0(0.0%)

[£]Continuous variables are presented as the mean and the standard deviation. Categorical variables are presented as the number, with the percentage in parentheses.

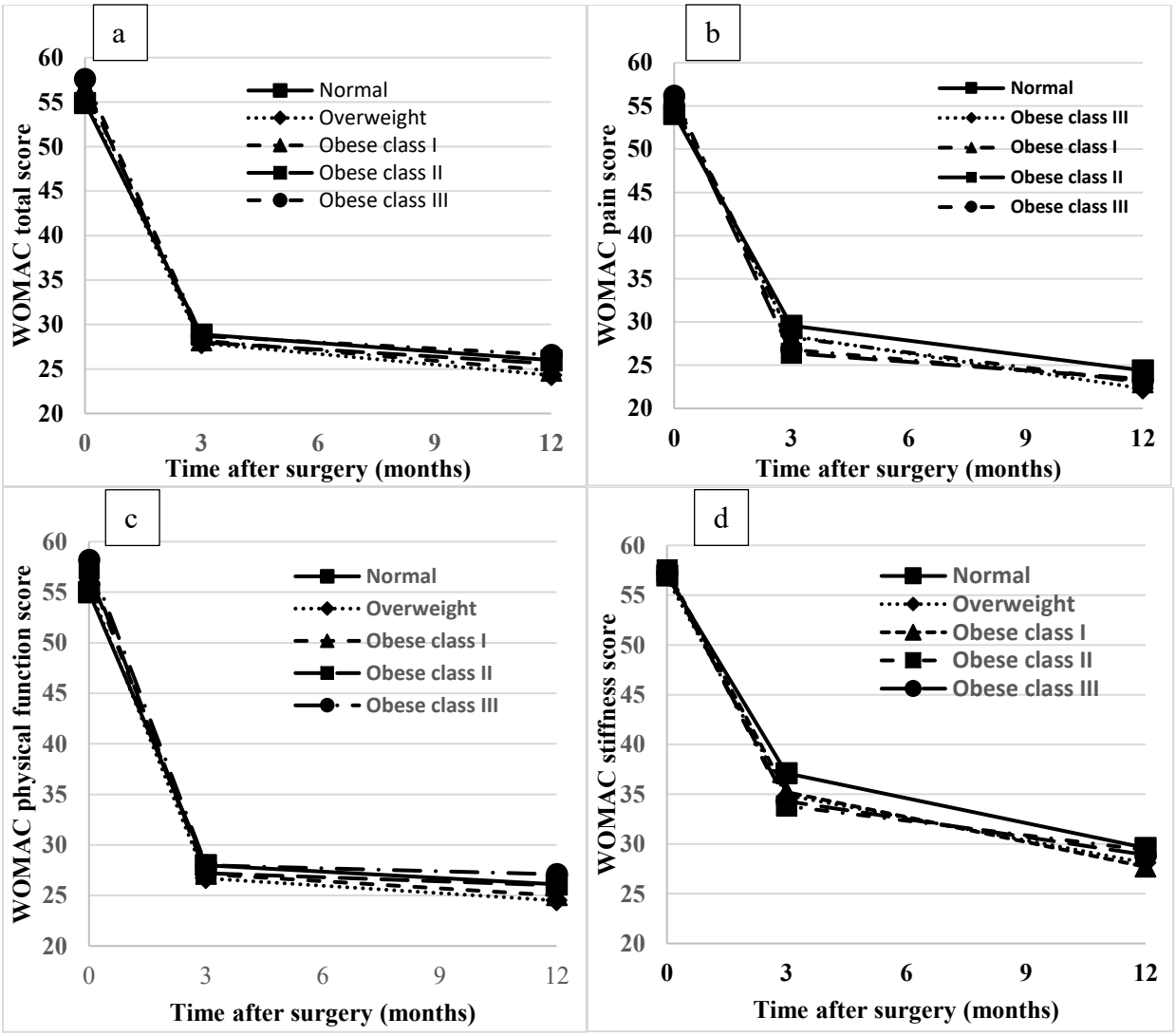

Figure 4.2. Adjusted mean for WOMAC total score (a), pain (b), physical function (c), and stiffness (d) by BMI group and time (baseline [preoperative] and 3, and 12 months post TKA). Each line represents a BMI group, normal weight (solid square; BMI≤24.99 kg/m^2 BMI of <25 kg/m^2), overweight (dashed diamond; 25≤BMI≤29.99 kg/m^2), class-I obese (dashed triangle; 30≤BMI≤34.99 kg/m^2), class-II obese (dashed square; 35≤BMI≤39.99 kg/m^2), and class-III obese (solid circle; BMI≥40 kg/m^2). Adjusted means were computed from a linear mixed effects model adjusting for age, sex, number of comorbidities, and zone of service. Least square mean values, which are used to generate the graphs are provided in the Supplement as Table Chapter 4.2.S.

Table 4.2. Mean changes in WOMAC and EQ5D by BMI group: Results from Mixed Effect Model[£]

	Pre to 3 months	3 to 12 months	Pre to 12 months
Outcomes	**Mean change (95% C.I)**	**Mean change (95% C.I)**	**Mean change (95% C.I)**
Total Score†			
Normal	-25.9(-28.3, -23.5)	-3.1(-6.8, 0.6,)	-29.0(-32.5, -25.5)
Overweight	-27.5(-28.7, -26.3)	-2.0(-5.5, 1.5)	-29.5(-31.3, -27.7)
Obese I	-28.5(-29.7, -27.3)	-3.3(-5.1, -1.5)	-31.8(-33.6, -30.0)
Obese II	-28.9(-30.5, -27.3)	-2.1(-4.5, 0.3)	-31.0(-33.2, -28.8)
Obese III	-29.1(-30.7, -27.5)	-1.6(-4.1, 0.9)	-30.7(-32.9, -28.5)
			Mean improvement= -30.4
Pain †			
Normal	-24.4(-26.9, -21.9)	-5.3(-9.2, -1.4)	-29.8(-33.3, -26.3)
Overweight	-26.5(-27.9, -25.1)	-4.0(-7.5, -0.5)	-30.6(-32.4, -28.8)
Obese I	-27.6(-28.8, -26.4)	-5.2(-7.2, -3.2)	-32.8(-34.6, -31.0)
Obese II	**-28.9(-30.5, -27.3)**	-2.6(-5.0, -0.2)	-31.5(-33.7, -29.3)
Obese III	**-29.5(-31.3, -27.7)**	-3.2(-5.7, -0.7)	-32.7(-35.2, -30.2)
			Mean improvement = -31.5
Function†			
Normal	-26.8(-29.2, -24.4)	-2.1(-5.8, 1.6)	-28.9(-32.2, -25.6)
Overweight	-28.8(-30.0, -27.6)	-0.6(-4.1, 2.9)	-29.4(-31.2, -27.6)
Obese I	-29.7(-30.9, -28.5)	-2.1(-3.9, -0.3)	-31.9(-33.7, -30.1)
Obese II	-30.1(-31.7, -28.5)	-0.9(-3.3, 1.5)	-31.0(-33.2, -28.8)
Obese III	-30.3(-31.9, -28.7)	-0.5(-3.0, 2.0)	-30.8(-33.0, -28.6)
			Mean improvement = -30.4
Stiffness†			
Normal	-19.8(-22.5, -17.1)	-7.6(-11.9, -3.3)	-27.4(-31.5, -23.3)
Overweight	-21.8(-23.2,20.4)	-5.4(-9.3, -1.5)	-28.6(-30.6, -26.6)
Obese I	-22.2(-23.6, -20.8)	-7.5(-9.7, -5.3)	-29.8(-31.8, 27.8)
Obese II	-23.7(-25.5, -21.9)	-4.2(-6.7, -1.7)	-27.9(-30.3, -25.5)
Obese III	-23.0(-25.0, -21.0)	-5.1(-8.0, -2.2)	-28.1(-30.5, -25.7)
			Mean improvement = -28.4
EQ5DΨ			
Normal	0.23(0.19, 0.27)	0.01(-0.07, 0.09)	0.23(0.17, 0.29)
Overweight	0.25(0.23, 0.27)	0.01(-0.05, 0.07)	0.26(0.22, 0.30)
Obese I	0.25(0.23, 0.27)	0.01(-0.03, 0.05)	0.27(0.23, 0.31)
Obese II	0.29(0.27, 0.31)	0.01(-0.05, 0.03)	0.28(0.24, 0.32)
Obese III	0.30(0.27, 0.32)	0.01(-0.05, 0.03)	0.29(0.25, 0.33)
			Mean improvement = 0.27

[£]Significant ($p<.05$) mean changes are **bolded.** Negative mean changes for WOMAC scores (total, pain, function, and stiffness) indicate improvement.

† Scale of 0 to 100, with 100 being the worst. Ψ1.00 indicating full health and 0 representing death.

4.7. Supplementary Materials

Table 4.1.S. Comparison of patient characteristics between those included (BMI data available) vs. excluded (no BMI data available) in the analysis[£]

	Included (N=7714)	Excluded(N=5650)	P-Value
Age (yrs)	65.5±1.1	66.5±1.1	0.34
Sex			
Female N (%)	4732(61.1)	3016(58.8)	0.51
Male N (%)	3016(38.9)	2330(41.2)	0.51
# of Comorbidities			
0	6141(79.3)	4457(78.9)	0.92
1	1439(18.6)	1046(18.5)	0.96
2	163(2.1)	141(2.5)	0.56
3	5(0.1)	5(0.1)	0.44

[£]Continuous variables are presented as the mean and the standard error of mean. Categorical variables are presented as the number, with the percentage in parentheses.

Table 4.2.S. Adjusted mean comparison between those included (BMI data available) vs. excluded (no BMI data available) cohorts for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales and EuroQol-5D (EQ5D) [£]

		Included cohort (With BMI records)		Excluded cohort (Without BMI records)			
Outcomes	**Time**	**N**	**Mean**	**N**	**Mean**	**SEM**	**P-Value**
Total Score							
	Pre	7714	55.6	5650	54.8	0.53	0.13
	Post 3 months	3846	26.3	2302	25.7	0.73	0.35
	Post 12 months	1663	25.3	1074	23.2	1.45	0.10
Pain							
	Pre	7714	54.6	5650	53.6	0.56	0.10
	Post 3 months	3846	23.9	2302	23.2	0.70	0.15
	Post 12 months	1663	24.6	1074	21.6	1.49	0.06
Function							
	Pre	7714	56.0	5650	55.2	0.55	0.16
	Post 3 months	3846	28.0	2302	28.1	0.75	0.84
	Post 12 months	1663	26.0	1074	22.6	1.41	0.07
Stiffness							
	Pre	7714	55.0	5650	54.3	0.61	0.26
	Post 3 months	3846	33.5	2302	32.2	0.85	0.10
	Post 12 months	1663	24.2	1074	22.5	1.53	0.27
EQ5D							
	Pre	3848	0.45	2763	0.47	0.009	0.04
	Post 3 months	1579	0.76	1274	0.75	0.009	0.69
	Post 12 months	534	0.68	435	0.67	0.02	0.75

£ Adjusted means and standard error of mean differences were calculated from linear mixed model adjusted for age, sex, number of comorbidities, and zone of service.

Table 4.3.S. Least square means of pain, physical function, stiffness, and total score at preoperative and 3- and 12- months following surgery for different body mass index groups

Outcomes	Baseline Mean (95% C.I)	3 months Mean (95% C.I)	12 months Mean (95% C.I)
Total Score†			
Normal	54.9(50.8, 59.0)	28.9(24.5, 33.3)	26.0(20.9, 31.1)
Overweight	55.4(51.5, 59.3)	27.9(23.9, 31.9)	24.3(20.2, 28.5)
Obese I	56.7(52.8, 60.5)	28.2(24.2, 32.1)	24.8(20.7, 28.9)
Obese II	56.9(52.9, 61.6)	28.0(23.9, 32.0)	25.6(21.3, 29.9)
Obese III	57.6(53.7, 61.6)	28.7(24.6, 32.8)	26.6(22.2, 31.1)
Pain†			
Normal	54.1(49.8, 58.5)	29.6(25.0, 34.2)	24.4(19.1, 29.7)
Overweight	54.9(50.8, 59.1)	28.4(24.2, 32.6)	22.3(17.9, 26.7)
Obese I	55.8(51.7, 59.9)	28.2(24.0, 32.4)	23.0(18.7, 27.4)
Obese II	55.3(51.1, 59.5)	26.4(22.1, 30.7)	23.4(18.8, 28.0)
Obese III	56.2(52.0, 60.4)	26.8(22.5, 31.1)	23.2(18.6, 27.9)
Function†			
Normal	55.0(50.7, 59.3)	28.0(23.5, 32.5)	26.1(21.0, 31.2)
Overweight	55.5(51.4, 59.3)	26.7(22.6, 30.8)	24.5(20.2, 28.7)
Obese I	56.9(52.8, 60.9)	27.1(23.0, 31.2)	25.0(20.8, 29.2)
Obese II	57.3(53.3, 61.4)	27.2(23.0, 31.4)	26.0(21.6, 30.5)
Obese III	58.2(54.1, 62.3)	28.0(23.8, 32.2)	27.1(22.6, 31.7)
Stiffness†			
Normal	57.0(52.4, 61.6)	37.1(32.2, 42.0)	29.6(23.8, 35.3)
Overweight	56.7(52.4, 61.1)	34.9(30.5, 39.3)	28.1(23.5, 32.8)
Obese I	57.5(53.2, 61.8)	35.2(30.8, 39.7)	27.7(23.1, 32.8)
Obese II	57.5(53.1, 61.9)	33.8(29.2, 38.3)	29.4(24.5, 34.2)
Obese III	57.2(52.8, 61.6)	34.3(29.8, 38.9)	28.9(23.9, 33.8)
EQ5DΨ			
Normal	0.46(0.37, 0.55)	0.69(0.6, 0.79)	0.69(0.58, 0.80)
Overweight	0.44(0.35, 0.53)	0.70(0.61, 0.79)	0.70(0.61, 0.80)
Obese I	0.45(0.36, 0.54)	0.70(0.61, 0.79)	0.71(0.62, 0.81)
Obese II	0.42(0.33, 0.51)	0.70(0.61, 0.80)	0.70(0.60, 0.80)
Obese III	0.41(0.32, 0.50)	0.71(0.62, 0.80)	0.72(0.62, 0.82)

† Scale of 0 to 100, with 100 being the worst. Ψ1.00 indicating full health and 0 representing death.

Table 4.4.S. Regression coefficient (standard error) of model parameters for different dependent variables

Model parameters	Dependent variable			
	Total score	**Pain β(SE)**	**Stiffness β(SE)**	**Function β(SE)**
(Intercept)	60.5(1.9)	69.1(2.0)	74.2(2.1)	56.4(1.9)
Length of surgery	-0.006	-0.075	-0.005	-0.003
BMI groups				
BMI2 (Overweight)	0.5(0.9)	0.8(1.0)	-0.2(1.0)	0.5(0.9)
BMI3 (Obese Class I)	1.7(0.9)	1.7(0.9)	0.5(1.0)	1.9(0.9)
BMI4 (Obese Class II)	2.0(0.9)	1.1(1.0)	0.5(1.1)	2.4(1.0)
BMI5 (Obese Class III)	2.7(1.0)	2.0(1.0)	0.2(1.1)	3.2(1.0)
Time				
Time2 (post 3 months)	-26.0(1.2)	-24.6(1.3)	-19.9(1.4)	-27.0(1.2)
Time3 (post12months)	-28.9(1.8)	-29.8(1.8)	-27.4(2.1)	-28.9(1.8)
Sex				
Male	-3.0(0.4)	-3.4(0.4)	-4.3(0.4)	-2.6(0.4)
Age	-0.1(0.0)	-0.2(0.0)	-0.3(0.0)	-0.1(0.0)
Zone of Service				
Central	1.2(0.5)	2.3(0.6)	1.5(0.6)	1.0(0.6)
Edmonton	2.4(0.4)	2.2(0.4)	2.3(0.5)	2.6(0.4)
# of Comorbidities				
1	2.7(0.5)	2.7(0.5)	1.3(0.5)	3.1(0.5)
2	6.9(1.3)	7.3(1.4)	4.3(1.5)	7.0(1.4)
3	2.7(7.7)	0.8(8.1)	-1.8(8.6)	3.8(7.9)
Time × BMI groups				
BMI 2: Time 2	-1.5(1.3)	-2.0(1.4)	-1.9(1.6)	-1.8(1.4)
BMI 3: Time 2	-2.5(1.3)	-3.0(1.4)	-2.4(1.6)	-2.7(1.4)
BMI 4: Time 2	-2.9(1.4)	-4.4(1.5)	-3.8(1.7)	-3.1(1.4)
BMI 5: Time 2	-3.0(1.4)	-4.8(1.6)	-3.0(1.7)	-3.2(1.5)
BMI 2: Time 3	-2.1(2.0)	-2.8(2.1)	-1.2(2.3)	-2.1(2.0)
BMI 3: Time 3	-2.9(2.0)	-3.0(2.0)	-2.4(2.3)	-3.0(2.0)
BMI 4: Time 3	-2.4(2.1)	-2.1(2.2)	-0.7(2.4)	-2.4(2.1)
BMI 5: Time 3	-2.1(2.1)	-3.1(2.2)	-0.9(2.5)	-2.2(2.1)

BMI:1 (Normal), Time: 1 (pre), Sex: Female, Zone: South, Comorbidities: Zero, and interaction of BMI 1by Time 1 were reference groups in multiple linear mixed effect models

Results generated using raw data with range of 0-96 for total score, 0-68 for physical function, 0-20 for pain, and 0-8 for stiffness)

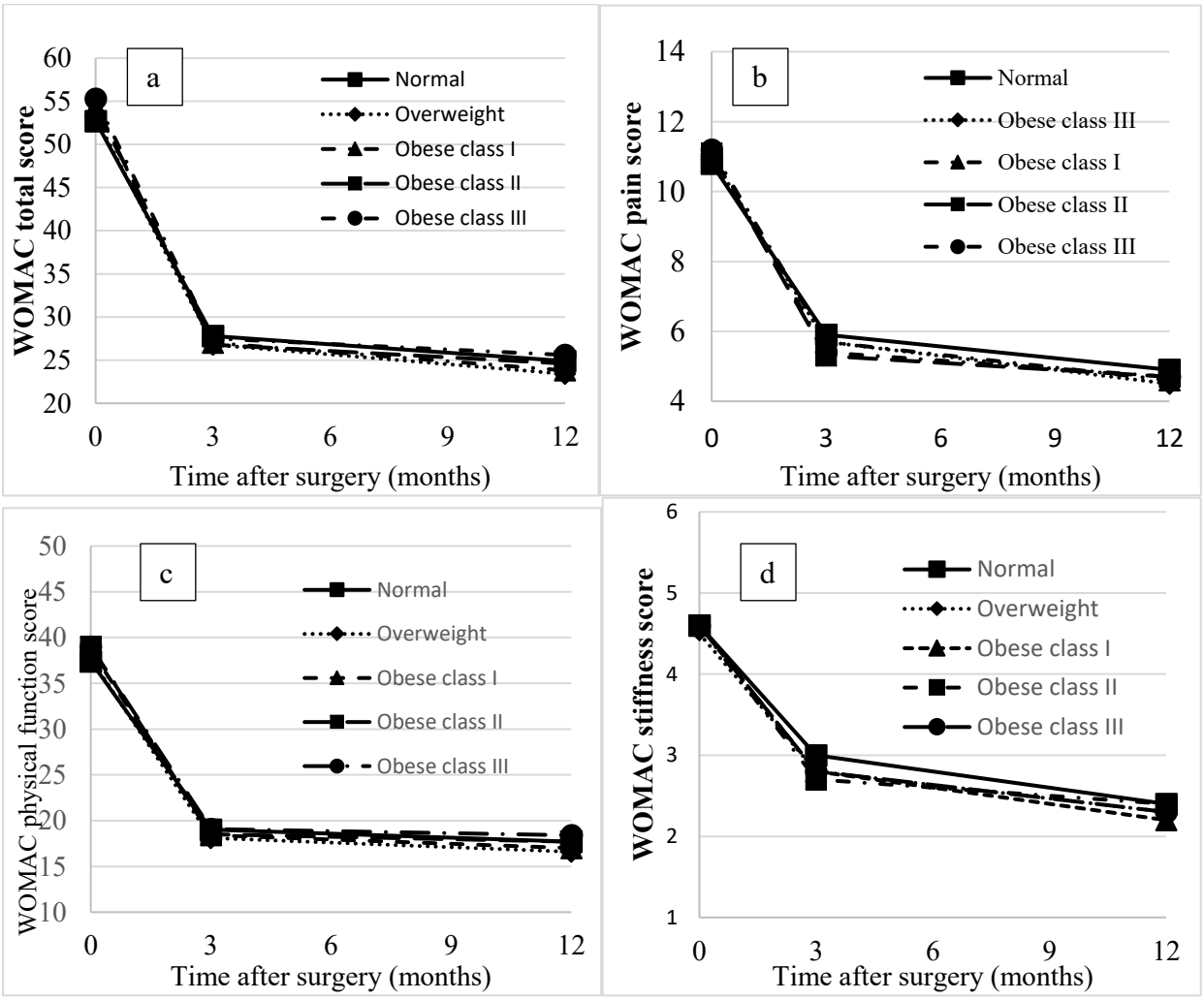

Figure 4.1.S. Adjusted mean for WOMAC total score (a), pain (b), physical function (c), and stiffness (d) by BMI group and time (baseline [preoperative] and 3, and 12 months post TKA). Each line represents a BMI group normal weight (solid square; BMI≤24.99 kg/m^2 BMI of <25 kg/m^2), overweight (dashed diamond; 25≤BMI≤29.99 kg/m^2), class-I obese (dashed triangle; 30≤BMI≤34.99 kg/m^2), class-II obese (dashed square; 35≤BMI≤39.99 kg/m^2), and class-III obese (solid circle; BMI≥40 kg/m^2). Adjusted means were computed from a linear mixed effects model adjusting for age, sex, number of comorbidities, and zone of service. Least square mean values, which are used to generate the graphs are provided in the Supplement as Table 4.5.S.

Table 4.5.S. Least square mean of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales using raw data at preoperative, 3- and 12-month postoperative

Outcomes	Pre	3-month	12-month
	Mean (95% C.I)	**Mean (95% C.I)**	**Mean (95% C.I)**
Total Score (scale 0-96)			
Normal	52.7(56.7,40.3)	27.8(32.0,22.1)	24.9(29.8,21.2)
Overweight	53.2(56.9,40.5)	26.8(30.6,20.9)	23.4(27.4,19.5)
Obese I	54.4(58.1,41.4)	27.0(30.8,21.2)	23.8(27.8,19.9)
Obese II	54.6(58.4,41.8)	26.8(30.7,21.3)	24.6(28.7,20.7)
Obese III	55.3(59.1,42.4)	27.5(31.4,21.9)	25.6(2.2,21.5)
Pain (scale 0-20)			
Normal	10.8(10,11.7)	5.9(5,6.9)	4.9(3.8,5.9)
Overweight	11.0(10.2,11.8)	5.7(4.8,6.5)	4.5(3.6,5.4)
Obese I	11.2(10.3,12)	5.7(4.8,6.5)	4.6(3.7,5.5)
Obese II	11.1(10.2,11.9)	5.3(4.4,6.1)	4.7(3.8,5.6)
Obese III	11.2(10.4,12.1)	5.4(4.5,6.2)	4.7(3.7,5.6)
Function (scale 0-68)			
Normal	37.4(34.5,40.3)	19.0(16.0,22.1)	17.7(14.3,21.2)
Overweight	37.7(35,40.5)	18.1(15.3,20.9)	16.6(13.7,19.5)
Obese I	38.7(35.9,41.4)	18.4(15.7,21.2)	17.0(14.1,19.9)
Obese II	39(36.2,41.8)	18.5(15.7,21.3)	17.7(14.7,20.7)
Obese III	39.6(36.8,42.4)	19.1(16.2,21.9)	18.4(15.4,21.5)
Stiffness (scale 0-8)			
Normal	4.6(4.2,4.9)	3.0(2.6,3.4)	2.4(1.9,2.8)
Overweight	4.5(4.2,4.9)	2.8(2.4,3.2)	2.3(1.9,2.6)
Obese I	4.6(4.3,5.0)	2.8(2.5,3.2)	2.2(1.9,2.6)
Obese II	4.6(4.3,5.0)	2.7(2.3,3.1)	2.4(2.0,2.7)
Obese III	4.6(4.2,4.9)	2.8(2.4,3.1)	2.3(1.9,2.7)

Table 4.6.S. Mean Changes by BMI Group: Results from Mixed Effect Model Using raw data

Outcomes	Pre to 3 M Mean change (95% C.I)	3 to 12 months Mean change (95% C.I)	Pre to 12 months Mean change (95% C.I)
Total Score (scale 0-96)			
Normal	-25.0(-27.2, -22.7)	-2.8(-6.4, -0.8)	-27.8(-31.1, -24.4)
Overweight	-26.4(-27.6, -25.3)	-3.4(-5.2, -1.6)	-29.8(-31.5, -28.2)
Obese I	-27.4(-28.5, -26.2)	-3.2(-4.9, -1.5)	-31.0(-32.7, -29.3)
Obese II	-27.8(-29.2, -26.3)	-2.3(-4.5, -0.1)	-30.1(-32.1, -28.0)
Obese III	-27.8(-29.3, -26.3)	-2.0(-4.3, 0.4)	-29.8(-32.0, -27.5)
			Mean improvement = -29.7
Pain (scale 0-20)			
Normal	-4.9(-5.4, -4.4)	-1.0(-1.8, -0.3)	-6.0(-6.7, -5.2)
Overweight	-5.3(-5.6, -5.0)	-1.2(-1.6, -0.8)	-6.5(-6.9, -6.2)
Obese I	-5.5(-5.8, -5.3)	-1.0(-1.4, -0.7)	-6.7(-7.1, -6.3)
Obese II	**-5.8(-6.1, -5.5)**	-0.6(-1.1, -0.1)	-6.4(-6.8, -5.9)
Obese III	**-5.9(-6.2, -5.5)**	-0.7(-1.2, -0.2)	-6.6(-7.1, -6.1)
			Mean improvement = -6.4
Function (scale 0-68)			
Normal	-18.3(-20.0, -16.7)	-1.3(-3.8, 1.2)	-19.6(-22.0, -17.3)
Overweight	-19.6(-20.4, -18.8)	-1.5(-2.7, -0.3)	-21.1(-22.3, -19.9)
Obese I	-20.2(-21.0, -19.4)	-1.4(-2.7, -0.2)	-22.0(-23.3, -20.8)
Obese II	-20.5(-21.5, -19.5)	-0.8(-2.4, 0.7)	-21.3(-22.7, -19.8)
Obese III	-20.5(-21.6, -19.4)	-0.6(-2.3, 1.1)	-21.1(-22.7, -19.5)
			Mean improvement = -21.0
Stiffness (scale 0-8)			
Normal	-1.6(-1.8, -1.4)	-0.6(-0.9, -0.3)	-2.2(-2.5, -1.9)
Overweight	-1.7(-1.9, -1.6)	-0.5(-0.7, -0.4)	-2.3(-2.4, -2.1)
Obese I	-1.8(-1.9, -1.7)	-0.6(-0.8, -0.4)	-2.3(-2.5, -2.2)
Obese II	-1.9(-2.0, -1.8)	-0.4(-0.6, -0.1)	-2.2(-2.4, -2.1)
Obese III	-1.8(-2.0, -1.7)	-0.4(-0.7, -0.2)	-2.3(-2.5, -2.1)
			Mean improvement = -2.3

[£]Significant mean changes are bolded. Negative mean changes for WOMAC scores (total, pain, function, and stiffness) indicate improvement.

Chapter 5

Dietary Fat Intake, Physical Activity, and Their Relationship with Osteoarthritis Symptoms

5.1. Background

Osteoarthritis (OA) is a highly prevalent, costly, and disabling disease that affects 1 in 8 (13%) Canadians [230]. The prevalence of OA is expected to continue to rise due to the aging population and increased obesity and physical inactivity [231]. With the lack of disease modifying therapies, OA requires long-term management, which eventually leads to a higher health care utilization and increases the medical costs in this population. Therefore, there is an urgent need for effective and accessible approaches to aid in the management of this common condition. The involvement of inflammatory pathways in OA pathogenesis is well known, and reducing inflammation is considered to be a key factor in the management of OA. In order to reduce inflammation in patients with OA, available international guidelines all recommend targeting modifiable risk factors, including diet and physical activity/exercise [12].

Specific unfavorable dietary patterns may play an important role in the initiation and progression of many chronic diseases, such as type II diabetes mellitus [232-234]. The association between a high-fat diet and early onset of OA in a mouse model has been known since 1950 [29]. Increased dietary fat has been shown to alter systemic levels of pro-inflammatory cytokines and trigger cartilage degradation in animal models [30, 31]. For example, in a mouse study, a high–fat diet increased the levels of serum leptin, adiponectin, interleukin-8 (IL-8) and IL-1α, and also induced symptomatic characteristics of OA [32]. In humans, a recent cohort of participants with radiographic knee OA and baseline dietary data were followed yearly out to 48 months to study the association of dietary fat intake with radiographic progression of knee OA. They revealed that

higher total fat or saturated fatty acids (SFA) intakes were associated with increased radiographic progression of knee OA, while higher polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) intakes appeared to be associated with reduced progression [235]. Thus, due to a lack of evidence, we cannot evaluate the dietary intake of fat including SFA and TFA and their association with the performance-based and self-reported pain and function in patients with OA.

Given the substantial body of evidence that has demonstrated beneficial effects of exercise intervention for patients with OA [2, 33, 79, 236, 237], exercise therapy is now regarded as a first-line intervention. However, patients with knee OA often can not comply with exercise regimen due to pain and limited function [33, 35]. As walking is the most common form of physical activity that older adults with knee OA engage in daily, understanding the relationship between steps/day and health outcomes is useful for patients and arthritis health-related professionals [33]. The results regarding the association between steps/day and health outcomes in patients with OA are mixed from no association [37] to a positive association with function [125, 126], and pain [127] measures. Several factors affect physical activity including age, sex, body composition, severity of knee OA, and comorbidities [54, 235]. In the existing literature, researchers have not adjusted physical activity outcomes for confounding factors, reported the step/day count to compare with recommended guidelines, or used a sufficient sample size [34, 37, 38, 128]. Thus, our understanding of physical activity in terms of step count and its association with health outcomes is incomplete.

The objectives of the study were to examine the dietary intake of total fat and SFA as well as the level of physical activity in participants with and without osteoarthritis. We also investigated the relationship between nutrient intake (including total fat and SFA) and physical activity

measures with both performance-based and self-reported measures of function and pain, in adults with and without knee OA.

5.2. Methods

1.1.1 Study Design

A cross-sectional study was conducted. This study was approved by the University of Alberta Health Research Ethics Board (Appendix B) and Edmonton Bone and Joint Center Research Approval Committee (Appendix C).

1.1.2 Participants

Patients, age 45 to 75 years, with clinically and radiographically diagnosed moderate to severe unilateral knee OA who were referred to the Edmonton Hip and Knee Clinic were eligible to participate. Recruitment was initiated at the screening visit by the musculoskeletal specialist, or nurse, who asked patients whether they were interested/willing to participate in the study. If the patient was interested, then the healthcare provider introduced the researcher to the patient. Participants who had evidence of post-traumatic arthritis, neurological conditions that may impair their mobility or systemic inflammatory diseases (e.g., rheumatoid arthritis) were excluded from the study. Patients with uncontrolled diabetes and those with unstable angina or cardiac complications that may affect their level of activity (e.g., left ventricular ejection fraction <25%) and those who were undertaking weight loss or anabolic therapies (within the previous 3 months) were also excluded.

The “healthy control” group was recruited from a population of healthy people with no history of injury in lower extremities (ankle, knee, and hip) or any symptoms that affect their ability to walk or climb one flight of stairs (up and down). The recruitment for healthy participants was

conducted using flyer advertisements (Appendix D), which was approved by the University of Alberta's Ethics committee. All participants received an information sheet (Appendix F) explaining the study and then met with the researcher who explained the study in detail, answered questions, and obtained written informed consent (Appendix G).

1.1.3 Procedure

Anthropometric measurements including weight (kg), height (cm), and waist girth circumference (WC; cm) were taken and rounded to the nearest 0.1 centimeter. BMI was calculated as weight (kg) divided by height squared (m^2). Performance-based and self-reported measures were used to evaluate symptoms in both groups. Performance-based measures including 6 Minute Walk Test (6MWT; Appendix H), and stair test (Appendix I) were used to measure physical function and followed the Osteoarthritis Research Society International (OARSI) guidelines [238, 239]. Western Ontario and McMaster University Osteoarthritis Index (WOMAC; Appendix J) subscales of pain, function, stiffness and total scores, and the Lower Extremity Function Scale (LEFS; Appendix K) were used as self-reported measures. All measures have been shown to have high validity and reliability [240, 241].

Nutrient intakes were collected using a 3-day diet records (Appendix L) to determine the amount of food consumed for three consecutive days (two weekdays and one weekend day). Diet records provide reliable and detailed information on nutrient intake, and three-day diet records, specifically, have been used to evaluate habitual dietary intakes in multiple populations including patients with OA [242-245]. Participants received instructions (Appendix M), for completing the 3-day diet record. Participants were also instructed not to change their routine eating habits during the 3 days of food records. Each diet record was reviewed by one study investigator, who telephoned participants to collect missing details and clarify data entries where necessary. The

recorded foods were inputted into the Food Processor Software (v. 10.11, 2012, ESHA Research, Salem, Oregon, USA), using the Canadian Nutrient File when applicable. Daily food intake records with biologically implausible total calorie intake were removed from the analysis. The cut-offs used for implausible total calorie intake were based on previous studies, which were <800 or >4200 kcal/d for men and <500 or >3500 kcal/d for women [246-251]. Therefore, a total of 17 (5%) out of 294 daily observations were removed based on these criteria. ESHA software output (Appendix N) includes the amounts of energy intake (kcal/d), fat (kcal/d), fat (g/d), saturated fat (kcal/d), mono fat (g/d), poly fat (g/d), trans fat (g/d), cholesterol (mg/d), omega 3 (g/d), omega 6 (g/d), carbohydrates (g/d), protein (g/d), fiber (g/d), sugar (g/d), calcium (mg/d), phosphorus (mg/d), water (g/d), vitamin C (mg/d), vitamin D (mg/d), vitamin K (mg/d), vitamin B1 (mg/d), vitamin B3 (mg/d), and vitamin B12 (mg/d).

To monitor participants' physical activity, a Fitbit Zip was used. Fitbit Zip is a low-cost wearable device regarded as convenient and comfortable to wear, which has an expanded battery life of almost 4 to 6 months. Fitbit Zip has been previously validated among older adults for measuring step count and has been shown to be a valid and reliable method to measure steps and distance [140]. Physical activity measures attainable from the Fitbit Zip include steps (count/day), distance (meter/day), sedentary (min/day), lightly active (min/day), fairly active (min/day; moderate intensity), and very active time (min/day; vigorous intensity) [252]. It should be noted that this device does not provide information on the type of physical activity (e.g., walking, cycling). The device has a silicon clip that can be attached essentially anywhere on the body. Instructions were provided to participants regarding the appropriate wear and positioning of the accelerometer as follows. Participants were instructed to wear the accelerometer on their belt/waist, with the display facing outward, upon arising in the morning and continuing until going

to bed at night for three consecutive days (two weekdays and one weekend day). When the Fitbit Zip was returned, the device was synced, and its data was uploaded to the fitbit.com dashboard. Participants' minute-by-minute step counts were downloaded through Fitbit's application program interface. To accurately represent participants' daily physical activity, the daily average of the total number of steps taken over three days was calculated and used in the analysis.

1.1.4 Statistical Analysis

Baseline characteristics were examined for normality of distribution using the Shapiro-Wilk test. In the descriptive analysis, all baseline characteristics of participants were compared between the group of patients with knee OA and that of the healthy controls using an independent Student's t-tests or non-parametric tests when applicable. The primary analysis was done to compare the physical activity and nutrient intakes between the group of patients with knee OA and the healthy non-OA participant group. The primary outcomes were each of the nutrient intakes (e.g. total fat, SFA, TFA) and physical activity measures (e.g. steps/day and distance). The initial analysis compared means for each of the physical activity measures between the two groups using independent Student's t-test statistics. Since there was a high correlation between each of the nutrients with total energy intake, the means of each nutrient measure were adjusted for total energy intake [253] and compared between groups using linear regression modeling. Linear mixed-effect models were used to compare the physical activity and nutrient intake measures between two groups, adjusting for confounders (sex, age, and BMI). The association between each of the main dependent variables including steps/day for physical activity level and SFA for nutrient intake with independent variables (sex, age, BMI, and WC) were determined in univariate fashion using Pearson correlation and t-test when applicable. Independent variables of group, sex, age, BMI, and WC with $p<.20$ were included in the full model. We examined for multicollinearity

among the independent variable(s) using the variance-inflation factor (VIF). Variance-inflation factor of 4 [254] has been considered as the cut-off criterion to remove predictor variables that are highly correlated, which ensures stability and reliability of the developed model. Then, WC was removed from the full model due to collinearity with BMI. Nutrients were adjusted relative to total energy intake to examine their effect independent of the total amount of energy intake [253].

The secondary analysis involved examining the association between nutrient intake and physical activity with both performance-based (6MWT and stair test) and self-reported measures (WOMAC pain and LEFS). Dependent variables included each of the WOMAC subscales, LEFS, 6MWT, and stair test. Univariate regression analyses between each of the dependent variables with each of the independent variables (nutrient intakes and physical activity measures) were performed to find potential predictors (Table 5.S.1). Predictors (independent variables) with a significant ($p<.20$) regression coefficient were tested for multicollinearity using VIF measures, setting a VIF of 4 as the cut-off criterion [254]. Best linear subset regression modeling with minimization of Mallow's CP and maximizing R squared was used to select the best model. The selected model was used to quantify the relationship between each of the dependent variables and individual predictor variables. All statistical analyses were performed using the R software program Version 0.99.902.

5.3. Results

A total of 60 patients with knee OA and 50 healthy controls were recruited. One patient and one healthy person dropped out of the study after the initial visit and thus their data were removed from further analysis. Thus, 59 patients with knee OA and 49 healthy controls were included in the analyses. The baseline characteristics of participants are shown in Table 1. Overall, patients with knee OA were older and had higher BMI and waist circumference ($p<.0001$) compared to

healthy controls. As expected, patients with moderate to severe OA had worse LEFS, WOMAC pain, function, stiffness, and total WOMAC scores. Performance in the stair test and 6MWT were significantly ($p<.0001$) worse amongst the patients with OA when compared to healthy controls.

Group differences in physical activity and nutrient intake measures are presented in Table 5.2. Results of unadjusted means for physical activity revealed that patients performed significantly fewer steps per day ($p<.0001$), walked shorter distances ($p<.0001$), spent less time being fairly active ($p=.009$) and very active ($p<.0001$), and spent more time being sedentary ($p=.009$) than those in the healthy control group. However, after adjusting for confounding factors (i.e. sex, BMI, and age), only steps per day ($p=.04$) and time spent in very active movements ($p=.02$) were significantly different between the two groups. A significant ($p=.02$) interaction between group and sex was observed for lightly active movements (Table 5.1.S). Males in the OA group spent significantly more time ($p=.03$) doing light activity compared to males in the healthy control group.

Based on unadjusted nutrient intake, patients with OA had significantly higher intake of total energy (kcal/d), total fat (kcal/d and g/d), SFA (kcal/d and g/d), and TFA (g/d), and a lower intake of carbohydrates (g/day) and proteins (g/d and g/kg body weight) than healthy controls. When nutrient intake was adjusted based on the sex, BMI, and age of participants, patients with OA had significantly higher intake of total energy, SFA, and TFA than healthy controls (Table 5.2).

The results of separate multiple regression models for self-reported (WOMAC pain, stiffness, function, and total, as well as LEFS) and performance-based (6MWT, and stair test) measures are presented in Table 5.3. Steps per day had a high association with all self-reported and performance-based measures. Increasing 1000 steps per day, independent of other variables (SFA, TFA, age, and BMI), was associated with a significant reduction (improvement) of 1.9 scores in WOMAC

pain (p =.03), 2.1 scores in WOMAC stiffness (p=.03), 1.7 scores in WMOAC function (p=.06), 1.7 score in WOMAC total (p=.04), and 1.1 seconds in the stair test (p=.003). Increasing 1000 steps per day was associated with a significant increase (improvement) of 1.8 score in LEFS (p=.02) and 14.7 meters in 6MWT (p=.001). Saturated fatty acids intake was significantly associated with pain, stiffness, LEFS, and 6MWT, where increasing intake of 10 gram SFA, independent of other variables, was associated with a significant increase (worsening) of 3.7 score in pain (p=.13) and 3.5 score in stiffness (p=.15). Also, increasing 10 gr SFA intake was associated with a reduction (worsening) of 4.9 score in LEFS (p=.01) and 17.5 meters in 6MWT (p =.15). Trans fat intake was significantly associated with WOMAC pain, function, and total score, as well as distance walked during the 6MWT, where increasing 1 gr TFA intake was associated with a significant increase (worsen) of 4.5 scores in pain (p=.09), 5.8 scores in function (p=.02), 5.6 score in total score (p =.02), and 18.8 meters in 6MWT (p=.02). Non-demographic factors (age and BMI) account for 33%, 31%, 29%, and 30%, respectively, of WOMAC pain, stiffness, function, and total score as well as 34%, 45%, and 32%, for LEFS, 6MWT, and stair test, respectively.

5.4. Discussion

The current study reports physical activity and nutrient intake in a group of patients with moderate to severe primary unilateral knee OA and compares them with a group of healthy controls. In this study, groups were matched for sex, but patients with knee OA had higher BMI compared to the healthy participants, which may introduce bias into our study. To address this concern, two steps were taken. First, the relationship between BMI and each of performance-based and self-reported measures within patient with OA group was visually inspected by drawing scatter plot (along with regression equation). The direction and magnitude of these relationships were also assessed. Visual assessment of the scatterplots (Figure 5.1) showed a weak association between

BMI with self-reported (WOMAC pain, stiffness, and function and LEFS score) and performance-based measures (stair test and 6MWT). The regression coefficients also demonstrated that a small proportion of the variation in self-reported (1 to 3%) and performance-based measures (9 to 12%) were accounted by changes in BMI. This implies that apparently increasing BMI had little effect on the self-reported and the performance-based measures within patients with OA in the current study. The results on the relationship between BMI and self-reported and performance-based measures are mixed in the literature, ranging from no association [255] to strong association [256, 257]. The controversy could be related to the inclusion of patients with different severity of disease and implementing different outcome measures. It has been also suggested that in the absence of matching, confounders can be neutralized at the stage of analysis, given that the confounders have been measured properly [258]. Thus as a second step, the putative confounders including BMI were considered as independent variables in the continuous form in the multiple regression analyses.

The results of the current study demonstrated that patients with knee OA were particularly inactive compared to healthy controls, as monitored using accelerometer-based devices. Patients with knee OA spent less time performing very active movements (vigorous) than healthy controls. The current study also demonstrated that patients with knee OA had significantly higher levels of total energy intake, SFA, and TFA compared to healthy controls. Significant associations between steps per day or nutrient intake and health outcomes (performance-based and self-reported measures of pain and physical function) were observed. An increase in steps was associated with better WOMAC pain, stiffness, function, and LEFS as well as the stair test, and 6MWT. Conversely, an increase in SFA or TFA was associated with worse WOMAC pain, stiffness, function, LEFS, and 6MWT. These results may imply that increase in steps/day and reduction in

SFA and TFA intake would be associated with better performance-based and self-reported outcomes.

Walking is one of the most common types of unstructured physical activity that older adults with knee OA engage in daily, and that has the potential to improve overall health [125]. Step count is gaining widespread attention since it can be easily communicated to the public and directly translated into the clinical setting. It follows that quantifying and examining steps/day may be an important behavioral measure to monitor for patients with knee OA. The results of the current study showed that patients with knee OA were less active than non-OA controls (5319 vs. 6839 steps/day, respectively) after adjusting for putative confounders (age, sex, and BMI); these findings are in line with previous studies [37, 38, 128]. For example, a study by Verlaan et al. [38] reported that patients with knee OA walked fewer steps per day (p=.001, 4402 steps/day) compared to healthy subjects (6943 steps/day). Our results are also in line with a systematic review suggesting that older adults with chronic diseases accumulate 3500–5500 steps/day, and healthy older adults accumulate between 6000 to 8000 steps/day [259, 260]. There are a few studies [38, 261] that did not show a clear difference in steps/day between patients with OA and healthy controls. There may be several reasons related to this discrepancy, such as the inclusion of patients who varied extensively with respect to the severity of disease (including patients at risk and from early-stage knee OA up to pre-TKA) and the healthy control groups from the general population who had different comorbidities. It is expected that patients at risk for, and in the early stage of, knee OA exhibit the same level of physical activity compared to the general population [261].

The benefits of regular exercise on reducing pain and improving physical function in patients with knee OA have been documented in a recent systematic overview [33] of 240 review studies involving 24,583 participants. However, patients with knee OA often do not comply with exercise

regimens due to pain and limited function [33, 35]. For people with symptoms of knee OA, even 10-minute bouts of exercise can be challenging [33]. Since walking is the preferred form of activity for older patients, understanding the relationship between steps/day and health outcomes is useful for patients and arthritis health-related professionals [33]. Our findings quantified the association between physical activity and performance-based as well as between physical activity and self-reported function. Results of the current study indicate that increasing steps/day would be associated with improvement in WOMAC pain, stiffness, physical function scores, LEFS score, 6MWT distance, and the stair test. These results are in line with previous studies in the OA population demonstrating the positive independent association of physical activity with physical function [125, 126, 262] and pain [127].

Due to the lack of evidence quantifying SFA and TFA intake of patients with OA and comparing those intakes with healthy controls, a direct comparison of our results is not possible. However, data from patients with other chronic diseases such as heart failure [263] and diabetes [264] demonstrated that a high fat intake was more prevalent in cases than healthy controls.

Animal models have demonstrated an association between high-fat diet and early onset of OA since 1950 [265]. Since then, animal models have been used to test the hypothesis that high-fat diet induces and accelerates the progression of osteoarthritis [266]. A recent meta-analysis [267] of 14 publications on the effect of a high-fat diet on the onset or progression of osteoarthritis in mice indicated that a high-fat diet induced or exacerbated the progression of OA in mice. It is difficult to establish the role of diet in the etiology of knee OA in humans due to the lack of sensitive markers of nutritional status, the human body's adaptability to the varying levels of nutrient intake, and the complexity and slow progression of OA [267]. Our results indicate that a

reduction in SFA and TFA intake, independent of other variables, would be associated with improving pain, stiffness, function, LEFS, and 6MWT.

Very few human studies have evaluated the role of fat intake in knee OA progression. A cohort study with 251 healthy participants indicated that increased SFA intake was associated with an increased incidence of bone marrow lesions, which may predict knee OA progression [268]. A large prospective study in patients with OA also found that higher intakes of total and saturated fat were associated with increased knee joint space-width loss, whereas the higher intakes of MUFAs and PUFAs were associated with reduced radiographic progression of OA [235].

Of note, the minimal clinically important difference (MCID) values after rehabilitation programs for WOMAC pain, stiffness, and physical function (on the scale of 0-100), LEFS, and 6MWT were reported as 7.09, 16.2, 11.25, 12, and 50 meters, respectively [214, 269]. The results indicate that in order to see clinically beneficial improvement in WOMAC pain, stiffness, and function, adding 3730, 7710, 6620 steps/day, respectively, independent of other factors might help. Besides, adding 6666, and 3400 steps/ day, independent of other factors, might also improve LEFS, and 6MWT, respectively, to be considered as clinically beneficial. In terms of dietary intake of SFA, and TFA, guidelines recommended that adults should limit the SFA intake to no more than 10% of the total calories (22g/day for a person eating 2000 calorie/day) and eliminate TFA from the diet. Our results indicate that the OA group consumed 27.8 grams of SFA and 1.43 gram TFA. A reduction of 5.8 grams in SFA intake (from 27.8 to 22 gr/day), independent of other variables, would be associated with improving 2.3, 2.0, and 2.8 score, respectively, in WOMAC pain, stiffness, and LEFS, as well as 10.2 meters in 6MWT. The results also show that eliminating TFA from diets of patients with OA (from 1.43 to zero gr/d), independent of other factors, would be associated with 6.4 scores change in pain, 8.3 scores change in function, 8 scores change in total,

and 26.9 meters in 6MWT. Although reducing the SFA and TFA intake would be associated with significant improvement (statistically) in performance-based and self-reported outcomes, these improvements did not reach the MCID for the outcomes.

These findings contribute to the knowledge of the physical activity habits of patients with knee OA compare to healthy participants. Importantly, more walking and consuming lower amount of SFA and TFA were associated with improved pain and physical function scores. Therefore, we recommend that health care providers should promote walking and eliminating SFA and TFA in patients with knee OA as a realistic and feasible lifestyle factor, which may relieve pain and maintain functional independence and may delay the onset of disability.

5.5. Limitations

There are limitations to this study. Accelerometers are known to miss certain activities such as water activities and cycling. It is possible that participation in non-stepping activities biased our study results. However, considering that these activities are generally not very common among patients with OA, then this may have minimal effect on the results of this study. It is also possible that wearing an accelerometer may have made individuals more aware of their activity level and may have encouraged participants to be more active. To minimize this effect, the accelerometer used in this study did not provide feedback to the participants. The reported steps/day in this study is a reasonable estimate since the values are similar to previously published reports [38] and are within the range reported by the Canadian Health Measure Survey [270]. Although 3-day food records are a standard method to assess dietary intake, they are based on self-report, which induce the risk of under-reporting/over-reporting in patients due to social desirability related to dietary report in patients and people with obesity [271]. However, the results of the current study demonstrated that patients with OA consumed higher amounts of SFA and TFA compared to the

healthy controls suggesting that the dietary intake records of the participants in this study were representative of their habitual intake [272]. As this is a cross-sectional study, it does not provide evidence that the observed associations are causal. A prospective longitudinal study with a larger sample size is needed to investigate the causal association of nutrient intake and physical activity with OA symptoms. Obesity may be a factor linking fat intake to OA symptoms. However, the association between fat intake and OA symptoms remained significant even after adjusting for BMI. Another limitation of this study is that groups were matched for sex, but not age and BMI. However, visual assessment and regression analysis demonstrated that BMI had little effect on the self-reported and performance-based measures among patients with OA. Besides, potential confounders such as BMI and age that could affect the outcomes were accounted for in the analysis. This has been suggested and recommended in previous research in the absence of matching [258].

5.6. Conclusion

The results of this study provide information about the steps/day and dietary intake of patients with knee OA and add to the literature showing that a higher intake of SFA and TFA is associated with worse self-reported and performance-based function, and an increase in steps/day was associated with improved self-report and performance-based physical function. The results indicate that following a healthy lifestyle, including walking, reducing SFA, and eliminating TFA may be an effective strategy for knee OA management. These lifestyle strategies seem more attractive than medications in terms of risk/benefit and more likely to be implementable.

Table 5.1. Baseline characteristics for original dataset and sex and BMI[*] matched groups

	Groups		p-Value
	OA[¥]	Healthy	
N	59	49	
Female (N)	41	32	
Baseline characteristics			
Age (years)	65.7±5.8	55.3±7.4	<.0001
BMI ±SD (kg/m^2)[*]	35.9±7.6	28.5±6.2	<.0001
Waist Circumference ±SD (cm)	118.2±22.1	93.4±14.7	<.0001
Performance-based outcomes			
6min-walk ±SD (meter)	290.0±98.6	588.0±63.8	<.0001
Stair Test ±SD (seconds)	25.7±13.0	6.7±1.2	<.0001
Self-reported outcomes			
LEFS ±SD (out of 80) [€]	30.5±13.8	78.3±4.3	<.0001
WOMAC (out of 100) [§]			
Pain ±SD	45.0±20.2	1.5±3.4	<.0001
Function ±SD	47.8±18.2	1.5±3.5	<.0001
Stiffness ±SD	57.7±19.1	6.2±11.2	<.0001
Total ±SD	48.1±17.8	1.9±3.6	<.0001

[*]BMI: Body Mass Index;
[¥]OA: Subjects who had moderate to severe osteoarthritis based on the Kellgren Lawrence classification.
[€]LEFS: Lower Extremity Function Scale, 80 being the best.
[§]WOMAC: Western Ontario and McMaster University Osteoarthritis Index, 100 being the worst.

Table 5.2. Unadjusted means ± standard deviation and adjusted means ± standard error for physical activities and nutrients by group

	Unadjusted mean ± standard deviation			Adjusted mean ± standard error*		
	Group			Group		
	OA¥	Control	p-Value€	OA¥	Control	p-Value€
Physical activities‡						
N	57	49		57	49	
Steps/day	4530±2105	7550±2937	**<.0001**	5319±432	6839.0±483	**.04**
Distance (meters)	3130±1460	5060±2160	**<.0001**	3720±310	4500±350	NS
Sedentary (min)	1282±62.2	1248±68	**.009**	1261±10.9	1127±12.2	NS
Light active (min)	149±59.0	165±66.4	NS	168±10.5	144±11.8	NS
Fairly active (min)	4.8±6.9	10.4±12.9	**.009**	6.7±1.8	9.1±2.0	NS
Very active (min)	3.76±6.2	17.3±20.3	**<.0001**	5.3±2.6	15.7±2.9	**.02**
Nutrients†						
N	53	45		53	45	
Total energy (kcal/d) ‡	2110.8±408	1827.0±416	**.001**	2049±69.1	1877±79.5	**.02**
Total fat (kcal/d)	781.0±241	684.0±263	**.01**	757±32.5	684±36.5	NS
Total fat (g/d)	87.0±26.9	76.2±29.3	**.01**	84.4±3.6	76.1±4.1	NS
SFA (kcal/d) Φ	244.0±96.3	207.0±104.9	**.01**	250.0±13.1	204.0±14.8	**.04**
SFA (g/d) Φ	27.1±10.7	23.0±11.7	**.01**	27.8±1.5	22.7±1.7	**.04**
Mono fat (g/d)	30.3±13.7	27.5±15.0	NS	29.1±1.9	27.2±2.9	NS
Poly fat (g/d)	16.5±8.0	14.7±8.8	NS	14.8±1.0	15.5±1.2	NS
TFA (g/d) §	1.38±1.1	0.93±1.2	**.01**	1.43±0.15	0.91±0.20	**.05**
Cholesterol (mg/d)	344 ±236	279±258	NS	371.0±31.8	264.0±35.7	NS
Omega 3 (g/d)	1.98±1.47	1.72±1.59	NS	1.79±0.20	1.84±0.20	NS
Omega 6 (g/d)	13.5±7.1	12.5±7.7	NS	12.2±0.9	13.3±1.0	NS
Omega 3/ Omega 6	0.15±0.10	0.15±0.11	NS	0.14±0.01	0.15±0.01	NS
Mono fat /saturated fat	1.16±0.57	1.27±0.62	NS	1.07±0.07	1.28±0.08	NS
Poly fat/saturated fat	0.66±0.41	0.70±0.44	NS	0.57±0.05	0.75±0.06	NS
Carbohydrates (g/d)	214±69.2	246±75.4	**.004**	216.0 ±9.4	246.0±10.6	NS
Protein (g/d)	85.0±24.6	81.5±26.9	NS	88.5±3.3	78.5±3.7	NS
Protein/bodyweight (g/kg)	0.88 ±0.42	1.07±0.45	**.005**	0.97±0.05	0.94±0.05	NS

* The results are from the linear mixed models using the full model that includes sex, group, sex×group, body mass index, age, and total energy intake as independent variables.

¥OA: Subjects who had moderate to severe osteoarthritis.

ΦSFA: Saturated fatty acids;

§TFA: Trans fatty acids

‡Variables are adjusted for all factors in the full model except total energy intake.

€ Significant P-values are bolded. P-values for other factors and adjusted mean for sex×group are presented in Table S1.

†Vit C (mg/d), Vit D (mg/d), Calcium (mg/d), Phosphorus (mg/d), Water (g/d), Fiber (g/d), Sugar (g/d), Vit K (mg/d), Vit B1 (mg/d) , Vit B3 (mg/d), and Vit B12 (mg/d) were dropped from Table 5.2 since they were neither significantly different nor our main interest.

Table 5.3. Regression correlation coefficients between self-reported and performance-based measures and each of physical activities and nutrients among the study population[§]

Variable		WOMAC Pain	WOMAC Stiffness	WOMAC Function	WOMAC Total Score	LEFS	6MWT	Stair Test
Intercept	**β***	-75.38	-99.1	-85.1	-83.6	169.4	1176	-25.2
	C.I[¥]	-120.8 to -29.8	-148 to -49	-130 to -39.8	-128 to -38	128 to 210	952 to 1400	-44.2 to -6.1
	p[‡]	.001	.0001	.0001	.0001	.0001	.0001	.01
Non-demographic factors (NDF)								
Steps (1000)	**β**	-1.90	-2.10	-1.70	-1.75	1.82	14.70	-1.13
	C.I	-3.7 to -0.2.2	-4.1 to -0.18	-3.4 to 0.09	-3.5 to 0.01	0.21 to 3.42	6.03 to 23.4	-1.88 to -0.39
	p	.03	.03	.06	.04	.02	.001	0.003
	p.R^{2}[€]	0.23	0.27	0.23	0.24	0.27	0.37	0.32
SFA (10 gr)	**β**	3.7	3.5	---[†]	---[†]	-4.9	-17.5	---
	C.I	-1.1 to 8.6	-1.4 to 8.4			-9.1 to -8.0	-41.6 to 6.2	
	P	.13	.15			.01	.15	
	p.R^{2}	0.07	0.04			0.07	0.06	
Trans (1 gr)	**β**	4.5	---[†]	5.8	5.6	---[†]	-18.8	---[†]
	C.I	-0.82 to 9.8		0.92 to 10.8	0.75 to 10.5		-45.1 to 7.52	
	p	.09		.02	.02		.15	
	p.R^{2}	0.03		0.06	0.06		0.02	
Demographic factors								
BMI(kg/m^{2})	**β**	0.47	0.98	0.55	0.58	-0.74	-5.29	0.46
	C.I	-0.14 to 1.09	0.31 to 1.65	-0.06 to 1.2	-0.02 to 1.2	-1.3 to -0.19	-8.34 to 2.24	0.20 to 0.72
	p	.13	.004	.07	.05	.009	.008	<.001
	p.R^{2}	0.01	0.04	0.02	0.02	0.03	0.04	0.07
Age (year)	**β**	1.35	1.70	1.59	1.56	-1.49	-9.7	0.53
	C.I	0.79 to 1.89	1.1 to 2.3	1.04 to 2.14	1.02 to 2.10	-1.9 to 0.98	-12.47 to -7.0	0.31 to 0.77
	p	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
	p.R^{2}	0.13	0.17	0.19	0.18	0.17	0.19	0.12
R^{2} of NDF		0.33	0.31	0.29	0.30	0.34	0.45	0.32
R^{2} for model		0.48	0.53	0.49	0.51	0.55	0.67	0.51
Adj. R^{2} for model		0.46	0.51	0.47	0.48	0.53	0.65	0.50

[§] = The full model included Steps, SFA, TFA, BMI, and Age.

*β = Beta; regression coefficients

[¥]C.I= Confidence Interval

[‡]P= P-Value

[€]p.R^{2} = Partial R squared

[†] This covariate was not included in the best linear subset modeling with minimization of Mallow's CP and maximizing R squared.

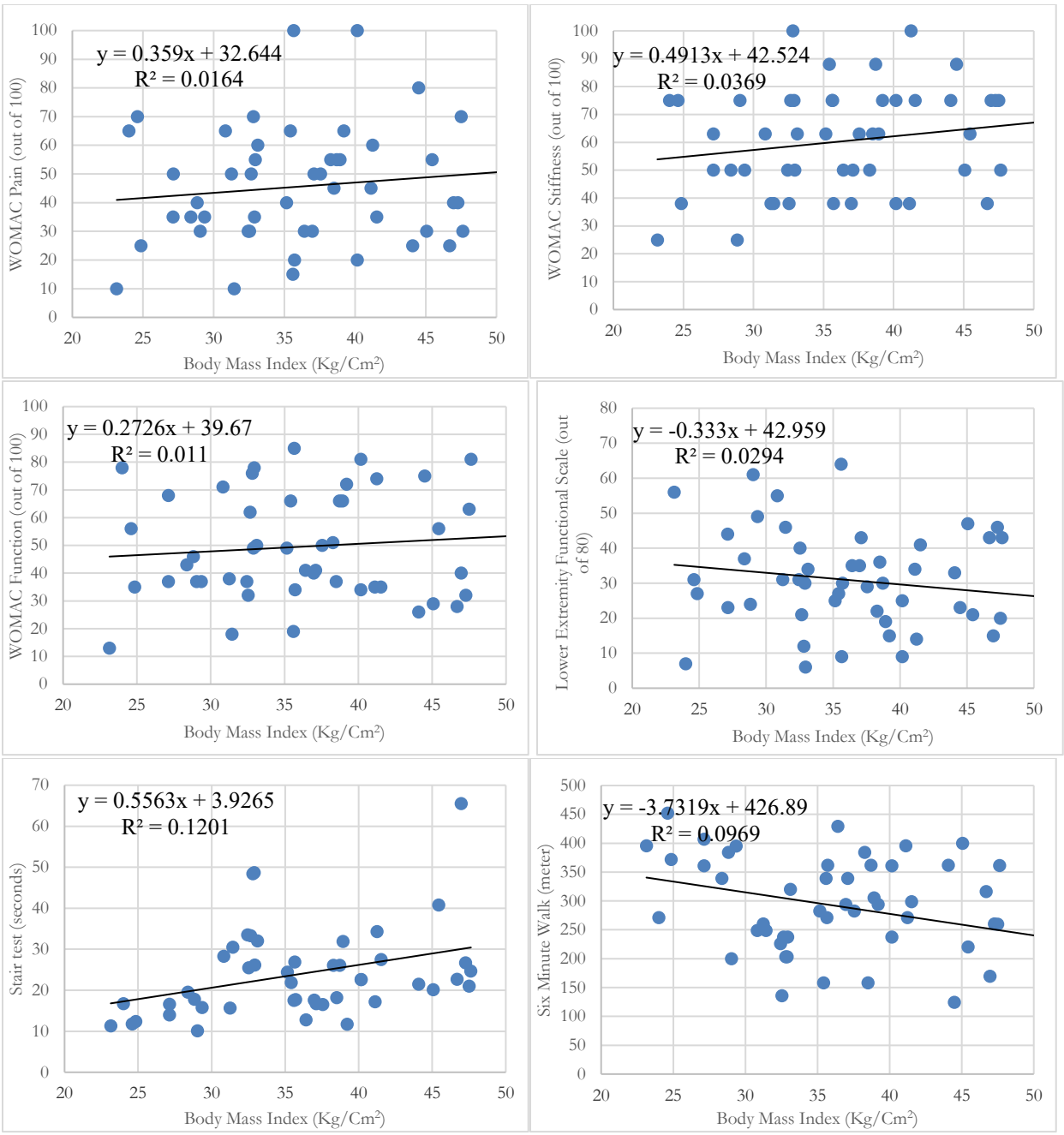

Figure 5.1. Scatter plot for each of self-reported and performance-based measures with Body Mass Index (Kg/Cm^2) within OA patient group only

5.7. Supplementary Materials

Table 5.1.S. Regression correlation coefficients and 95% confidence intervals for self-reported and performance-based function from univariate analysis among the study population

	Pain	Stiffness	Function	Total	LEFS	6MWT	Stair test
Variable							
1000 Steps/day	**-4.5 -6.2 to -2.8**	**-5.0 -7.5 to -3.7**	**-4.5 -6.2 to -2.8**	**-4.6 -6.3 to -2.9**	**4.7 3.0 to 6.0**	**34.0 25.0 to 40.0**	**-2.3 -3.0 to -1.6**
Distance (1000 meter)	**-6.1 -8.5 to -3.6**	**-7.4 -10.2 to -4.5**	**-6.0 -8.5 to 3.5**	**-6.1 -8.7 to -3.6**	**6.3 3.8 to 8.7**	**46.5 32.3 to 60.7**	**-3.11 -4.2 to -2.1**
Sedentary time (min)	**0.10 0.02 to 0.18**	**0.14 0.04 to 0.22**	**0.09 0.007 to 0.17**	**0.09 0.01 to 0.18**	**-0.10 -0.15 to 0.02**	**-0.99 -1.47 to -0.51**	**0.07 0.03 to 0.10**
Light active time (min)	-0.05 -0.15 to 0.03	-0.07 -0.17 to 0.02	-0.03 -0.12 to 0.05	-0.05 0.13 to 0.04	0.05 -0.04 to 0.13	**0.68 0.15 to 1.22**	**-0.05 -0.1 to -0.01**
Fairly active time (min)	**-0.56 -1.06 to -0.05**	**-0.65 -1.23 to -0.07**	**-0.60 -1.1 to -0.09**	**-0.60 -1.1 to -0.09**	**0.63 0.14 to 1.13**	**4.78 1.74 to 7.82**	**-0.32 -0.53 to -0.09**
Very active time (min)	**-0.66 -0.98 to -0.34**	**-0.80 -1.17 to -0.43**	**-0.70 -1.0 to -0.37**	**-0.70 -1.0 to -0.37**	**0.68 0.37 to 1.0**	**4.39 2.43 to 6.35**	**-0.24 -0.38 to -0.09**
Total energy (kcal/d) ‡	**0.01 -0.002 to 0.024**	0.01 -0.001 to 0.026	**0.01 0.001 to 0.03**	**0.01 0.001 to 0.03**	**-0.01 -0.03 to 0.01**	-0.07 -0.14 to 0.01	0.004 -0.00 to 0.00
Total fat (kcal/d)	**0.027 0.005 to 0.049**	**0.03 0.007 to 0.05**	**0.03 0.002 to 0.48**	**0.03 0.003 to 0.49**	**-0.03 -0.05 to -0.1**	**-0.19 -0.32 to -0.05**	**0.01 0.00 to 0.02**
Total fat (g/d)	**0.24 0.04 to 0.44**	**0.29 0.06 to 0.52**	**0.23 0.03 to 0.43**	**0.23 0.04 to 0.44**	**-0.28 -0.47to -0.08**	**-1.67 -2.91 to -0.42**	**0.09 0.01 to 0.18**
Saturated fat (kcal/d)	**0.096 0.04 to 0.15**	**0.09 0.02 to 0.1**	**0.08 0.27 to 0.15**	**0.09 0.03 to 0.15**	**-0.09 -0.15 to -0.35**	**-0.56 -0.94 to -0.17**	**0.03 -0.00 to 0.05**
Saturated Fat (g/d)	**0.86 0.32 to 1.41**	**0.82 0.19 to 1.45**	**0.80 0.24 to 1.36**	**0.82 0.27 to 1.37**	**-0.85 -1.38 to -0.32**	**-5.03 -8.45 to-1.61**	**0.25 -1.59 to 0.49**
Mono fat (g/d)	0.32 -0.13 to 0.78	0.49 -0.03 to 1.0	0.31 -0.15 to 0.77	0.32 -0.13 to 0.80	-0.36 -0.81 to 0.09	-1.51 -4.37 to 1.35	0.09 -0.11 to 0.29
Poly fat (g/d)	0.67 -0.14 to 1.48	0.73 -0.19 to 1.6	0.70 -0.11 to 1.53	0.69 -0.12 to 1.51	**-0.82 -1.62 to -0.02**	-4.9 -9.9 to 0.13	0.20 -0.16 to 0.57
Trans fat (g/d)	**10.2 4.3 to 16.0**	**8.4 1.5 to 15.3**	**9.8 3.8 to 15.8**	**9.7 3.7 to 15.7**	**-8.45 -14.3 to -2.6**	**-59.3 -96.2 to -22.4**	2.08 -0.69 to 4.85
Cholesterol (mg/d)	0.006 -0.02 to 0.04	0.01 -0.01 to 0.05	0.08 -0.02 to 0.38	0.08 -0.02 to 0.39	-0.02 -0.05 to 0.01	-0.13 -0.32 to 0.06	0.007 -0.01 to 0.02
Omega 3 (g/d)	2.2 -2.72 to 7.11	**1.8 -3.8 to 7.5**	2.3 -2.7 to 7.3	2.2 -2.8 to 7.2	-2.46 -7.3 to 2.4	**-31.9 -62.1 to -1.75**	1.4 -0.75 to 3.56
Omega 6 (g/d)	0.55 -0.39 to 1.49	0.58 -0.49 to 1.67	0.59 -0.36 to 1.56	0.58 -0.37 to 1.53	-0.73 -1.66 to 0.18	-4.05 -9.95 to 1.84	0.08 -0.34 to 0.50
Carbohydrate (g/d)	-0.08 -0.07 to 0.07	0.05 -0.08 to 0.07	-0.07 -0.06 to -0.07	0.05 -0.06 to 0.07	-0.01 -0.07 to 0.6	0.05 -0.39 to 0.48	-0.002 -0.03 to 0.03
Protein (g/d)	0.16 -0.07 0.39	0.11 -0.15 to 0.38	0.20 -0.03 to 0.44	0.19 -0.05 to 0.42	**-0.24 -0.48 to -0.02**	-0.95 -2.43 to 0.52	0.048 -0.06 to 0.15
BMI	**1.4 0.77 to 1.99**	**1.7 1.0 to 2.4**	**1.4 0.75 to 2.0**	**1.4 0.79 to 2.02**	**-1.52 -2.1 to -0.93**	**-11.2 -14.7 to -7.7**	**0.78 0.51 to 1.05**
Age	**1.9 1.33 to 2.41**	**2.3 1.7 to 2.9**	**2.04 1.5 to 2.58**	**2.03 1.50 to 2.56**	**-2.0 -2.5 to -1.5**	**-13.8 -16.8 to -10.7**	**0.79 0.55 to 1.0**

Significant correlations at the level of <0.01 are bolded. Significant correlations at the level of >0.01 and <0.05 are bolded and underlined. Significant correlations at the level of >0.05 and <0.20 are underlined.

Table 5.2.S. Adjusted means for physical activities and nutrients by sex within each group *

	Group (GRP)				p-value€				
	OA		Control		GRP	Sex	GRP× SEX	Age	BMI
	Male	Female	Male	Female					
Physical activity‡									
N	17	40	17	32					
Steps/day	5522±606	5116±527	7065±702	6613±504	**.04**	**.10**	NS	NS	**<.001**
Distance (meter)	3930±44	3500±38	4510±51	4480±37	NS	NS	NS	NS	**<.001**
Sedentary time (min)	1250±15.3	1272±13.3	1283±17.7	1259±12.7	NS	NS	NS	NS	**<.001**
Light active time (min)	180±14.8	154±12.9	127±17.1	162±12.3	NS	NS	**.02**	NS	**<.001**
Fairly active time (min)	6.8±2.5	6.7±2.20	11.6±2.93	6.6±2.11	NS	NS	NS	NS	NS
Very active time (min)	3.43±3.7	7.1±3.2	18.0±4.3	13.4±3.1	**.02**	NS	NS	NS	NS
Nutrients†									
N	16	37	16	29					
Energy intake (kcal/d) ‡	2219±100	2078±82.0	2111±115	1642±83.1	**.02**	**<.001**	**.05**	NS	NS
Fat (kcal/d)†	718±46.9	796±37.6	667±52.7	701±41.0	NS	NS	NS	NS	NS
Fat (g/d)	80.0±5.2	88.8±4.2	74.3±5.8	78.0±4.6	NS	NS	NS	NS	NS
Saturated fat (kcal/d)	256±19.0	245±15.2	209±21.3	199±16.6	**.04**	**.01**	NS	NS	NS
Saturated fat (g/d)	28.5±2.1	27.2±1.7	23.2±2.4	22.1±1.8	**.04**	**.01**	NS	NS	NS
Mono fat (g/d)	26.9±2.7	31.3±2.2	26.2±3.0	28.3±2.4	NS	NS	NS	NS	NS
Poly fat (g/d)	13.8±1.5	15.8±1.3	13.2±1.7	17.8±1.3	NS	NS	NS	NS	NS
Trans fat (g/d)	1.6±0.2	1.3±0.2	0.8±0.2	1.1±0.2	**.05**	NS	NS	NS	NS
Cholesterol (mg/d)	403±41.9	239±36.8	292±51.5	236±14.1	NS	**.05**	NS	NS	NS
Omega 3 (g/d)	1.7±0.3	1.8±0.2	1.6±0.3	2.1±0.2	NS	NS	NS	NS	NS
Omega 6 (g/d)	11.6±1.3	12.8±1.1	11.5±1.5	15.0±1.2	NS	NS	NS	NS	NS
Omega 3/ Omega 6	0.15±0.02	0.16±0.02	0.15±0.02	0.14±0.01	NS	NS	NS	NS	NS
Mono fat /saturated fat	0.9±0.1	1.2±0.1	1.2±0.1	1.3±0.1	NS	**.04**	NS	NS	NS
Poly fat/saturated fat	0.5±0.1	0.6±0.1	0.7±0.1	0.8±0.1	NS	**.007**	NS	NS	NS
Carbohydrates (g/d)	220±13.6	212±10.9	251±15.3	241±11.9	NS	**<.001**	NS	NS	NS
Protein (g/d)	92.3±4.7	84.8±3.8	76.9±5.4	80.0±4.2	NS	**.002**	NS	NS	NS
Protein/bodyweight (g/kg)	0.95±0.06	0.99±0.05	0.82±0.07	1.04±0.05	NS	NS	NS	NS	**<.001**

* The results are from the multiple regression of the full model that includes sex, group, sex × group, body mass index, age, and total energy intake as independent variables.

¥OA: Subjects who had moderate to severe osteoarthritis.

‡Variables are adjusted for all factors in the full model except total energy intake.

€ Significant P-values are bolded.

†Vit C (mg/d), Vit D (mg/d), Calcium (mg/d), Phosphorus (mg/d), Water (g/d), Fiber (g/d), Sugar (g/d), Vit K (mg/d), Vit B1 (mg/d) , Vit B3 (mg/d), and Vit B12 (mg/d) were dropped from Table 5.2.S since they were neither significantly different nor our main interest.

Chapter 6

General Discussion and Conclusion

6.1. Introduction

Osteoarthritis (OA) is a heterogeneous disorder characterized by progressive loss of cartilage, alteration of adjacent bones, and the associated local low-grade inflammation. Among all joints, knee is the most commonly affected joint [273]. In the last few years, the concept of OA has evolved from being a mechanical wear and tear condition to a systemic disease that affects joint mechanics and function and interacts with the body as a whole [58]**.** The overall treatment goal of OA is to relieve pain, as well as to improve function and health-related quality of life [5, 6]. In the absence of disease-modifying treatments, guidelines recommend targeting modifiable risk factors [7-9]. In all stages of knee OA, identifying and addressing modifiable risk factors is essential in managing OA, including the trajectory of recovery following total knee arthroplasty (TKA) [10]. Modifiable risk factors related to lifestyle, such as obesity, dietary imbalance, and physical inactivity, might alter disease onset and progression through a combination of mechanical and systemic mechanisms [8, 10]. The purpose of this work was to identify modifiable risk factors including obesity, nutrient intake, and physical activity in patients with knee osteoarthritis and examine their association with performance-based (6MWT and stair test) and self-reported outcome measures (WOMAC subscale and LEFS). In the following sections, I will describe the main hypotheses of my thesis. Then, I will discuss the main results of each study, overall strengths and limitations, and recommendations for future studies.

6.2. Hypotheses and Main Results

In study 1, it was hypothesised that 1) higher BMI groups categorized according to the World Health Organization (WHO) would have the same odds of perioperative/postoperative

complications compared to normal BMI group; 2) patients with comorbidities would have the same odds of perioperative/postoperative complications compared to patients without comorbidities. Based on the results of this study, both hypotheses were rejected; patients with higher BMI were more likely to have pulmonary embolism, deep wound infection, as well as readmission within 30 days post TKA compared to patients with normal BMI. In addition, patients with comorbidities were more likely to have blood transfusion, infection, pulmonary embolism, and be readmitted to the hospital within 30 days post TKA compared to patients with no comorbidities. In study 2, it was hypothesised that 1) WOMAC subscales scores would be same across all BMI groups preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months following TKA; 2) EQ5D index would be same across all BMI groups preoperatively, pre- to 3 months postoperatively, as well as 3 to 12 months following TKA. These two hypotheses were retained since patients across all BMI groups had similar WOMAC subscales and EQ5D index preoperatively and at different time intervals, following surgery. In study 3, it was hypothesised that 1) patients with moderate to severe unilateral knee OA will have same steps/day and fat intake (SFA and TFA) compared to healthy controls; 2) steps/day and fat intake (SFA and TFA) would be associated with WOMAC subscales, LEFS, 6MWT, and stair test. The results of study 3 demonstrated that patients with knee OA walked fewer steps/day, but had higher levels of total energy intake, SFA, and TFA intake compared to the healthy control group. Increase in steps/day and reduction in SFA and TFA intake were associated with better performance-based (6MWT and stair test) and self-reported outcomes (WOMAC subscales and LEFS).

6.3. Risks and benefits of TKA in patients with higher BMI

Total knee arthroplasty is a commonly used and effective intervention for severe arthritis. Although the effectiveness of arthroplasty has been well documented [201, 220, 221, 226],

surgeons remain hesitant to perform the surgery on patients with higher BMI (>30kg/m^2), and they reluctant to put patients on the waiting list for surgery, believing that the surgery is not appropriate and has a high risk for these patients. All patients with a BMI higher than 30 usually receive a uniform recommendation and are linked to optimization programs, including the Arthritis Society's Lifestyle Makeover Challenge and Weight Watchers before the surgery to optimize their weight [274]. Surgeons make these decisions based on the evidence from available literature on the association between obesity and TKA outcomes that has grouped patients into BMI below or above 30 kg/m^2 [164]. It is almost universally agreed that the risks of TKA are higher among patients with obesity (BMI>30kg/m^2) [164, 165]. Increased rates of wound-healing complications, superficial and deep infections, early revisions, and poor functional outcomes following TKA have been reported in patients with BMI>30 kg/m^2 [164, 165]. However, defining obesity simply based on BMI below or above 30 kg/m^2 leaves out critical information because the degree of obesity also plays an important role in determining the risk of adverse outcomes following TKA. There is limited information about the risks and benefits of the TKA with regard to different grades of BMI categorized according to the World Health Organization (WHO) classification [157]. Understanding the risk and benefits of surgery for different groups of BMI would help surgeons and health care professionals provide each patient with realistic expectations for recovery in regard to their BMI, and to help them understand the risks and benefits of the proposed intervention.

In study 1, using the WHO classification of obesity, we found the likelihood of having different complications varied among different grades of BMI. Obese class I and II groups had higher odds of one complication (pulmonary embolism), whereas the Class III group had higher odds of three complications (pulmonary embolism, deep wound infection a readmission within 30-days) compared to normal BMI group, suggesting that only higher grades of obesity might lead to

adverse effects following TKA [174]. It is noteworthy that patients with obesity were less likely to have blood transfusions. Since patients with higher BMI have larger blood volume, the actual rate of blood volume loss following TKA might be lower in these patients, which could eventually lead to lower rates of blood transfusion compared to patients with normal BMI [182, 275].

Since patients in the higher spectrum of BMI (especially class III) are at a greater risk of poor outcomes, surgeons remain uncertain about whether these patients receive similar benefits (reduced pain, improved function and quality of life) from TKA compared to patients in the normal BMI group [276]. In study 2, we demonstrated that all patients regardless of their BMI received similar benefits from surgery in terms of pain and function and quality of life at 12 months following TKA, though our patients had higher level of WOMAC pain and function scores compared to the US patients at 12 months following TKA [221]. One plausible explanation is that Canadian patients who undergo TKA spend more time on waiting lists, which has been shown to result in progressive loss of mobility, deterioration in pain and health-related quality of life, and high psychological distress [276, 277]. Thus, patients with long waiting time for surgery start from a lower level of functional reserves and mental health. This may explain the comparatively worse outcomes of surgery in Canadians in terms of pain, function, and health-related quality of life following TKA [221, 277]. In Canada, 6 months waiting time is considered as a benchmark for the knee replacement surgery. The proportion of patients receiving surgery within the recommended benchmark timeframe varied from 42% to 89% for knee replacement across all provinces; 69% of patients in Alberta received care within the benchmark [274]. Given that postponing the surgery for a longer time would lead to the higher levels of self-reported and quality of life after surgery [278]. Then, surgery should not be delayed to the point that deteriorates preoperative pain, function, and quality of life in patients.

Overall, the first two studies of this thesis on the risks and benefits of TKA for patients with knee OA provide insight into the relationship between different grades of obesity on complications and functional recovery following TKA. Obesity places patients at increased risk of adverse events after TKA [174, 279], though the level of risk depends on the severity of obesity [174]. However, not only did patients with obesity experience improvement in pain and function, but, at 12 months following TKA, they achieved outcomes similar to those of patients in the normal BMI group. The clinical implication of these two studies for surgeons and healthcare providers is that the resistance to performing TKA in patients with BMI >30 may be unwarranted. The current practice of denying and postponing the surgery in patients with BMI higher than 30 [280, 281], has been shown to impair pain, function and deteriorate health related quality of life [276, 277]. Then, it is recommended that health care professionals educate patients in higher BMI groups about realistic expectations for recovery and provide different resources to manage the patients' weight [62]. However, as indicated in the newly released obesity guidelines, weight loss should not be imposed on everyone with a high BMI and should be done in collaboration with patients [62]. An important takeaway is that healthcare providers and surgeons should consider performing TKA in patients with high BMI in the absence of weight loss or willingness to lose weight as studies show that delaying the surgery will lead to worse outcomes as well as higher anxiety and depression in patients [278]. Health care providers should address patients' willingness and mental health status, address the root causes of obesity, and provide different resources to design an individualized treatment program [62]. The main message from these two studies is that while it is important to recognize and work vigorously to collaborate with patients to minimize complications, delaying the surgery in all patients with BMI >30 might be unwarranted.

6.4. Dietary Fat Intake, Physical Activity, and Their Relationship with Osteoarthritis Symptoms

Given that physical activity and nutrition have been recommended by clinical practice guidelines as important modifiable risk factors to be considered in the management of OA [100, 103] the assessment and monitoring of these factors in relation with performance-based and self-reported measures are essential [103]. As shown in study 3, we found that patients with knee OA walked fewer steps and had higher levels of total energy intake, SFA, and TFA compared to the healthy participants. The lower amount of steps/day in patients with knee OA was expected since it has been reported that these patients limit their level of actual physical activity to avoid pain or due to their inability to perform certain activities. Another possible contributor to fewer steps/day in patients with knee OA is the fear of movement or kinesiophobia, stemming from the belief that physical activity will cause pain, and re-injury [282]. Higher intake of calories specifically from SFA and TFA in our patient group may be related to their lifestyle practices [283].

We also demonstrated that an increase in steps/day and reduction in SFA and TFA intake were associated with better performance-based (6MWT and stair test) and self-reported outcomes (WOMAC subscales and LEFS). Activities such as walking are beneficial in reducing pain and disability in people with knee OA [33, 35]. The mechanism behind these benefits might be related to reduced systematic concentration of pro-inflammatory cytokines such as TNF-α and CRP levels and increased anti-inflammatory cytokines such as IL-6 [284]. Other mechanisms such as improvement in joint proprioception, muscle strength, and balance may also play a role [285, 286]. In addition, SFA and TFA may act differently to regulate skeletal muscle, function, and pain. In an experimental study with cultured muscle cells [287], SFA administration to muscle cells has been reported to increase the expression of pro-atrophic genes [288] and loss of muscle fibers, which has been linked to functional impairment in patients with OA [289]. High fat diet also

elevates FFAs and cytokines in the circulatory systems, which trigger inflammatory pathways and may lead to pain and impaired mobility, which are the key clinical features of OA.

The results of the third study have clinical implications for health care providers and patients in the context of OA symptom management. The improvement in self-reported and performance-based outcomes may be achieved with dietary changes (including reducing TFA and SFA intake) and increased walking that are both feasible and realistic. For example, increasing 1000 steps/day combined with 10 gr decrease in SFA intake (roughly equivalent to half a tablespoon of butter or oil) and eliminating TFA from daily diet (1.45 gr/day; half a teaspoon of shortening) would be associated with clinically meaningful improvement in WOMAC pain (MCID=7.09) and function (MCID=11.25) [214]. The findings of this study contribute to the knowledge of the physical activity (walking) habits of patients with the common chronic condition of knee OA. Importantly, walking more and consuming lower intake calories/day from SFA and TFA were associated with improved physical function and reduced pain. Therefore, promoting physical activity in patients with knee OA may help reduce pain, maintain functional independence and delay the onset of disability.

6.5. Strengths and Limitations

The first and second studies of this thesis included the dataset routinely checked by ABJHI for quality assurance. These data were extracted from the provincial database of patients who underwent TKA between 2012 and 2019. Patients were categorized into five groups, based on the WHO classification, which allowed us to examine the impact of different levels of BMI on complications and comorbidities following TKA. Weight and height measures were recorded in the clinics and not self-reported, which provide more reliable results. For the second study, large samples of patients (N=7714) with WOMAC scores and EQ5D index (N=3848) were extracted.

This large dataset provided sufficient sample size and statistical power within each of the five levels of BMI to draw conclusions about the impact of different levels of BMI on surgery outcomes. There are some limitations related to this dataset that need to be acknowledged. Forty-three percent of patients had missing weight and height records, and thus were excluded from our analyzed dataset. However, there were no significant differences in demographics or physical characteristics between the excluded and included cohorts. Only perioperative and postoperative complications within 30 days of TKA were examined, but many of the potential postoperative complications may have occurred after this time period and thus are not reflected in the data set. Patients who had baseline and at least 1 follow-up visit (postoperative month 3 or 12) for WOMAC and EQ5D questionnaires were included in the analysis. However, linear mixed effect models used to analyze the data allow for missing data. We also defined obesity based on BMI which is not a measure of body composition; as higher BMI can be the result of either greater fat or fat-free mass [193]. Other measures of obesity such as waist circumference or classification methods such as Edmonton Obesity Staging System [194] could be considered as an alternative method/assessment model to study their association with surgery outcomes. This is discussed in more detail under the "Future Studies" section.

The third study of this thesis is the first-in-its-kind to examine the physical activity and nutrient intake among patients with knee OA comparing them with that of healthy controls. This study also demonstrated the relationship between dietary intake of SFA and TFA and self-reported or performance-based measures of pain and physical function. Physical activities were objectively measured using an accelerometer, and food intake was monitored for 3 days and later followed up by phone calls to assure the accuracy of intake data. This study was a cross-sectional and thus we cannot infer causality of the observed associations. A prospective longitudinal study with a larger

sample size is needed to confirm the association between nutrient intake, physical activity, and symptoms of OA. In this study, we used an accelerometer, and it is also possible that participants become more encouraged to be more active when wearing an accelerometer (i.e. Hawthorne Effect). To minimize this effect, the accelerometer used in this study did not provide feedback to the participants. This study was matched for sex, but not age and BMI. Further investigation showed that there is no or very weak association between BMI and the outcome measures. We also adjusted for potential confounders such as BMI and age in the analyses, which has been recommended in the literature in the analysis of the unmatched groups [258].

6.6. Future Studies

Obesity is the most common comorbidity among patients with osteoarthritis, and the rise in prevalence of obesity made surgeons acutely aware of the implication of this comorbidity. Our results, in line with other studies [174, 279], showed that patients with higher BMI were more likely to be at a higher risk for peri/postoperative complications and receive similar benefits in terms of health outcomes. However, the risk and benefits associated with BMI >50 kg/m^2 is still unclear for surgeons [197]. Future studies are suggested to investigate the risks and benefits of TKA in patients with BMI >50 kg/m^2. Our results also demonstrated that patients with higher BMI compared to patients with normal BMI received similar benefits from TKA in terms of self-reported pain, function, and quality of life measures. However, further investigation is needed on the association between BMI levels with performance-based outcomes such as 6MWT following TKA.

The anthropometric classifications of obesity using BMI and waist circumference (WC) are useful in population studies and have played a key role in demonstrating the increase in obesity and its relationship to morbidity and mortality [194]. However, these anthropometric measures

have well-known limitations when it comes to guiding clinical decisions on an individual level [194]. For example, BMI can not be used to directly differentiate lean and fat tissue. Thus, at a given BMI, substantial variation in adiposity can occur [290]. There is also a large inter-individual variation in the amount of visceral fat present in individuals with the same WC [291]. As indicated in the new obesity guideline, anthropometric measures of obesity do not directly reflect on the presence of health risks such as comorbidities. In the recently-released Canadian Obesity Guideline, Obesity is defined as "a chronic disease characterized by excessive or abnormal body fat that impairs health" and a shift from anthropometric measures of obesity towards a comorbidity-centred approach has been recommended [62]. This shift may also help differentiate and detect individuals with health risks related to body composition. Several alternative clinical staging systems and assessment models that have incorporated the health risks and comorbidities into the assessment have been recommended [292]. One possible method/assessment model is the Edmonton Obesity Staging System (EOSS). It is a five-stage obesity classification system that considers the obesity-related comorbidities, physical, and psychological parameters in order to determine the optimal obesity treatment (Table 6.1). It is intended to complement the anthropometric measures [194].

A recent review examined the usefulness of the EOSS for stratifying the presence and severity of weight-related health problems in clinical and community settings [293]. They provided support for the usefulness of EOSS in clinical practice to predict the risks of complications and benefits of surgical and non-surgical weight management. They also summarized that although EOSS may be useful in guiding informed treatment and prioritizing decisions to optimize patient outcomes, it should be applied with caution for population health planning due to the inconsistency of study results [293]. In the current study, BMI has been used as a measure of obesity, however, as the

recently released obesity guideline on obesity pointed, BMI is not able to reflect on the presence of health risk. Then, further studies need to investigate the impact of obesity using EOSS system on the surgery outcomes in patients who undergo TKA since EOSS considers the presence of health risk to classify obesity.

Walking and light activities are the most common form of activities that patients with moderate to severe knee OA participate in. Dietary imbalance also plays an important role in the initiation and progression of many chronic diseases [232-234], including OA. The findings from the third study of this thesis demonstrated that steps/day and SFA and TFA intakes are associated with self-reported and performance-based measures. Future studies are needed to evaluate the impact of ambulatory activities (walking) and nutrient intake (SFA and TFA) on OA disease progression in patients with mild / at risk of OA. The effectiveness of the intervention could be assessed using biological biomarkers of disease activity such as synovial fluid, serum, and sophisticated imaging modalities such as MRI [25]. Diets consist of multiple components that make the association between diet and disease progression multifaceted [294, 295]. Studies are needed to understand the interaction between dietary components with biological markers of inflammation (e.g., C-reactive proteins) and symptomatic and/or radiographic progression of OA. This will serve to develop future clinical nutrition guidance in patients with osteoarthritis [296].

6.7. Conclusion

Taken as a whole, the findings of these three studies provide valuable information that furthers our understanding of the interplay between obesity, physical activity, SFA, and TFA in relation to health-related outcomes in patients with knee OA. The key findings of this thesis were that patients with knee OA who had a higher BMI or comorbidities were more likely to experience peri/postoperative complications following TKA. Furthermore, patients with knee OA who had a

higher BMI achieved similar benefits with respect to self-reported pain, physical function, stiffness, and quality of life at 12 months, and most of the improvement occurred by 3 months following TKA. This study highlights the importance of physical activity and nutrition as modifiable risk factors across the study populations. Subjects who had higher levels of SFA and TFA intake had worse performance-based and self-reported outcomes, while subjects who were more active (had more steps/day) had better performance-based and self-reported measures of function and pain.

Table 6.1. Edmonton Obesity Staging System [194]

Stage	Description	Management
1	No apparent obesity-related risk factors (e.g., blood pressure, serum lipids, fasting glucose, etc. within normal range), no physical symptoms, no psychopathology, no functional limitations and/or impairment of well being	Identification of factors contributing to increased body weight. Counseling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity.
2	Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g., dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations and/or mild impairment of well being	Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status.
3	Presence of established obesity-related chronic disease (e.g., hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living and/or well being	Initiation of obesity treatments including considerations of all behavioral, pharmacological and surgical treatment options. Close monitoring and management of comorbidities as indicated
4	Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations and/or impairment of well being	More intensive obesity treatment including consideration of all behavioral, pharmacological and surgical treatment options. Aggressive management of comorbidities as indicated.
5	Severe (potentially end-stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well being	Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy and psychosocial support.

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Appendix A - Ethics approval

Approval Form

Date:	June 9, 2015
Study ID:	Pro00053754
Principal Investigator:	Linda Woodhouse
Study Title:	Impacts of obesity on quality of life, function, and pain after total knee arthroplasty
Approval Expiry Date:	Wednesday, June 08, 2016

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application, including the following documents, has been reviewed and approved on behalf of the committee;

- Proposal (3/16/2015)
- List of Variables (6/3/2015)

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a retrospective review of anonymized BJHSCN administrative data for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (Wednesday, June 08, 2016), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-6041. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Anthony S. Joyce, Ph.D.
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix B - Ethics approval

Notification of Approval

Date:	February 20, 2019
Study ID:	Pro00083386
Principal Investigator:	Fatemeh Baghbaninaghadehi
Study Supervisor:	Linda Woodhouse
Study Title:	**Dietary intake and physical activity of patients with osteoarthritis (OA) compared to healthy non-OA participants**
Approval Expiry Date:	Wednesday, February 19, 2020
Approved Consent Form:	Approval Date — Approved Document 2/20/2019 — AppendixE- Consent form 2/20/2019 — Appendix D-info sheet for control 2/20/2019 — Appendix D-info sheet for OA patients

Thank you for submitting the above study to the Research Ethics Board 2. Your application has received a delegated review and been approved on behalf of the committee.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Research Ethics Board does not encompass authorization to access the staff, students, facilities or resources of local institutions for the purposes of the research.

Sincerely,

Ubaka Ogbogu, LLB, BL, LLM, SJD
Chair, Research Ethics Board 2

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix C - Ethics approval

Edmonton Bone and Joint Centre
Alberta Hip and Knee Clinic
#2068 9499 – 137 Avenue
Edmonton, AB T5E 5R8

February 19, 2019

Dear Dr. Woodhouse;

We are writing to advise you about your research at the Edmonton Bone and Joint Centre entitled:
Dietary intake and physical activity of patients with osteoarthritis (OA) compared to healthy non-OA participants

We discussed your project on February 19, 2019.

Your project request was:

	Approved NOTE: Please respond in writing or by email to confirm that you will proceed with the research and the anticipated start date.
X	Approved with the following caveats: ○ Recruitment needs to be done only at the screening clinic to enroll non-operative patients. ○ There are concerns regarding matching across the groups. OA group is more likely to be older with higher BMI compared to the healthy group. ○ When ready to recruit, please contact: ▪ Denise Hill, Executive Director Phone: (780) 377-1414 e-mail: dhill@edmontonboneandjoint.ca NOTE: Please respond in writing or by email to confirm that you will proceed with the requested changes before starting your research.
	Not Approved

If you have further questions or concerns, please feel free to contact me at 780-492-8626 or by email at lauren.beaupre@ualberta.ca

Edmonton Bone and Joint Centre Research Approval Committee

Appendix D - Flyer

Participant needed for physical activity and dietary intake study

We are looking for volunteers:

- **45-75 years old**
- **No lower extremity injuries**
- **Able to walk or climb one flight of stairs**

You will be asked to :

- **Attend only one visit to perform tests and complete a 3-day food and activity monitoring**

Your visit will take 45 min and you will complete :

- **6 -Minute walk around cones set 20 meter apart**
- **Stair test** (Walking up and down the 9 steps in your usual manner)
- **2 Questionnaires**

Interested ?

Contact Fatemeh Baghbani. PhD Cand. Rehabilitation Medicine
Phone:
Email: baghbani@ualberta.ca
Exercise Physiology Lab, University of Alberta- Corbett Hall , 1-3, 8205, 114 ST NW

University of Alberta Ethics ID:pro00083386

Appendix E - Information sheet for patients with OA

Title of Study: Dietary Intake and Physical Activity of People with Knee Osteoarthritis (OA).

Principal Investigator:

Dr. Linda Woodhouse Phone: E-mail: linda.woodhouse@ualberta.ca

Co-Investigators:

Dr. Susan Armijo Olivo Phone: E-mail: sla4@ualberta.ca
Dr. Carla Prado Phone: E-mail: carla.prado@ualberta.ca
Dr. Mary Forhan Phone: E-mail: forhan@ualberta.ca
Dr. Leah Gramlich Phone: E-mail: lg3@ualberta.ca

Study Coordinator:

Fatemeh Baghbani, MSc, PhD Candidate
Phone: E-mail: baghbani@ualberta.ca

Why am I being asked to take part in this research study?

There are two main risk factors to OA. Risks that we cannot control such as genetics, sex, age and the ones that we have control over, which are called modifiable risk factors. Modifiable risk factors consist obesity, physical activity, and diet. Guidelines recommend targeting modifiable risk factors to manage swelling and the associated pain. In this study, we are focusing on modifiable risk factors including physical activity and diet. Osteoarthritis studies in animals showed that consuming high amount of fat in the diet flares up inflammation throughout the body through circulation and triggers OA-like changes in knee. Studies have also shown that regular physical activity reduces swelling and the associated symptoms. However, there are a lack of studies on humans determining the amount of fat intake and physical activity in patients with OA and examining the relationship between dietary fat/physical activity and OA symptoms. In this study, we will determine whether participants with OA eat more fat in their daily diet or are less physically active than healthy controls. We will also determine that whether OA symptoms are related to dietary fat intake or level of physical activity. We will recruit a total of 120 participants; 60 with knee OA and 60 healthy controls without any lower extremity OA.

What is the reason for doing the study?

We will monitor your dietary intake and physical activity; we will compare your results with those of healthy controls. We hope to understand the relationship between your OA symptoms, dietary intake, and physical activity. This study is the basis to understand the lifestyle of patients with OA.

What will I be asked to do?

If you agree to participate, you will be asked to attend only one clinic visit, which will take about 45 minutes. The day and time of your visit will be decided by you and the study coordinator. At your clinic visit, you will be asked to complete two questionnaires. Performance-based functional measures of stair test, and Six Minute Walk Test (6MWT) will also be collected. The study coordinator will then show you how to complete a three-day food recall and use a Fitbit device to monitor your physical activity level (steps/day) for three consecutive days (2 weekdays and one weekend day). You should not change your usual activity level or diet during these three days.

Variable	First visit	Day one	Day two	Day three
Height	*			
Weight	*			
Waist circumference	*			
6MWT	*			
WOMAC	*			
Stair test	*			
LEFS	*			
Dietary intake		*	*	*
Physical activity		*	*	*

If you were interested, then the healthcare provider will introduce the researcher to you. Then, study coordinator will meet with you to explain the study in detail. Once any and all of your questions have been answered, you will be asked to sign the consent form. Then, your height, weight, and waist circumference will be measured, and you will be asked to walk for about 6 minutes. You will walk back and forth around cones set 20 meters apart. This is a very low risk of physical discomfort with this test. Then, the research coordinator will ask you to complete WOMAC questionnaire. Then you will complete second performance-based test. In this test you will be asked walk up and down one flight of stairs in your usual manner and at a comfortable speed. Then, you will be asked to complete the second questionnaire and the researcher will instruct you on how to complete a three-day food recall and use a Fitbit device to monitor your physical activity level (steps/day) for three consecutive days.

The study coordinator will call or email you three days after your visit to make sure that you have completed your food dairy and used Fitbit device on for 2 weekdays and one weekend day. You will also be reminded to bring back the Fitbit and food dairy to the clinic or to research coordinator office at Exercise Physiology Lab located at Corbett Hall.

What are the risks and discomforts?

The risk of flare-ups or temporary physical discomfort associated with the 6minute walk or stair test is very low. The test will be done by a trained researcher and in a supervised environment, which lowers the risk further than that encountered in everyday life. In addition, you will determine how hard you push yourself.

What are the benefits to me?

There are no direct benefits to you for participating in this study. We hope the study will give us more information about bodies' reaction to the diet and exercise in patients with OA. After the completion of the study, we will provide you with a summary of your results. Then, you will learn about the amount of calories you have burned each day, your activity level and dietary intake.

Do I have to take part in the study?

No. Taking part in this study is your choice. You may stop participating in the study at any time. You are free to leave the study at any time by contacting the study coordinator, without having to give a reason and without affecting your future medical care.

Will I be paid to be in the research?

No, there will be no payment. There is also no cost associated with participating.

Will my information be kept private?

During the study, we will collect your health information. This will be kept private, and we will not release your information containing your name outside of the study investigator's office and it will not be listed in the research when published. We will create an excel file with your ID linked to the study data we collect. The file will be encrypted and only PI and the research coordinator (Fatemeh Baghbani) will have access to it. Beyond that, the collected data and input will remain anonymous. By signing this consent form you are giving permission for the study staff to collect your health information and use it for research purposes. We will remove all your identifiable information. If you leave the study, we will not collect any new information from you.

What if I have questions?

If you have any questions about the research now or later, please contact the principal investigator (Dr. Linda Woodhouse) or the study coordinator (Fatemeh Baghbani) to answer any questions you have about this study.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780.492.2615. This office has no affiliation with the study investigators.

Appendix F - Information sheet for healthy participants

Title of Study: Dietary Intake and Physical Activity of People with Knee Osteoarthritis (OA).

Principal Investigator:

Dr. Linda Woodhouse Phone: E-mail: linda.woodhouse@ualberta.ca

Co-Investigators:

Dr. Susan Armijo Olivo Phone: E-mail: sla4@ualberta.ca
Dr. Carla Prado Phone: E-mail: carla.prado@ualberta.ca
Dr. Mary Forhan Phone: E-mail: forhan@ualberta.ca
Dr. Leah Gramlich Phone: E-mail: lg3@ualberta.ca

Study Coordinator:

Fatemeh Baghbani, MSc, PhD Candidate Phone: , E-mail: baghbani@ualberta.ca

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Why am I being asked to take part in this research study?

There are two main risk factors to Osteoarthritis (OA). Risks that we cannot control such as genetics, sex, age and the ones that we have control over, which are called modifiable risk factors such as obesity, physical activity, and diet. Guidelines recommend targeting modifiable risk factors to manage swelling and the associated pain. In this study, we are focusing on modifiable risk factors including physical activity and diet. Osteoarthritis studies in animals showed that consuming high amount of fat in the diet flares up inflammation throughout the body through circulation and triggers OA-like changes in knee. Studies have also shown that regular physical activity reduces swelling and the associated symptoms. However, there are a lack of studies on humans determining the amount of fat intake and physical activity in patients with OA and examining the relationship between dietary fat/physical activity and OA symptoms. In this study, we will determine whether participants with OA eat more fat in their daily diet or are less physically active than healthy controls. We will also determine that whether OA symptoms are related to dietary fat intake or level of physical activity. We will recruit a total of 120 participants; 60 with knee OA and 60 healthy controls without any lower extremity OA.

What is the reason for doing the study?

We will monitor your dietary intake and physical activity; we will compare your results with that of patients with knee OA. We hope to understand the relationship between the OA symptoms, dietary intake, and physical activity in patients with OA. This study is the basis to understand the lifestyle of patients with OA.

What will I be asked to do?

If you agreed and eligible to participate, you will be asked to attend only one visit, which will take about 45 minutes. The day and time of your visit will be decided by you and the study coordinator. Then, you will visit the researcher in the Exercise physiology Lab located at Corbett Hall and the researcher will provide you with an information sheet and a consent form to sign. In that visit, you will be asked to complete two questionnaires. Performance-based functional measures of stair test, and Six Minute Walk Test (6MWT) will be collected. Then, study coordinator will show you how to complete a three-day food recall and use a Fitbit Zip to monitor your physical activity level (steps/day) for three consecutive days (2 weekdays and one weekend day). You should not change your usual activity level or diet during these three days.

Variable	First visit	Day one	Day two	Day three
Height	*			
Weight	*			
Waist circumference	*			
6MWT	*			
WOMAC	*			
Stair test	*			
LEFS	*			
Dietary intake		*	*	*
Physical activity		*	*	*

If you were interested to participate in the study, then, study coordinator will meet with you to explain the study in detail, answer any and all questions, and you will be asked to sign the consent form. Then, your height, weight, and waist circumference will be measured, and you will be asked to walk for about 6 minutes. You will walk back and forth around cones set 20 meters apart. This is a very low risk of physical discomfort with this test. Then, the research coordinator will ask you to complete WOMAC questionnaire and you will complete second performance-based test. In this test, you will be asked to walk up and down one flight of stairs in your usual manner and at a comfortable speed. Then, you will be asked to complete the second questionnaire and the researcher will instruct you on how to complete a three-day food recall and use a Fitbit device to monitor your physical activity level (steps/day) for three consecutive days.

The study coordinator will call or email you three days after your visit to make sure that you have completed your food dairy and used Fitbit device on for 2 weekdays and one weekend day. You will also be reminded

to bring back the Fitbit and food dairy to the research coordinator office at Exercise Physiology Lab located at Corbett Hall.

What are the risks and discomforts?

The risk of flare-ups or temporary physical discomfort associated with the 6minute walk or stair test is very low. The test will be done by a trained researcher and in a supervised environment, which lowers the risk further than that encountered in everyday life. In addition, you will determine how hard you push yourself.

What are the benefits to me?

There are no direct benefits to you for participating in this study. We hope the study will give us more information about bodies' reaction to the diet and exercise in patients with OA. After the completion of the study, we will provide you with a summary of your results. Then, you will learn about the amounts of calories you have burned each day, your activity level and dietary intake.

Do I have to take part in the study?

No. Taking part in this study is your choice. You may stop participating in the study at any time. You can withdraw by contacting a study coordinator, without having to give a reason. Phone number: (780) 802-7603.

Will I be paid to be in the research?

No, there will be no payment. However, we will reimburse your parking cost for about $10.00. There is also no cost associated with participating.

Will my information be kept private?

During the study, we will collect your health information. This will be kept private, and we will not release your information containing your name outside of the study investigator's office and it will not be listed in the research when published. We will create an excel file with your ID linked to the study data we collect. The file will be encrypted and only PI and the research coordinator (Fatemeh Baghbani) will have access to it. Beyond that, the collected data and input will remain anonymous. By signing this consent form you are giving permission for the study staff to collect your health information and use it for research purposes. We will remove all your identifiable information. If you leave the study, we will not collect any new information from you.

What if I have questions?

If you have any questions about the research now or later, please contact the principal investigator (Dr. Linda Woodhouse) or the study coordinator (Fatemeh Baghbani) to answer any questions you have about this study.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780.492.2615. This office has no affiliation with the study investigators.

Appendix G - Consent form

Title of Study: Dietary Intake and Physical Activity of People with Knee Osteoarthritis (OA).

Principal Investigators:
Dr. Linda Woodhouse Phone: E-mail: linda.woodhouse@ualberta.ca

Study Coordinator:
Dr. Susan Armijo Olivo Phone: E-mail: sla4@ualberta.ca
Dr. Carla Prado Phone: E-mail: carla.prado@ualberta.ca
Dr. Mary Forhan Phone: E-mail: forhan@ualberta.ca
Dr. Leah Gramlich Phone: E-mail: lg3@ualberta.ca

Study Coordinator:
Fatemeh Baghbani, MSc, PhD Candidate
Phone: E-mail: baghbani@ualberta.ca

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐

Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name: _____

Who explained this study to you? _____

I agree to take part in this study:

Signature of Research Participant _____

(Printed Name) _____

Date:_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee_____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A SIGNED COPY GIVEN TO THE RESEARCH PARTICIPANT.

Appendix H - 6 minute Walk Test Score Sheet

Verbal instruction:

"For this test, do the best you can by going as fast as you can, but don't push yourself to a point of overexertion or beyond what you think is safe for you.
1. Start with both feet on the start line.
2. On start, walk as quickly but as safely as possible around the course / up and down the hallway.
3. Continue the course / walkway to cover as much ground as possible over 6 minutes.
4. Walk continuously if possible, but do not be concerned if you need to slow down or stop to rest. The goal is to feel at the end of the test that no more ground could have been covered in the 6 minutes.
5. You can sit down to rest if you require".
6. Get ready and START".

6 minute Walk Test (6MWT)

Performance Measure

Considerations	
Which type of TJA is it appropriate for?	THA and TKA
What part of the TJA continuum is it appropriate for?	Pre-op Post-acute Active Living
What domain(s) does it measure within the ICF?	Activity
Who completes it?	Patient and clinician
What does it measure?	Submaximal aerobic capacity and ability to walk over longer distances[1-2]
What equipment is required?	30 metre pre-measured walking area with interval markings every 3 meters, cones or brightly colored tape to mark boundaries, stop watch or timer, chairs for rest at each end, usual walking aid[1-2]
How long does it take?	~ 10 mins to complete and score
How do I do it?	Instructions available at: www.oarsi.org/research/physical-performance-measures www.thoracic.org/statements/resources/pfet/sixminute.pdf
How good is it?	**Validity**: Construct – good to excellent for O_2 consumption post-TKA[2]; Concurrent – excellent, highly correlated with 30 minute walk test post-TKA[3] **Reliability**: Test-retest – excellent for THA and TKA[2,4-6] **Responsiveness**: Able to detect initial deterioration and then improvement in early post-op THA and TKA and most responsive performance measure post PT intervention for knee OA[2] and post-TKA[7] **Floor/ceiling effects**: Not established[4,8,9] but possible ceiling effects for people with normal or high exercise capacities[7]
How is it scored?	Total distance walked in 6 minutes (meters to the nearest m)
What do the results mean?	Greater distance = better performance For healthy Caucasians aged 45-85 years, avg distance men = 682 m; females= 643 m[2,8] Normative data available at: www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=895 MDC: 61.34 m for THA and TKA[4] MCID: Small MCID of 20 m and substantial MCID of 50 m for

Developed by the BC Physical Therapy Total Joint Arthroplasty and Outcome Measures Knowledge Translation Task Force: Dr. Marie Westby, Ronda Field, Maureen Duggan, Dolores Langford, Robyn Laytham, Steven Longstaff, Lauren Welch, Alison Hucns. Dec 2014.
A Physical Therapy Knowledge Broker project supported by: UBC Department of Physical Therapy, Physiotherapy Association of BC, Vancouver Coastal Research Institute and Providence Healthcare Research Institute.

	community-dwelling elders[2]
Where can I get it?	www.thoracic.org/statements/resources/pfet/sixminute.pdf www.rehabmeasures.org/default.aspx Multiple language versions available

References

1. Six Minute Walk Test Form QXQ SMW version 1,0 7/12/11
   www.rheumatology.org/Practice/Clinical/Clinicianresearchers/Outcomes_Instrumentation/Six_Minute_Walk_Test_%28SMWT%29/
2. Bennell K, Dobson F. Measures of physical performance assessments. Patient outcomes in rheumatology, A review of measures. Arth Care Res.2011;63(11):S350-S370.
3. Ko V, Naylor JM et al. The six-minute walk test is an excellent predictor of functional ambulation after total knee arthroplasty. BMC MSK Disorders 2013;14:145. Available at: www.biomedcentral.com/1471-2474/14/145
4. Kennedy DM, Stratford PW et al. Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty. BMC Musculoskelet Disord 2005;6:3.
5. Unver B, Kahraman T et al. Reliability of the six-minute walk test after total hip arthroplasty. Hip Int 2013;23(6):541-5.
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7. Parent E, Moffet H: Comparative responsiveness of locomotor tests and questionnaires used to follow early recovery after total knee arthroplasty. Arch Phys Med Rehabil 2002;83(1):70-80.
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9. Dobson F, Hinman RS et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013;21(8):1042-52. Manual available at: www.oarsi.org/sites/default/files/docs/2013/manual.pdf

Developed by the BC Physical Therapy Total Joint Arthroplasty and Outcome Measures Knowledge Translation Task Force: Dr. Marie Westby, Ronda Field, Maureen Duggan, Dolores Langford, Robyn Laythorn, Steven Longstaff, Lauren Welch, Alison Hoens. Dec 2014.
A Physical Therapy Knowledge Broker project supported by: UBC Department of Physical Therapy, Physiotherapy Association of BC, Vancouver Coastal Research Institute and Providence Healthcare Research Institute.

Available at https://med-fom-clone-pt.sites.olt.ubc.ca/files/2014/04/TJA-OM-Summary-6-MWT-Dec-8-2014.pdf

Appendix I - Stair climb test &record sheet

Stair Climb Test (SCT)

Performance Measure

Considerations	
Which type of TJA is it appropriate for?	THA and TKA
What part of the TJA continuum is it appropriate for?	Pre-op Post-acute Active Living
What domain(s) does it measure within the ICF?	Activity
Who completes it?	Patient and clinician
What does it measure?	Functional strength, balance and agility through ascending and descending a set number of steps.[1]
What equipment is required?	Stairs (8 – 14 steps) with handrails, stopwatch Where possible, the 9-step stair test with 20cm (8 inch) step height (range 16-20 cm) and handrail is recommended.[2]
How long does it take?	~ 2 mins to complete and score[1-2]
How do I do it?	Instructions available at: www.oarsi.org/sites/default/files/docs/2013/manual.pdf The patient should use the assistive device (if any) normally used to perform the activity at the time of testing.[2]
How good is it?	**Validity:** Criterion – good, correlates well with figure-8 walk test, gait speed and chair rise test after TKA; Construct – good, negatively correlates with lower limb strength in knee OA.[1] **Reliability:** Inter-rater - excellent in people following TKA using 11 steps.[3] Test-retest - excellent in patients with advanced hip and knee OA awaiting TJA using 9 steps.[4] **Responsiveness:** 9-step test responsive in detecting initial deterioration and subsequent improvement in patients during post-acute phase after TJA.[5] **Floor/ceiling effects:** Not established in TJA
How is it scored?	Total time to ascend and descend steps is recorded to the nearest 100th of a second.
What do the results mean?	Lower values = better performance MDC: 5.5 sec in patients with advanced hip and knee OA awaiting TJA (9 steps)[4] and 2.6 secs in patients after TKA (11 steps).[3] MCID: No values established for TJA No formal normative values for TJA.[1]

Developed by the BC Physical Therapy Total Joint Arthroplasty and Outcome Measures Task Force: Dr. Marie Westby, Ronda Field, Maureen Duggan, Dolores Longford, Robyn Laythom, Steven Longstaff, Lauren Welch, Alison Hoens. March 2014; revised May 2015
A Physical Therapy Knowledge Broker project supported by: UBC Department of Physical Therapy, Physiotherapy Association of BC, Vancouver Coastal Research Institute and Providence Healthcare Research Institute.

Where can I get it?	Available at: www.oarsi.org/sites/default/files/docs/2013/manual.pdf

References

1. Bennell K, Dobson F et al. Measures of physical performance assessments. Arthritis Care Res 2011;63(S11):S350-S370.
2. Dobson F, Hinman RS et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1042-52. Manual available at: www.oarsi.org/sites/default/files/docs/2013/manual.pdf
3. Almeida GJ, Schroeder CA, et al. Interrater reliability and validity of the stair ascend/descend test in subjects with total knee arthroplasty. Arch Phys Med Rehabil. 2010;91(6):932-8.
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Developed by the BC Physical Therapy Total Joint Arthroplasty and Outcome Measures Task Force: Dr. Marie Westby, Ronda Field, Maureen Duggan, Dolores Longford, Robyn Laythorn, Steven Longstaff, Lauren Welch, Alison Hoens. March 2014, revised May 2015
A Physical Therapy Knowledge Broker project supported by: UBC Department of Physical Therapy, Physiotherapy Association of BC, Vancouver Coastal Research Institute and Providence Healthcare Research Institute.

Stair Climb Test Score Sheet
Verbal instruction:

"For this test, do the best you can by going as fast as you can but don't push yourself to a point of overexertion or beyond what you think is safe for you.

5. Start with both feet on the bottom landing.

6. On start, go to the top of the stairs as fast but as safe as you can, turn around and return back down and stop with both feet back on the ground landing.

7. Use the rail only if needed.

8. Get ready and START".

Appendix J - The Western Ontario McMaster Osteoarthritis Index (WOMAC)

Your Full Name: _____ Today's Date:
_____/_____/_____
Month Day Year

WOMAC OSTEOARTHRITIS INDEX

1. The following questions concern the amount of pain you are currently experiencing in your knees. For each situation, please enter the amount of pain you have experienced in the past 48 hours.

		None	mild	moderate	severe	extreme
A. Walking on a flat surface	A.	☐	☐	☐	☐	☐
B. Going up or down stairs	B.	☐	☐	☐	☐	☐
C. At night while in bed	C.	☐	☐	☐	☐	☐
D. Sitting or lying	D.	☐	☐	☐	☐	☐
E. Standing upright	E.	☐	☐	☐	☐	☐

2. Please describe the level of pain you have experienced in the past 48 hours for each one of your knees.

		None	mild	moderate	severe	extreme
A. Right knee	A.	☐	☐	☐	☐	☐
B. Left knee	B.	☐	☐	☐	☐	☐

3. How severe is your stiffness after first awakening in the morning?

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

4. How severe is your stiffness after sitting, lying, or resting later in the day?

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

5. The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours, in your knees.

What degree of difficulty do you have with:

		None	mild	moderate	severe	extreme
A. Descending (going down) stairs	A.	☐	☐	☐	☐	☐
B. Ascending (going up) stairs	B.	☐	☐	☐	☐	☐
C. Rising from sitting	C.	☐	☐	☐	☐	☐
D. Standing	D.	☐	☐	☐	☐	☐
E. Bending to floor	E.	☐	☐	☐	☐	☐
F. Walking on a flat surface	F.	☐	☐	☐	☐	☐
G. Getting in/out of car	G.	☐	☐	☐	☐	☐
H. Going shopping	H.	☐	☐	☐	☐	☐
I. Putting on socks/stockings	I.	☐	☐	☐	☐	☐
J. Rising from bed	J.	☐	☐	☐	☐	☐
K. Taking off socks/stockings	K.	☐	☐	☐	☐	☐
L. Lying in bed	L.	☐	☐	☐	☐	☐
M. Getting in/out of bath	M.	☐	☐	☐	☐	☐
N. Sitting	N.	☐	☐	☐	☐	☐
O. Getting on/off toile	O.	☐	☐	☐	☐	☐
P. Heavy domestic duties (mowing the lawn, lifting heavy grocery bags)	P.	☐	☐	☐	☐	☐
Q. Light domestic duties (such as tidying a room, dusting, cooking)	Q.	☐	☐	☐	☐	☐

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix L - Lower Extremity Functional Scale (LEFS)

Study Title: Dietary Intake and Physical Activity of Patients with Knee Osteoarthritis (OA)
Participant ID: **Today's Date**:_____/_____/_____

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for each activity.

Today, do you or would you have any difficulty at all with:

(Circle one number on each line)

Activities	**Extreme Difficulty or Unable to Perform Activity**	**Quite a bit of difficulty**	**Moderate difficulty**	**A little bit of difficulty**	**No difficulty**
a. Any of your usual work, housework or school activities.	0	1	2	3	4
b. Your usual hobbies, recreational or sporting activities	0	1	2	3	4
c. Getting into or out of the bath.	0	1	2	3	4
d. Walking between rooms.	0	1	2	3	4
e. Putting on your shoes or socks.	0	1	2	3	4
f. Squatting.	0	1	2	3	4
g. Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
h. Performing light activities around your home.	0	1	2	3	4
i. Performing heavy activities around your home.	0	1	2	3	4
j. Getting into or out of a car.	0	1	2	3	4
k. Walking 2 blocks.	0	1	2	3	4
l. Walking a mile.	0	1	2	3	4
m. Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
n. Standing for 1 hour.	0	1	2	3	4
o. Sitting for 1 hour.	0	1	2	3	4
p. Running on even ground.	0	1	2	3	4
q. Running on uneven ground.	0	1	2	3	4
r. Making sharp turns while running fast.	0	1	2	3	4
s. Hopping.	0	1	2	3	4
t. Rolling over in bed.	0	1	2	3	4
COLUMN TOTALS					

Score variation 6 LEFS points
MDC_{90} & MCID = 9 LEFS points Score _____/80

Available at https://www.honorhealth.com/sites/default/files/documents/medical-services/leg-functional-scale-form.pdf

Appendix M - Three-day food recall questionnaire

3-Day Food Intake Record

Please keep a record of *everything* you **EAT** and **DRINK** for **3 days –** 2 weekdays and 1 weekend day. Include all meals, snacks, and beverages, and the time of day you are eating or drinking. **Please pick days that are TYPICAL for your current eating patterns.**

Please also record the supplements (i.e. vitamins, minerals, protein powders, sport supplements, shakes, etc.) in detail, including: the **name or supplement,** the **amount** you take, **how often** you take it, **when you started** the supplement, and **your reason for taking it.**

The purpose of filling out these food records is to help better understand **WHAT** you are eating, **WHEN** you are eating, and **HOW MUCH** you are eating. Please be as honest and accurate as you can, as the information you provide will help you better reflect on your eating habits.

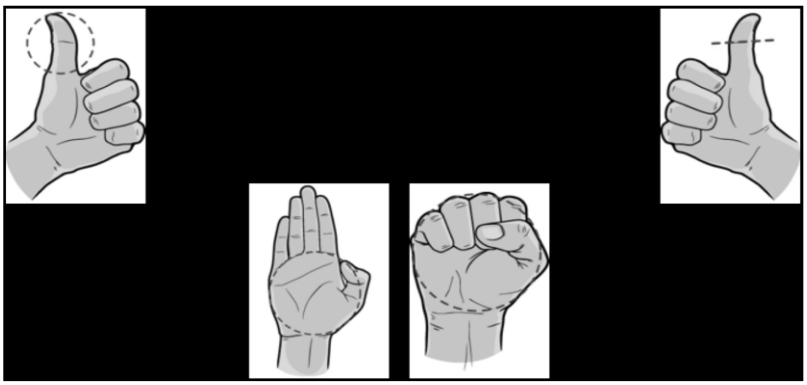
FOOD/BEVERAGE RECORDING INSTRUCTIONS:

1. **Record all food and beverages consumed during a 24 hour period. Provide the following:**
   - **Type of Food Eaten:** e.g. chicken noodle soup
   - **Brand Name:** e.g. Campbell's, Lipton, Weight Watchers
   - **Food or Beverage Characteristics:**
     - **Colour**: e.g. green vs. yellow beans; white vs. whole wheat bread
     - **Fat Content:** % fat (e.g. skim, 1%, 2% or homo milk), leanness of meat (e.g. extra lean ground beef), fat claims (e.g. "light", "low-fat"), was skin removed from poultry?
     - **Freshness**: e.g. fresh, frozen, canned, or dried?
     - **Other Details:** e.g. 25% reduced sodium, "diet" products, etc.
   - **Time of Day** you ate or drank

2. **Please MEASURE and describe the amount of food eaten as best as possible. Diet records are only reliable with accurate measurements.**
   - **Always estimate portion sizes of food after cooking.**
   - **Use household measures to specify serving sizes.**

     1 cup = 250mL = 8 fluid oz 1 tablespoon (Tbsp) = 15mL
     1 ounce (oz) = 30g 1 teaspoon (tsp) = 5mL
   - **Measuring cups (examples):** Put cooked pasta or rice into a measuring cup to record the correct amount before placing it on your plate. Measure your cereal out before pouring into a bowl, and don't forget to measure your milk as well!
   - **Teaspoons/tablespoons (examples):** Measure out butter, margarine, mayonnaise, salad dressings, ketchup, mustard, ground flaxseed, sugar, milk/cream, and other condiments, seasonings, and toppings before adding to your food or beverages.
   - **Count the number of food items if practical:** e.g.: 20 grapes, 15 baby carrots, 8 medium-sized shrimp, etc.
   - **Fluids:** Record amounts in fluid ounces (oz), milliliters (mL), or in cups. Remember 1 cup = 250mL = 8 fl. oz

- **Use food labels to estimate quantities:** Food labels can help you estimate the quantity of food eaten based on weight or volume. For example, write down a 355mL can of pop, 1/2 of a 60g can of tuna, a 37g granola bar, etc.
- **Use your hand to estimate portion sizes quickly:**
  Whole Thumb = 1 Tablespoon Tip of your Thumb = 1 Teaspoon
  Palm of Your Hand = 3 oz of meat Fist = 1 cup (250mL)



3. **Record if anything was ADDED when preparing the food,** such as oil (list specific kind), sauce, butter, margarine, or other condiments or seasonings.

4. **For COMBINATION DISHES such as lasagna, casseroles, chili, soups, or stews include a description of the main ingredients.** E.g. Lasagna: lean ground beef (1/4 cup per piece), mozzarella cheese (1 oz per piece), cottage cheese (1 oz per piece), 1/2 cup tomato sauce, 2 noodles, 1/4 cup spinach.

5. **Include SNACK FOODS eaten.** Don't forget to include candy, chips, cookies, popcorn, ice cream, and beverages such as soft drinks, juice, coffee, or tea.

6. **Use the "notes" column to record any additional PRODUCT INFORMATION** if available (e.g. 6 crackers – 80 calories, 2.5g fat, 1g fibre, 210mg sodium).

7. **Don't forget to write down any ALCOHOLIC BEVERAGES consumed and how much you drank.** This includes all wine, beer, and liquor.

When in doubt… include more details!

Available at https://www.starfht.ca/3_Day_Food_Intake_Record_STARFHT.pdf

Appendix N - Instructions for recording daily food intake

The purpose of this study is to discover everything you eat and drink during a three-day period. It is important to record ALL foods and beverages – whether it is a full course meal at home or a quick can of pop at school/work. Before you start recording your intake, please read the following instructions and the Sample Day.

The Three-Day Dietary Intake Record has a separate section for every day (see Day 1, Day 2, Day 3 on top each page). Each day is broken up into 6 eating times:

1. Morning meal 2. Midmorning snack 3. Midday meal
4. Afternoon snack 5. Evening meal 6. Evening snack

It is a good idea to carry your Dietary Intake Record book with you and record your entries as soon after eating as possible. Foods and beverages consumed away from home – at a friend's house, at the mall, at a restaurant- are just as important as those eaten at home. Please include the following information on your food record:

1. **FOOD AND BEVERAGE ITEMS** Column: Enter all foods and beverages consumed at the meal or snack time. Please record the specific type of food (for example: *WHOLE WHEAT* bread, *FROSTED FLAKES* cereal). In the same column, record all toppings or items added at the time of eating (for example: sugar, syrup, jam, butter, mayonnaise, gravy, milk, salt, etc.). For combination foods, please include detailed information on each item. For example: If you had a tuna sandwich, you would list the following foods and include detailed information for each of them: white bread, mayonnaise, celery, solid white tuna, salt.

2. **DESCRIPTION OF ITEM** Column: For every food or beverage item listed, include the following (if applicable):
   - **Brand**: *MIRACLE WHIP* mayonnaise, *PIZZA HUT DEEP DISH* pizza, *OREO* cookie
   - **Type of flavour**: *BLUEBERRY* muffins, *STRAWBERRY* yogurt
   - **Method of cooking**: *FRIED, BAKED, BBQ'D, HOMEMADE*
   - **All other relevant information included on food label**: *LOW FAT* ranch salad dressing, *28% M.F. (MILK FAT*) cheddar cheese, *LEAN* Ground Beef
3. **NUMBER OF UNITS** Column: In this area, record the number of units consumed. Include the amount of the food or beverage item and the amount of any topping or items added.

4. **UNIT OF MEASURE** Column: For every item consumed, enter the unit of measure you are using for this item. For example: enter the word "cup", "grams", "piece", "ounce", "number", "teaspoon", or "tablespoon". Enter a unit of measure not only for the menu

item, but for toppings or items added as well. Each entry must have its own unit of measure. Use measuring cups and spoons whenever possible.

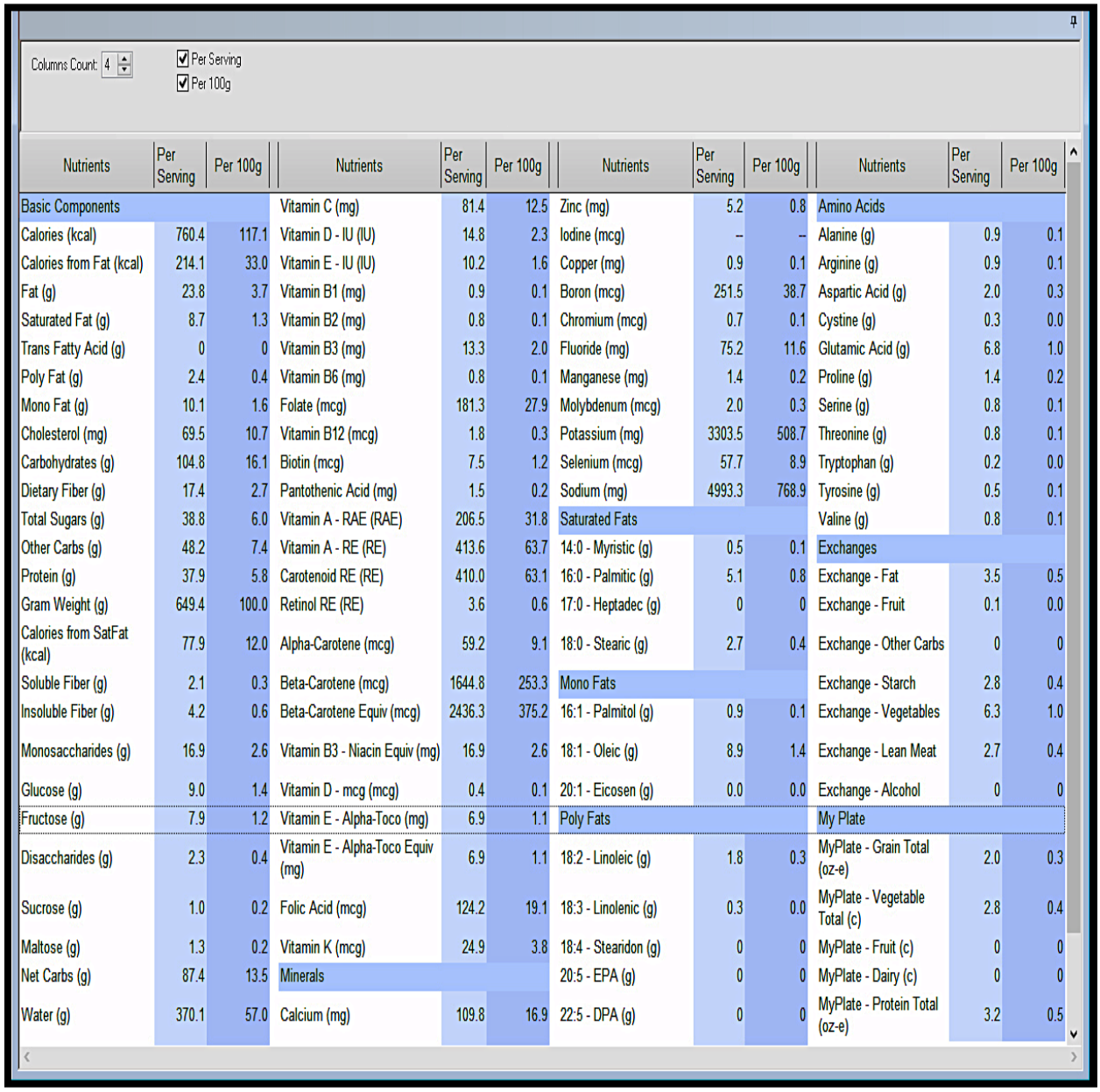
Fill in the blanks on the bottom of each record. Please list any vitamin or mineral supplements and/or herbal products taken, including quantities and detailed label information, if possible. Indicate the time of your meal or snack and where it was eaten (for example: at home, at a restaurant, in class). If you ate more than one snack between two meals, please indicate the time of each snack. If you did not eat a meal or snack, please place a check mark (✓) in the space provided on the bottom of the page, so that we do not think you forgot to record it.

Daily check: in the evening, after you have recorded everything for the day, go back over your entries to make sure you have included as much detail as possible for each item. Also check that the blanks are completed on the bottom of the page.

All foods and beverages you consume every day are important and your Dietary Intake Record should be as accurate as possible. It should also reflect the way you usually eat. Please do not change your normal eating habits for the 3 days you are recording your food intake. Your honesty is crucial to the success of this research study. We have provided a page at the back of your food record for you to include any additional information that will help us interpret your diet. Recipes and information from labels are particularly helpful.

Thank you for your participation and cooperation with this study. Please look closely at the Sample Day before beginning your Dietary Intake Record. **If you have any questions please phone:**

Appendix O - List of the nutrients extracted from ESHA software



Columns Count: 4 ☑ Per Serving ☑ Per 100g

Nutrients	Per Serving	Per 100g	Nutrients	Per Serving	Per 100g	Nutrients	Per Serving	Per 100g	Nutrients	Per Serving	Per 100g
Basic Components			Vitamin C (mg)	81.4	12.5	Zinc (mg)	5.2	0.8	Amino Acids		
Calories (kcal)	760.4	117.1	Vitamin D - IU (IU)	14.8	2.3	Iodine (mcg)	--	--	Alanine (g)	0.9	0.1
Calories from Fat (kcal)	214.1	33.0	Vitamin E - IU (IU)	10.2	1.6	Copper (mg)	0.9	0.1	Arginine (g)	0.9	0.1
Fat (g)	23.8	3.7	Vitamin B1 (mg)	0.9	0.1	Boron (mcg)	251.5	38.7	Aspartic Acid (g)	2.0	0.3
Saturated Fat (g)	8.7	1.3	Vitamin B2 (mg)	0.8	0.1	Chromium (mcg)	0.7	0.1	Cystine (g)	0.3	0.0
Trans Fatty Acid (g)	0	0	Vitamin B3 (mg)	13.3	2.0	Fluoride (mg)	75.2	11.6	Glutamic Acid (g)	6.8	1.0
Poly Fat (g)	2.4	0.4	Vitamin B6 (mg)	0.8	0.1	Manganese (mg)	1.4	0.2	Proline (g)	1.4	0.2
Mono Fat (g)	10.1	1.6	Folate (mcg)	181.3	27.9	Molybdenum (mcg)	2.0	0.3	Serine (g)	0.8	0.1
Cholesterol (mg)	69.5	10.7	Vitamin B12 (mcg)	1.8	0.3	Potassium (mg)	3303.5	508.7	Threonine (g)	0.8	0.1
Carbohydrates (g)	104.8	16.1	Biotin (mcg)	7.5	1.2	Selenium (mcg)	57.7	8.9	Tryptophan (g)	0.2	0.0
Dietary Fiber (g)	17.4	2.7	Pantothenic Acid (mg)	1.5	0.2	Sodium (mg)	4993.3	768.9	Tyrosine (g)	0.5	0.1
Total Sugars (g)	38.8	6.0	Vitamin A - RAE (RAE)	206.5	31.8	Saturated Fats			Valine (g)	0.8	0.1
Other Carbs (g)	48.2	7.4	Vitamin A - RE (RE)	413.6	63.7	14:0 - Myristic (g)	0.5	0.1	Exchanges		
Protein (g)	37.9	5.8	Carotenoid RE (RE)	410.0	63.1	16:0 - Palmitic (g)	5.1	0.8	Exchange - Fat	3.5	0.5
Gram Weight (g)	649.4	100.0	Retinol RE (RE)	3.6	0.6	17:0 - Heptadec (g)	0	0	Exchange - Fruit	0.1	0.0
Calories from SatFat (kcal)	77.9	12.0	Alpha-Carotene (mcg)	59.2	9.1	18:0 - Stearic (g)	2.7	0.4	Exchange - Other Carbs	0	0
Soluble Fiber (g)	2.1	0.3	Beta-Carotene (mcg)	1644.8	253.3	Mono Fats			Exchange - Starch	2.8	0.4
Insoluble Fiber (g)	4.2	0.6	Beta-Carotene Equiv (mcg)	2436.3	375.2	16:1 - Palmitol (g)	0.9	0.1	Exchange - Vegetables	6.3	1.0
Monosaccharides (g)	16.9	2.6	Vitamin B3 - Niacin Equiv (mg)	16.9	2.6	18:1 - Oleic (g)	8.9	1.4	Exchange - Lean Meat	2.7	0.4
Glucose (g)	9.0	1.4	Vitamin D - mcg (mcg)	0.4	0.1	20:1 - Eicosen (g)	0.0	0.0	Exchange - Alcohol	0	0
Fructose (g)	7.9	1.2	Vitamin E - Alpha-Toco (mg)	6.9	1.1	Poly Fats			My Plate		
Disaccharides (g)	2.3	0.4	Vitamin E - Alpha-Toco Equiv (mg)	6.9	1.1	18:2 - Linoleic (g)	1.8	0.3	MyPlate - Grain Total (oz-e)	2.0	0.3
Sucrose (g)	1.0	0.2	Folic Acid (mcg)	124.2	19.1	18:3 - Linolenic (g)	0.3	0.0	MyPlate - Vegetable Total (c)	2.8	0.4
Maltose (g)	1.3	0.2	Vitamin K (mcg)	24.9	3.8	18:4 - Stearidon (g)	0	0	MyPlate - Fruit (c)	0	0
Net Carbs (g)	87.4	13.5	Minerals			20:5 - EPA (g)	0	0	MyPlate - Dairy (c)	0	0
Water (g)	370.1	57.0	Calcium (mg)	109.8	16.9	22:5 - DPA (g)	0	0	MyPlate - Protein Total (oz-e)	3.2	0.5