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Impact of Diet and/or Exercise Intervention on Infrapatellar Fat Pad Morphology

A Secondary Analysis from a Randomized Controlled Trial

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SWORN DECLARATION

I hereby swear that I personally wrote this thesis, that I did not use any other sources or additional references than those I have comprehensively quoted, and that the work on hand or major elements of it have only been submitted here and nowhere else as examination performance except in form of an abstract for the World Congress on Osteoarthritis, to take place from April 30th to May 3rd 2015 in Seattle, USA, and to be published as an abstract in Osteoarthritis & Cartilage, the official journal of the Osteoarthritis Research Society International (OARSI).

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GERMAN ABSTRACT

Hintergrund: Adipositas erhöht die mechanische Belastung der Gelenke und verursacht gering-gradige chronische inflammatorische Veränderungen; daher stellt sie einen bedeutenden Risikofaktor für die Inzidenz und Progression der Gonarthrose dar. Der infrapatellarer Fettkörper (IPFP) sezerniert sogenannte Adipokine und könnte daher an intraartikulären Entzündungsprozessen beteiligt sein. In der vorliegenden Studie untersuchen wir, (1) ob Diät- und/oder Trainingsintervention mit Veränderungen des Volumens des IPFP einhergehen, (2) ob sich das Ausmaß der Veränderungen des IPFP zwischen den Interventionsgruppen unterscheidet und (3) ob die Veränderung des IPFP-Volumens mit der individuellen Gewichtsabnahme oder einer Veränderung der Körperzusammensetzung korreliert.

Methoden: In einer randomisierten, kontrollierten Interventionsstudie (Intensive Diet and Exercise for Arthritis [IDEA] trial) wurden 454 übergewichtige (BMI=27-41kg/m^2), ältere (≥55 Jahren) Patienten mit Gonarthrose (KLG 2-3) untersucht. Die 18 Monate dauernden Interventionen umfassten: Trainings- bzw. Kontrollgruppe (E), Diät (D) sowie Training und Diät (D+E). In einer Subpopulation (E: n=36; D: n=35; D+E: n=35) wurden magnetresonanztomographische Bilder des Kniegelenkes akquiriert. In der vorliegenden Sekundäranalyse wurde der IPFP in sagittalen T1-gewichteten Spin-Echo-Sequenzen ohne Fettunterdrückung segmentiert und dessen Volumen, Flächen und Dicke quantitativ analysiert. Longitudinale morphologische Veränderungen des IPFP wurden innerhalb und zwischen den Interventionsgruppen mit ANCOVA getestet. Der individuelle Zusammenhang zwischen Volumenänderungen des IPFP und Gewichtsveränderungen oder Veränderungen in der Körperzusammensetzung (DXA und CT) wurden anhand von Spearman-Korrelationen untersucht.

Ergebnisse: Die Körpergewichtabnahme im IDEA trial betrug in E -1,0%, in D -10,5% und in D+E -13,0%. Es wurde eine signifikante ($p<0,01$) Volumenreduktion des IPFP in E (-2,1%), D (-4,0%) sowie D+E (-5,2%) beobachtet. Die Volumenreduktion des IPFP war in D+E signifikant größer als in E ($p<0,05$). Es wurden statistisch signifikante Korrelationen ($p<0,01$) zwischen den Volumenänderungen des IPFP mit der individuellen Gewichtsabnahme ($r=0.40$), der Abnahme des totalen Körperfettes (DXA; $r=0.44$; $n=88$) sowie des subkutanen und intermuskulären Fettes im Oberschenkel (CT; $r=0.32$; $n=82$ und $r=0.29$; $n=82$) beobachtet.

Schlussfolgerungen: Dies ist die erste Studie, die zeigt, dass das Volumen des IPFP durch Diät und Training modifizierbar ist. Möglicherweise ist der IPFP an inflammatorischen Prozessen bei Gonarthrose beteiligt, spielt eine Rolle im Zusammenhang von Übergewicht und Gonarthrose und in deren durch Diät und Training bedingten symptomatischen Verbesserung.

ENGLISH ABSTRACT

Purpose: Obesity is associated with increased joint loading and chronic low grade inflammation; it therefore represents an important risk factor for incidence and progression of knee osteoarthritis (OA). The infrapatellar fat pad (IPFP) may contribute to intra-articular inflammation by secretion of adipokines. Here we study whether (1) diet and/or exercise interventions are associated with changes in IPFP morphology, whether (2) changes differ between different types of interventions, and (3) whether these changes correlate with changes in body weight or body composition.

Methods: A randomized controlled trial, the Intensive Diet and Exercise for Arthritis (IDEA) study, enrolled 454 overweight and obese (BMI=27-41kg/m^2) older adults (age ≥55yrs) with knee pain and radiographic OA (KLG 2-3). Participants were randomized to three 18-month interventions: exercise only control (E), diet only (D), and diet+exercise (D+E). In a subsample (E: n=36; D: n=35; D+E: n=35) magnetic resonance images were acquired. In this secondary analysis, the IPFP was segmented using a sagittal T1-weighted spin-echo sequence without fat suppression and its volume, surface areas and thickness were analyzed quantitatively. Within- and between-group comparisons of longitudinal changes in IPFP morphology were evaluated using ANCOVA. Correlations between changes in IPFP and those in body mass or composition (DXA and CT) were studied using Spearman correlations.

Results: Body weight loss in each group amounted to -1.0% in E, -10.5% in D, and -13.0% in D+E. A significant ($p< 0.01$) reduction in IPFP volume was observed in E (-2.1%), D (-4.0%) and D+E (-5.2%); The IPFP volume loss in D+E was significantly greater than that in E ($p<0.05$). Across the intervention groups, there was a significant correlation between IPFP volume change, individual weight loss (r=0.40), total body fat mass change (DXA; r=0.44; n=88), and subcutaneous and inter-muscular thigh fat change (CT; r=0.32 and r=0.29; n=82, respectively).

Conclusions: This is the first study to show that the IPFP volume can be modified by diet and exercise. The IPFP may be involved in the inflammatory status of OA joints, may represent a link between obesity and knee OA, and may mediate symptomatic improvement by diet and exercise.

1. INTRODUCTION

Osteoarthritis (OA) of the knee represents one of the leading causes for chronic disability among the elderly.[1] It has been estimated that loss of quality-adjusted life-years due to knee OA and/or obesity amounts to 10% to 25% of the remaining quality-adjusted survival of persons aged 50 to 84 years.[2] Obesity not only is one of the most important, but is also a potentially preventable risk factor for knee OA.[3]

It has recently been recognized that the obesity-related risk of incident and progression in knee OA may not only be conveyed by biomechanical factors (i.e. increased body weight) but also by endocrinological mechanisms, as reviewed by Issa and Griffin.[4] Fat cells are known to secret so-called adipokines (e.g. adiponectin and leptin), a group of adipocyte-derived pro-inflammatory proteins which mediate intra-articular inflammation and up-regulation of cartilage matrix turnover.[4] Leptin is of particular interest in this context, as it has been shown to induce the expression of metalloproteinases (MMP) and because of its positive correlation with MMP-1 and MMP-3 levels in synovial fluid from knees of OA patients.[5,6] Leptin has hence been suggested to be a mediator for cartilage degradation and loss[6–9] and is potentially considered as a metabolic link between obesity and OA[10–12]. In the randomized controlled "Intensive Diet and Exercise for Arthritis" (IDEA) trial, Messier et al.[13] showed that weight loss induced by "diet only" or "diet plus exercise" intervention was associated with a reduction in knee symptoms as well as a reduction in systemic inflammatory marker levels. In a mouse model, high-fat diet-induced obesity, in contrast, caused a significant increase in systemic leptin levels and led to the development of structural and symptomatic osteoarthritis.[14]

Recently, the infrapatellar fat pad (IPFP) has come into focus of OA research as it was found to be a local source of leptin and other pro-inflammatory cytokines.[6,15–18] The IPFP represents intra-capsular, extra-synovial located adipose tissue consisting of a central body with medial and lateral extensions.[19–21]

So far, only little research has been performed on the relationship between IPFP volume, obesity, and knee OA. The findings of a study of a small sample of patients with knee OA and controls was not able to demonstrate a significant relationship between IPFP volume and body weight, body mass index (BMI) or knee OA, but only involved a very small number of participants and may have been statistically underpowered.[22] The IPFP of patients with patellofemoral OA, however, was recently reported to be significantly larger compared to that of healthy controls[23] and may hence represent an important link between obesity and knee OA.

Chang et al.[24] demonstrated that high-fat feeding caused a significant increase in IPFP volume in mice. Further, the IPFP of subjects with knee OA was found to have high expression levels of enzymes involved in fat metabolism,[17] suggesting that it could be

responsive to the overall nutritional state. However, no previous study has explored the relationship between the longitudinal change in body weight and the morphology (e.g. volume) of the IPFP in humans, and no interventional trial has studied the impact of weight loss on IPFP volume. In this secondary analysis of the IDEA randomized control trial we therefore explored whether diet and/or exercise interventions over 18 months are associated with changes in IPFP morphology.

2. LITERATURE SURVEY

2.1 Osteoarthritis of the knee and the role of obesity

OA is characterized by chronic pain, functional impairment, stiffness, crepitus, peri-articular tenderness, swelling and structural alterations of the affected joint, as reviewed by Hunter and Felson.[25] Typical osteoarthritic structural alterations seen on x-ray have been used for defining and for staging knee OA. The frequently applied Kellgren and Lawrence grading scale (KLG)[26], for example, is based on the presence of osteophytes, peri-articular ossicles and subchondral pseudocysts, joint space narrowing and the sclerosis of subchondral bone.[26] Knee OA is graded from KLG 0 to 4 depending on the gradual presence of these alterations: KLG 0 is radiographically normal knee; KLG 2 is defined by the definite presence of an osteophyte whereas KLG 4 represents severe OA with total obliteration of the radiographic joint space.[26]

Radiographic knee OA among adults aged ≥45 years is common, considering its high prevalence in the population, i.e. the Framingham cohort (19.2%)[27] and the Johnston County Osteoarthritis Project (27.8%)[28]. It has been estimated that about 250 million people worldwide suffer from knee OA.[29]

Using data from the Johnston County Osteoarthritis Project cohort, Murphy et al.[30] estimated that the overall lifetime risk of developing symptomatic knee OA was as high as 44.7%. Obese individuals defined by a BMI of ≥30, however, have much greater lifetime risk (60.5%) of acquiring symptomatic knee OA than overweight (BMI <30 and ≥25; 46.9%) or underweight and normal weight subjects (BMI <25; 30.2%).[30] Knee cartilage defects detected on magnetic resonance (MR) imaging have also been found to be associated to the BMI.[11,31]

Other than obesity, age, knee injury, Heberden's nodes and certain occupational activities represent risk factors for knee OA, with obesity being preventable.[3,32,33] Both the length of the period of exposure to higher BMI throughout adulthood as well as a shift from normal to overweight during adulthood have been reported to significantly increase the risk for the development of knee OA.[34,35]

Although knee OA is not a fatal disease, it is a matter of public health concern considering its prevalence among the elderly[36], population aging , the rising prevalence of obesity over the past decades[37] and the influence of OA on quality of life. Losina et al.[2] estimated that loss of quality-adjusted life-years due to knee OA and/or obesity was as high as 10% to 25% of the remaining quality-adjusted survival of individuals aged 50 to 84 years in the United States. In this population it resembles a loss of 86.0 million quality-adjusted life-years.[2]

2.2 Systemic inflammation: the link between osteoarthritis and obesity

Formerly, the link between obesity and knee OA was primarily attributed to increased biomechanical joint loading, resulting from increased weight and malalignment of the knee joint.[38] OA was regarded as a “wear and tear condition” with almost no inflammation involved in its pathomechanism, as reviewed by Sowers and collegues.[39] However, obesity is also associated to OA in non-weight bearing joints such as the hand.[40–42] This suggests that the pathomechanism of OA does not only include biomechanical factors, but also systemic inflammatory mechanisms, as reviewed by Issa and Griffin.[4]

Today, adiposity is considered as a state of chronic “low grade” inflammation, which could contribute to the development of OA, as reviewed by Vincent and colleagues.[43] Circulating levels of several pro-inflammatory markers, such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) have been found to be elevated in obese people.[44–48] Interestingly, a variety of pro-inflammatory cytokines are involved in the pathogenesis of OA. TNF-α and IL-1β, for instance, have been found in higher concentrations in the synovial fluid and in the cartilage of osteoarthritic joints.[49,50] In chondrocytes, IL-1β is capable of inducing the synthesis of the inflammation-associated enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2, as well as the synthesis of the pro-inflammatory cytokine IL-6.[51,52] All three cytokines, IL-1β, TNF-α and IL-6, suppress the synthesis of collagen type 2 by chondrocytes,[53–55] an important compositional component of articular cartilage. Treatment of bovine and human cartilage cultures with TNF-α led to significant loss of sulphated glycosaminoglycans,[56] a structurally important protein of articular cartilage. In the Chingford Study, elevated serum IL-6 levels were found to be significant predictors of the incidence of subsequent radiographic knee OA.[57] Both IL-6 and TNF-α serum levels also were related to the presence of knee joint space narrowing.[58] Serum levels of the pro-inflammatory cytokines IL-17 and IL-18 were elevated among subjects with knee OA, and synovial fluid levels of these cytokines were found to be related to KLG scores.[59,60] In chondrocytes, IL-1, IL-17 and IL-18 induce the expression and synthesis of MMPs.[61–64] As reviewed by Meszaros et al.[65], MMPs contribute to the degradation of cartilage extracellular matrix proteins in OA.

2.3 The infrapatellar fat pad contributes to local inflammation in knee osteoarthritis

The IPFP is an intracapsularly but extrasynovially located adipose tissue,[21] consisting of a central body with medial and lateral extensions.[20] Anteriorly it is boarded by the patellar tendon and retinacula, superiorly by the inferior part of the patella and posteriorly by the femoral condyles, intercondylar notch, tibial plateau and the anterior horns of the menisci.[20] Its close relation to the synovium-lined knee joint cavity suggests that it could be a local source for inflammatory mediators involved in knee OA pathogenesis, as reviewed by Clockaerts and collegues.[66]

In a study exploring the inflammatory phenotype of the IPFP, detectable levels of IL-6, TNF-α, vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) were described in the IPFP and synovial fluid.[67] Distel et al.[15] reported later that the expression of IL-6, TNF-α and other pro-inflammatory cytokines including IL-1β, IL-8 and macrophage chemotactic protein-1 (MCP-1) was present in IPFP explants of obese patients with knee OA. Remarkably, expression and secretion levels of IL-6 and soluble IL-6 receptor (sIL-6R) were found to be significantly higher in the IPFP than in subcutaneous fat of patients with knee OA.[15,16] Further, treatment of IPFP explant cultures from knee OA patients with IL-1β led to increased expression levels of TNF-α, IL-6 and IL-1β as well as a greater TNF-α release.[68] Since IL-1β was found to be present in synovial tissue of osteoarthritic knee joints,[69] it may have an impact on inflammation of the IPFP. On the other hand, conditioned medium from cultures of the IPFP from osteoarthritic joints was shown to induce a strong inflammatory response in autologous fibroblast-like synoviocytes, which exceeded the extent of inflammation in this cell cultures caused by subcutaneous fat-conditioned medium.[70]

Besides these cytokines, there is a group of recently studied inflammatory mediators, the so-called adipokines, which are secreted by adipose tissues, as reviewed by Fantuzzi.[71] Among these, leptin and adiponectin are of particular interest, since they were found to be produced by the IPFP in subjects with knee OA.[6,15–17]

Leptin, for instance, appears to be associated to obesity in general, since both serum and knee synovial fluid leptin levels showed a significant positive correlation with BMI or percentage of body fat.[72–74] There was a correlation between serum and synovial fluid leptin concentrations.[75] Interestingly, synovial leptin levels in osteoarthritic joints appear to be higher compared to serum levels.[76] This finding may be attributed to a local production of adipokines by articular adipose tissues, such as the IPFP, but also osteophytes and the synovium.[18,76]

In OA patients, synovial fluid leptin concentrations were significantly higher than in healthy controls, with the highest levels measured in subjects with KLG 4.[9] Likewise, serum levels of leptin correlated negatively with cartilage thickness or volume of the knee.[7,11,77] Interestingly, the associations between these structural alterations of articular tissue and BMI, total fat ratio

or trunk fat ratio became statistically non-significant after an adjustment for serum leptin.[7,11] This suggested that leptin is involved in cartilage thinning.[7,11]

Leptin-deficient mice experienced massive weight and body fat gain, but no increase in the degradation of articular cartilage or a change in circulating levels of pro-inflammatory mediators were measured.[12] These findings support that leptin could be an important link between obesity and OA. However, in the case of hand OA, serum leptin levels were neither associated with Kallman[78] x-ray scores nor radiographic progression of hand OA.[79,80]

On the molecular level, Otero et al.[81] demonstrated that in vitro expression of iNOS and nitric oxide (NO) production in human primary chondrocytes can be stimulated by exposing culture cells to leptin and interferon gamma (INF-γ) in combination, in a dose-dependent manner. On the other hand, neither leptin nor INF-γ alone were able to stimulate iNOS expression.[81] The same authors showed that iNOS production of NO in human primary chondrocytes, triggered by IL-1, could be significantly increased by co-stimulation with leptin suggesting that leptin acts synergistically to IL-1.[82] However, Vuolteenaho et al.[83] demonstrated that in human OA cartilage, leptin without co-stimulation was indeed able to stimulate iNOS expression and to increase NO production in a dose-dependent manner, rendering it an even more potent pro-inflammatory mediator.

Leptin is also known to enhance COX-2 expression and prostaglandin E_2 (PGE_2) production as well as IL-6 and IL-8 synthesis.[83] Levels of leptin in synovial fluid correlated positively with MMPs.[84] In bovine and human cartilage explant cultures, leptin (either alone or in combination with IL-1) was found to up-regulate the expression of MMP-1, -3 and -13 and thereby to induce collagenolysis.[5,6] Further, in a rat model, intra-articularly injected leptin triggered the expression of MMP-2, -9 and aggrecanases, while it also caused a decrease in anabolic bFGF levels, eventually leading to proteoglycan loss.[8]

The majority of studies attribute catabolic effects to leptin. However, the injection of leptin into rat joints was also found to induce anabolic factors, including transforming growth factor beta 1 (TGF-β1) and insulin-like growth factor 1 (IGF-1) in a dose-dependent manner, and to increase proteoglycan synthesis.[73]

The role of adiponectin in the development of OA is less clear compared with leptin. On the one hand, adiponectin appeared to enhance the development of OA, as circulating levels in individuals with OA were found to be significantly higher than those in healthy controls.[85] Likewise, serum adiponectin levels were significantly higher in men with severe knee OA compared to those with mild OA.[86] Further, adiponectin levels in ex vivo cartilage cultures were highest among cultured probes obtained from patients with severe OA and correlated with NO, IL-6 and MMP-3 concentrations.[86] Independent of the BMI or the waist-to-hip ratio, adiponectin synovial fluid levels in women with knee OA were found to correlate positively with degenerative fragments of aggrecan in synovial fluid of the same joint.[87] In murine

chondrocytes cultures, treatment with adiponectin increased IL-6, MMP-3 and -9 concentrations and induced the expression iNOS in a dose-dependent manner, thereby leading to significant NO accumulation.[88] Up-regulation of MMP-3, iNOS or NO was also observed in human chondrocytes cultures treated with adiponectin.[89,90] In addition, concentrations of MMP-1, -13 and collagen type 2 degradation fragments increased significantly following treatment with adiponectin.[89]

On the other hand, findings suggest that adiponectin is protective against cartilage degradation and contradict the above reports. Honsawek et al.[91], for example, found that subjects with higher KLG scores had significantly lower plasma and synovial fluid adiponectin levels than those with lower KLG grades, and that plasma and synovial fluid levels of adiponectin correlated negatively with radiographic knee OA severity ($r=-0.68$, $p<0.001$). Further, adiponectin serum levels were found to be neither associated to radiographic Kallman scores of hand OA, nor to cartilage degeneration in knee OA.[72,79] Interestingly, the BMI was shown to be negatively correlated with serum and synovial fluid levels of adiponectin in knee OA,[72,91,92] while higher serum adiponectin levels were associated with a reduced subsequent risk of hand OA progression[80]. In cultured chondrocytes of knee and hip OA patients, adiponectin led to detectable levels of tissue inhibitor of metalloproteinase-2 (TIMP-2) and blocked the IL-1β induced MMP-13 expression to some extent.[92] In monocyte cells, adiponectin significantly increased expression levels of TIMP-1 and the anti-inflammatory cytokine IL-10.[93] Interestingly, in vitro chondrocytes proliferated and showed a significant increase in expression levels of collagen type 2, proteoglycans and other components of the cartilage extracellular matrix after administration of adiponectin.[94]

In summary, adiponectin appears to have both anabolic and catabolic effects on articular cartilage. Different isoforms of adiponectin with variable immunoregulatory properties may explain these controversial findings concerning the role of adiponectin in the etiopathogenesis of OA.[95]

2.4 The impact of weight loss on knee osteoarthritis

Weight loss is known to reduce the risk for symptomatic knee OA,[96] and change in body weight significantly affects knee joint load[97,98]. More specifically, weight loss to knee joint load reduction runs in a ratio of approximately one to four, so that for every kilogram lost, there is a 4-kilogram decrease in joint load.[99]

Recently, the IDEA trial[13], a diet and/or exercise intervention study among obese subjects with mild to moderate knee OA, revealed a dose-response reduction in knee compressive forces and self-reported Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)[100] knee function scores to weight loss. Further, weight loss not only reduced knee joint loading, but also IL-6 levels as a marker of systemic inflammation.[13] Another recent study suggested that weight change does not only affect WOMAC knee function scores in a dose-dependent manner but also WOMAC pain scores.[101] In the Arthritis, Diet, and Activity Promotion Trial (ADAPT)[102] and the IDEA trial[13], the combination of dietary and exercise intervention led to significant improvements in knee pain, self-reported physical function and mobility, and yielded a better clinical outcome than diet or exercise intervention alone. Nevertheless, diet-only induced weight loss was effective enough to significantly improve WOMAC scores.[102–104] To yield a clinically significant improvement with regard to self-reported disability, a meta-analysis among randomized controlled trials with weight loss interventions in obese individuals with knee OA estimated that a weight loss of at least 5.1% is needed.[105]

Although improvements in symptoms and ambulatory joint function in knee OA may lead to increased peak knee joint compressive forces, these changes in knee joint loading did not affect clinical or structural disease progression.[106] However, weight loss following low energy diet caused a significant loss of absolute leg muscle mass and knee flexor and extensor strength.[104] The addition of an exercise intervention, however, attenuated these unwanted side effects of dietary weight loss.[107–109] Further, a systematic comparison of 13 randomized control trials that included exercise interventions revealed that patients with knee OA did benefit from both aerobic and quadriceps strengthening exercise in terms of a reduction in pain and disability.[110]

Other than exercise or diet, biatric surgery was also shown to be effective in yielding weight loss and improving knee arthritis symptoms including pain, stiffness, physical function, quality of life, activities of daily living and sport activities.[111]

With regard to obesity induced, systemic “low grade” inflammation, several studies have described significant reductions of circulating levels of pro-inflammatory markers, such as IL-6,[13,112,113] CRP[112,113] and leptin[114], as well as cartilage degradation markers[112] following weight loss.

2.5 Infrapatellar fat pad morphology and its associations to knee osteoarthritis and obesity

So far, only little research has been performed on the relationship between IPFP volume, obesity and knee OA. The findings of a study of a small sample of patients with knee OA and controls showed no relationship between IPFP volume and body weight, BMI or knee OA.[22] Han et al.[115] confirmed that the IPFP maximal area on sagittal MR images, chosen as a surrogate of IPFP size, was not associated with the BMI or body and trunk fat. However, the IPFP was found to be associated with body weight, indicating that the relationship with body weight was confounded by height.[115] In terms of knee OA, they observed negative associations between IPFP maximal area and structural alterations of knee OA and some knee pain subscales cross-secctionally.[115] The same research group related the baseline IPFP maximal area to longitudinal changes in knee pain, knee cartilage volume and cartilage defects in older adults.[116] Larger baseline IPFP maximal area appeared to have a protective role with regard to knee symptoms and cartilage integrity in women but these associations were inconsistent with other findings of this study and were not reproduced in older men.[116]

In contrast, recent studies found that a larger IPFP volume was associated with greater knee pain in knee OA.[23,117] Further, the IPFP of patients with patellofemoral OA was reported to be significantly larger compared to that of healthy controls.[23]

The IPFP of subjects with knee OA was found to have high expression levels of enzymes involved in fat metabolism,[17] suggesting that it could be responsive to the overall nutritional state. Chang et al.[24] demonstrated that high-fat feeding and subsequent massive weight gain in mice caused a significant increase in IPFP volume of 54%.

These findings taken together with the apparent contribution of the IPFP to local inflammation in the knee joint motivates further studies into the associations between IPFP morphology and obesity and into its role in the etiopathogenesis of knee OA, particularly in context of an intervention targeted at reducing body weight.

3. HYPOTHESES TO BE TESTED IN THE CURRENT STUDY

In this secondary analysis of a randomized controlled trial on the effect of weight loss, induced by diet and exercise, on knee joint symptoms, knee joint loading, and systemic inflammatory markers,[13] we tested the following specific hypotheses:

Hypothesis 1:

There is a (statistically significant) reduction in IPFP volume in participants of the IDEA trial[13], who have undergone diet and/or exercise intervention.

Hypothesis 2:

The reduction in IPFP volume among participants of the IDEA trial is stronger in the diet only (n=35) and diet+exercise (n=35) intervention group than in the exercise only intervention group (n=36).

Hypothesis 3:

A reduction in IPFP volume correlates with individual levels of weight loss and changes in BMI, body fat and thigh fat, independent of the specific intervention.

4. MATERIAL AND METHODS

4.1 Study population

The participants used in this analysis were selected from the Intensive Diet and Exercise for Arthritis trial (IDEA)[13]. IDEA was a single blind, single-center, 18-month, randomized controlled trial[118], which was conducted from July 2006 to June 2011 at Wake Forest University and the Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
The study was approved by the human subjects committee of Wake Forest Health Sciences. Informed consent was obtained in writing from all participants.[118]

The IDEA trial included 454 ambulatory, community-dwelling persons aged ≥ 55 years with:

1. Kellgren-Lawrence grade (KLG)[26] 2-3 (mild to moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees.
2. Pain on most days of the month over the past 12 months due to knee OA.
3. A BMI ranging from 27 to 41 kg/m^2.
4. A sedentary lifestyle, i.e. < 30 min/week of formal exercise in the past 6 months.

Participants were recruited from the community over a 37-month period (November 2006 to December 2009). A stratified-block randomization method was used to assign all eligible persons to one of three intervention arms, stratified by BMI and gender:

1. Exercise-only control (E)
2. Diet-induced weight loss only (D)
3. Diet-induced weight loss plus exercise (D+E)

The E intervention group was designated as the comparison (control) group, because previous work indicated that aerobic walking or resistance training should be part of the standard of care for knee OA patients.[119] The trial design rationale and primary outcomes are reported elsewhere.[13,118]
Magnetic resonance images were obtained on a randomly selected subsample of 106 participants who have obtained both baseline and 18-month follow-up MR imaging.[120] The sample size per group was as follows: E: n=36, D: n=35, D+E: n=35.

4.2 Interventions

a) Exercise only intervention
The exercise intervention was identical for E and D+E.[118] 60 min sessions were conducted 3 d/wk for 18 months. During the first 6 months, participation was facility-based. After 6-month follow-up testing and a 2-week transition phase, participants opted to remain in the

facility program or to participate in a home-based program, or combine the two. The 3 d/wk program consisted of aerobic walking (15 minutes), strength training (20 minutes), a second aerobic phase (15 minutes), and cool-down (10 minutes).

b) Diet only intervention

Both the D and D+E groups received the same dietary intervention.[118] The weight loss goal was a mean group loss of at least 10% of baseline weight, with a desired range between 10% and 15%. The dietary plan was based on partial meal replacements, including up to 2 meal-replacement shakes per day (Lean Shake®, provided by General Nutrition Centers, Inc., Pittsburgh, Pennsylvania). For the third meal, participants followed a weekly menu plan and recipes that were 500-750 kcals, low in fat and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits.

The initial diet plan provided an energy-intake deficit of 800-1000 kcals/d as predicted by energy expenditure (estimated resting metabolism x 1.2 activity factor) with at least 1100 kcals for women and 1200 kcals for men. The calorie distribution goal was 15-20% from protein, <30% from fat, and 45-60% from carbohydrates, consistent with the Dietary Reference Intakes for Energy and Macronutrients[121] and previous successful weight loss programs[122]. As follow-up progressed, fewer meal replacements were consumed. Body weight was monitored weekly or biweekly during nutrition education and behavioral sessions: these included, one individual session and 3 group sessions per month between months 1-6, and biweekly group sessions and an individual session every 2 months between month 7-18.

c) Diet plus exercise intervention

Participants randomized to the D+E intervention received both interventions described as above.[118]

4.3 Image acquisition using magnetic resonance imaging

MR imaging could not be obtained from all IDEA participants due to budget restriction.

In a subsample of 106 participants (E: n=36; D: n=35; D+E: n=35), MR images of the most symptomatic knee were obtained at baseline and 18 month follow-up using a 1.5 Tesla (SIGNA HDx, General Electric Medical Systems, Milwaukee, Wisconsin) scanner and an extremity coil.[118] The following MRI sequences were obtained:

1. Double oblique coronal three-dimensional spoiled gradient-echo (SPGR) with fat suppression;
2. Axial non-fat-suppressed T1-weighted spin-echo (SE);
3. Double oblique coronal non-fat-suppressed T1-weighted SE;

4. Sagittal non-fat-suppressed T1-weighted SE;
5. Sagittal T2-weighted fast spin-echo (FSE) with fat suppression;
6. Double oblique coronal T2-weighted FSE with fat suppression.

IPFP segmentation was performed on the 2D sagittal non-fat-suppressed T1-weighted SE sequence (time of repetition = 600 ms, time of echo = 11 ms, contiguous slices with a thickness = 4.5 mm, in-plane resolution 0.625 mm × 0.625 mm, field of view = 16 cm, image matrix = 256 × 256 pixels).

4.4 Image analysis of the infrapatellar fat pad

All segmentations in this study were performed by the author, who was trained using standardized test data sets and who was blinded to the time of image acquisition (baseline or follow-up) and intervention. The imaging parameters (brightness, intensity, contrast, grey value limit) were adjusted manually in each image. The reader processed all slices that clearly depicted the IPFP. By applying different labels, the reader manually traced the anterior border of the IPFP (the one facing the patellar ligament) and the posterior border (the one facing the knee joint) [Fig. 1 a)]. The IPFP volume, the size of the anterior and posterior surface area, and the mean and maximal thickness from anterior surface (depth) were computed using custom image analysis software [Fig. 1 b)].

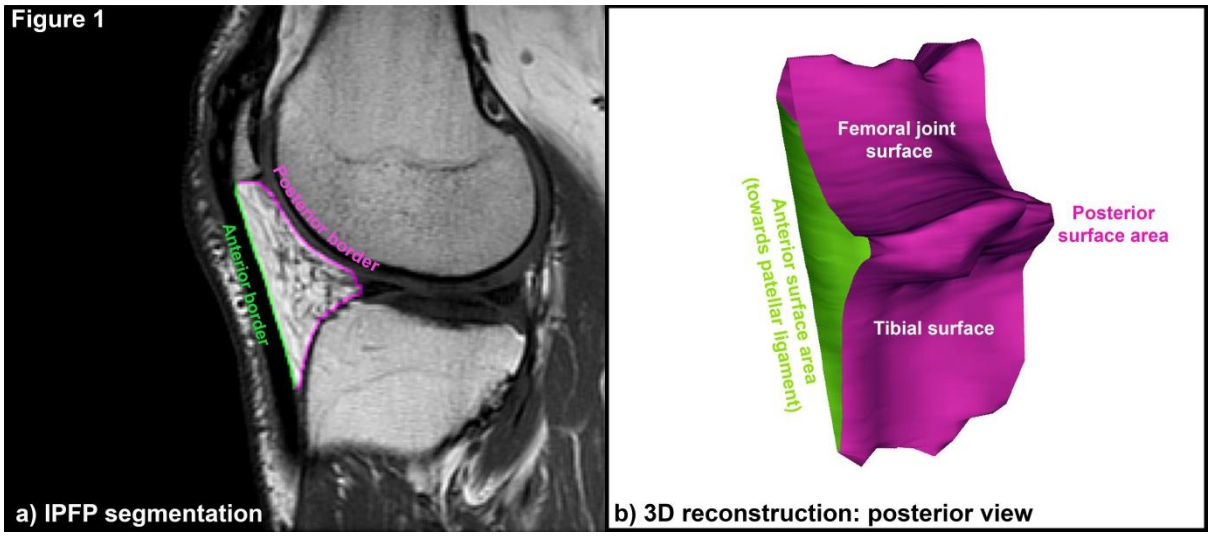


Figure 1: a) Sagittal MR image of the knee joint with segmentation of the infrapatellar fat pad (IPFP) anterior surface (green, facing the patellar ligament) and posterior surface (magenta, facing the inferior patellar pole, the distal femur and proximal tibia). **b)** 3D reconstruction of the IPFP from a posterior viewing angle. The anterior surface area is colored in green and the posterior surface area is colored in magenta.

4.5 Analysis of body and thigh composition

The BMI was calculated as mass (measured in kilograms on a standard calibrated scale) divided by the body height squared (measured in meters). The whole body lean mass (LM), fat mass (FM), and bone mass for baseline and 18-month follow-up were measured by dual x-ray absorptiometry (DXA) on a subsample of the IDEA study population (n = 88). DXA scans were obtained with a fan-beam scanner, Delphi A™, Hologi (Waltham, MA) using the manufacturer's recommendations for patient positioning, scan protocols, and scan analysis. Coefficients of variation (%CV) were 1.2% for whole body FM and 0.5% for whole body LM.[118] Baseline and 18-month follow-up computed tomography (CT) scans of the thigh were obtained in a subsample of the IDEA population (n = 82) with measurements of subcutaneous thigh fat, intra-muscular thigh fat and total thigh fat.

4.6 Statistical analysis

Baseline anthropometrics and quantitative measures of the IPFP were reported as means and standard deviations (SD). Within- and between-group comparisons of longitudinal changes in IPFP morphology were evaluated using ANCOVA, adjusting for baseline values of the outcome, baseline BMI, and sex. IPFP volume was considered the primary analytic focus of the current analysis, and IPFP anterior surface area, IPFP posterior surface area, IPFP mean and maximal thickness as exploratory focus. Correlations between IPFP change and body mass change, body composition change or thigh composition change (DXA and CT) were studied independent of intervention type, using Spearman correlations. The level of significance for all comparisons was set at 0.05. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

5. RESULTS

Across the three intervention groups, the mean weight at baseline was 93.5 ± 14.0 kg (mean ± SD), the mean BMI 33.9 ± 3.8 kg/m^2, the mean IPFP volume 26651.6 ± 6974.6 mm^3, the mean IPFP anterior surface area 2458.3 ± 562.4 mm^2, the mean IPFP posterior surface area 3732.7 ± 777.8 mm^2, the mean IPFP thickness from anterior surface 6.5 ± 0.6 mm, the maximal IPFP thickness from anterior surface 15.0 ± 1.6 mm and male sex frequency 27.4%. There were no significant differences in baseline age, sex, BMI and IPFP morphology between the three intervention groups. Descriptive statistics for the participants in each of the interventions are presented in Table 1.

Table 1: Baseline characteristics in exercise (E), diet (D) and diet+exercise (D+E) intervention groups.

Parameter	All (n=106)		E (n=36)		D (n=35)		D+E (n=35)	
	Mean or FR	SD or %	Mean or FR	SD or %	Mean or FR	SD or %	Mean or FR	SD or %
BMI [kg/m^2]	33.9	3.8	33.7	3.7	34.3	4.1	33.7	3.7
Body weight [kg]	93.5	14.0	91.6	13.0	96.9	15.7	91.9	13.0
Sex [male]	29	27.4	9	25.0	11	31.4	9	25.7
IPFP volume [mm^3]	26652	6975	25323	6252	28036	7621	26634	6934
IPFP anterior surface area [mm^2]	2458	562	2408	550	2527	617	2441	527
IPFP posterior surface area [mm^2]	3733	778	3593	742	3874	889	3735	685
IPFP mean thickness [mm]	6.5	0.6	6.4	0.5	6.6	0.7	6.5	0.7
IPFP maximal thickness [mm]	15.0	1.6	14.9	1.5	15.3	1.6	14.9	1.6

n = sample size, IPFP = infrapatellar fat pad, FR = frequency, SD = standard deviation

A significant ($p<0.01$) reduction in IPFP volume was observed in each of the three intervention groups over the 18-month observation period [Table 2 and Figure 2]: -2.1% in E, -4.0% in D and -5.2% in D+E; the % body weight loss from baseline in each group amounted to approximately -1.0% in E, -10.5% in D and -13.0% in D+E on average [Table 2]. There was a significant ($p<0.01$) within-group decrease in IPFP posterior surface area in all intervention groups, and a significant ($p<0.001$) within-group decrease in IPFP anterior surface area in the D+E intervention group. Other within-group changes in IPFP morphology did not reach statistical significance. Change in IPFP volume appeared to be more strongly driven by a change in posterior and anterior surface areas than by changes in IPFP thickness [Table 2].

Table 2: Mean changes (MC) within exercise (E), diet (D) and diet+exercise (D+E) intervention groups between baseline and 18-month follow-up in BMI, body weight and infrapatellar fat pad (IPFP) morphology; results for IPFP morphology were adjusted for baseline values of the outcome, baseline BMI, and sex.

IPFP parameter	E MC (95% CI)	D MC (95% CI)	D+E (95% CI)
BMI [kg/m^2]	-0.26 (-0.74, 0.22)	-3.45 (-4.46, -2.43)	-4.31 (-5.43, -3.20)
Body weight [kg]	-0.89 (-2.16, 0.39)	-10.18 (-13.16, -7.21)	-11.93 (-14.86, -9.01)
IPFP volume [mm^3]	-704[a] (-1217, -190)	-1074[b] (-1607, -540)	-1462[b] (-1994, -930)
IPFP anterior surface area [mm^2]	-20.7 (-73.5, 32.1)	-25.4 (-78.5, 27.6)	-71.4[a] (-120.0, -17.8)
IPFP posterior surface area [mm^2]	-90.3[a] (-156.7, -24.0)	-141.9[b] (-210.2, -73.6)	-182.0[b] (-250.5, -113.5)
IPFP mean thickness [mm]	0.00 (-0.09, 0.10)	0.00 (-0.09, 0.10)	-0.01 (-0.10, 0.09)
IPFP maximal thickness [mm]	0.00 (-0.25, 0.25)	-0.16 (-0.42, 0.09)	-0.06 (-0.32, 0.19)

CI = confidence interval, [a] = $p<0.01$, [b] = $p<0.001$

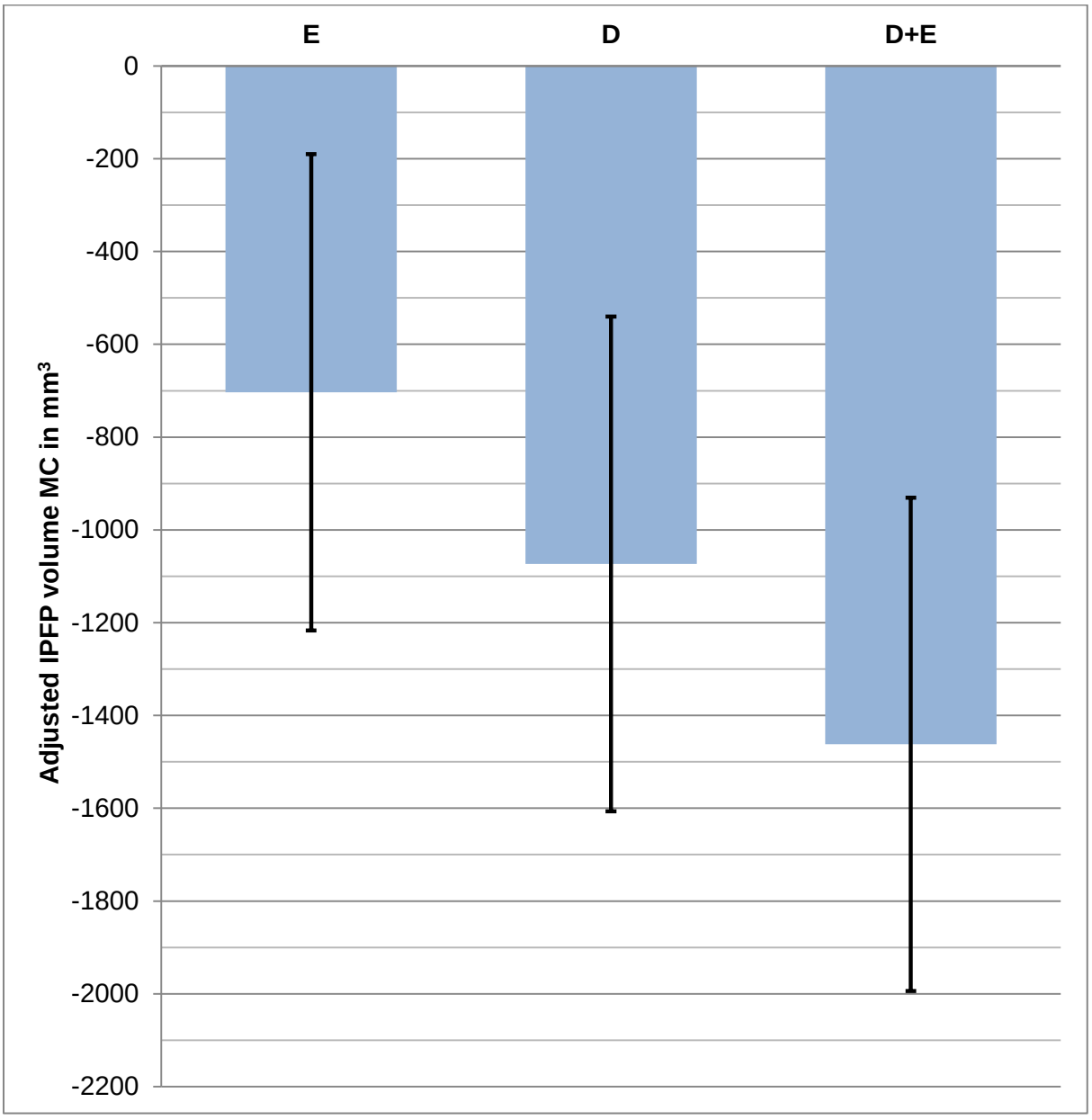
Between group comparisons revealed a significantly greater IPFP volume and IPFP posterior surface area reduction in the D+E group than in the E (control) group ($p<0.05$) [Table 3]; other between-group differences in the longitudinal changes in IPFP morphology were not statistically significant.

Table 3: Pairwise comparisons between intervention groups for mean changes (MC) in infrapatellar fat pad (IPFP) morphology between baseline and 18-month follow-up, adjusted for baseline values of the outcome, baseline BMI, and sex.

IPFP parameter	E vs. D (95% CI)	E vs. D+E (95% CI)	D vs. D+E (95% CI)
IPFP volume [mm3]	370 (-328, 1068)	759[a] (68, 1450)	389 (-307, 1085)
IPFP anterior surface area [mm2]	4.7 (-65.9, 75.4)	50.7 (-19.7, 121.0)	45.9 (-25.1, 117.0)
IPFP posterior surface area [mm2]	51.6 (-38.6, 141.7)	91.7[a] (2.3, 181.0)	40.1 (-49.8, 130.1)
IPFP mean thickness [mm]	0.00 (-0.13, 0.13)	0.01 (-0.11, 0.14)	0.01 (-0.11, 0.14)
IPFP maximal thickness [mm]	0.17 (-0.18, 0.51)	0.07 (-0.27, 0.40)	-0.10 (-0.44, 0.24)

CI = confidence interval, [a] = $p<0.05$, E = exercise, D = diet, D+E = diet+exercise, vs. = versus

Figure 2: Mean changes (MC) in IPFP volume within exercise (E), diet (D) and diet+exercise (D+E) intervention groups between baseline and 18-month follow-up in infrapatellar fat pad (IPFP) morphology, adjusted for baseline values of the outcome, baseline BMI, and sex. Error bars represent 95% confidence interval.



Across the intervention groups, there was a significant ($p<0.01$) correlation between IPFP volume change and weight loss ($r=0.40$), BMI change ($r=0.39$), total body fat mass change with DXA ($r=0.44$; $n=88$), total and subcutaneous thigh fat change with CT ($r=0.32$; $n=82$), and inter-muscular thigh fat change with CT ($r=0.29$; $n=82$) [Table 4]. Per regression analysis, for each percent of weight lost there was a 0.27% reduction in IPFP volume across all participants.

Table 4: Spearman correlations between infrapatellar fat pad (IPFP) volume changes and changes in body composition predictors. Sample sizes (n) vary based on predictor.

Body or thigh composition predictor	n	Correlation	P-value
Weight change [kg]	106	0.40	<0.0001
BMI change [kg/m^2]	106	0.39	<0.0001
DXA total fat mass change [kg]	88	0.44	<0.0001
DXA total fat mass change [%]	88	0.35	0.0010
CT total thigh fat change [cm^3]	82	0.32	0.0029
CT subcutaneous thigh fat change [cm^3]	82	0.32	0.0030
CT inter-muscular thigh fat change [cm^3]	82	0.29	0.0074

BMI = body mass index; DXA = dual x-ray absorptiometry, CT = computed tomography

6. DISCUSSION

This is the first study, and the first randomized controlled trial examining the effect of diet and/or exercise intervention, as well as weight loss and change in body composition on the IPFP morphology. The current study was conducted using MR imaging from a subsample of the IDEA trial[13] population. A custom image analysis software was used specifically for the quantitative analysis of the IPFP morphology.

In all three intervention groups we observed a reduction in IPFP volume, the combination of D+E intervention being more effective in reducing IPFP volume than E alone. Per regression analysis, for each percent of weight lost there was a 0.27% reduction in IPFP volume across all participants. Further, IPFP volume reduction was associated with DXA total fat mass loss and CT thigh fat mass loss, independent of the specific intervention. In general, therefore, the IPFP can be assumed to be responsive to diet-induced weight loss and to exercise.

Changes in IPFP volume appear to be driven by changes in the posterior and anterior surface area rather than by changes in mean IPFP thickness. This indicates that the IPFP may more likely expand or shrink medially and laterally with weight gain and loss than undergo a change in thickness (depth).

A key strength of the current study is its randomized controlled design, which allowed for a detailed analysis of the effects of the interventions on the IPFP volume and its association to obesity. The lack of a true control group without an active intervention, however, could imply some limitations to the interpretation of the effect size of the interventions on the IPFP. More precisely, the E (control) intervention group showed a statistically significant reduction in IPFP size in the absence of a relevant weight loss, which renders the interpretation of effectiveness of D and D+E intervention and that of weight loss somewhat challenging. Only the subsample of the IDEA trial population was analyzed, for which MR images of the knee joint (and DXA scans and CT scans of the thigh) were obtained. This could have affected power of analysis to such an extent that subtle differences in IPFP volume change between D and E as well as between D and D+E failed to reach significance. Although the difference in IPFP volume change between E and D+E reached $p<0.05$, this has still to be interpreted with some care, because 3 parallel tests were performed, and no adjustment for multiple comparisons was made. Nevertheless, the results provide a strong trend, indicating that D is more effective than E in reducing the IPFP volume, and we did find a statistically significant correlation between change in IPFP volume and body fat mass, further supporting the above findings that IPFP volume change is greater in intervention groups that achieved a greater reduction in body weight.

The fact that only a subsample of the IDEA trial population was studied here also represents a limitation when comparing the results of the current study to the primary and secondary

clinical, mechanistic, and inflammatory outcomes of the IDEA trial[13]. However, there was no indication that the subsample of the current study differed significantly from the entire IDEA trial population.[120] Further, within the subpopulation, no statistically significant between-group differences between demographic parameters of IPFP morphometric measures were found at baseline. Hence, the interpretability of the effect size of the interventions and weight loss was not affected from this perspective.

A strength of this study is that a quantitative method was applied for the measurement of the IPFP morphology. Segmentation was performed on all slices depicting the IPFP, in order to ensure that changes in the medial to lateral extensions are covered.[20] This potential effect may be missed when only one sagittal slice is measured.[115,116]

The IPFP has been found to be a local source of pro-inflammatory mediators, including a variety of cytokines as well as adipokines such as leptin and adiponectin.[15–17] Inflammatory activity of the IPFP has been shown to potentially affect synovial inflammation,[70] while levels of inflammatory mediators were found to be associated with cartilage degradation or thinning.[7,8,11,89] A change in IPFP volume may thus be potentially associated with changes in its inflammatory activity and the secretion of inflammatory mediators in the synovial fluid, with cartilage damage and with the onset or progression of knee OA.

In this study, however, no semi-quantitative assessment of Hoffa-synovitis or edema, vascularization, fat necrosis, fibrosis and effusion within the IPFP, were performed, limiting the possibilities for a precise interpretation of the relationship between IPFP volume changes and inflammation. Further, no inflammatory markers were obtained from the synovium. Therefore we plan to relate the quantitative IPFP measurements made here to semi-quantitative assessment of Hoffa synovitis and to serum markers of inflammation in future analyses.

Han et al.[115] reported that IPFP size was positively associated to body weight, but they found no relation to BMI or body fat, indicating that the relationship with body weight was confounded by height. It should be noted that in Hans' study the IPFP maximum area, measured on a single MR imaging slice, was chosen as a surrogate for IPFP size. This approach is problematic, since the maximal area does not cover morphological changes taking place in the peripheral IPFP and in medial-lateral directions, thereby compromising the validity of the conclusions made. A systematic study on the relationship between IPFP volume and the BMI in men and women is currently underway by our group, also including a comparison of potential differences between subjects with and without symptomatic knee OA.

Our results seem to differ from a study where the actual IPFP volume was measured in a cohort consisting of 15 subjects with knee OA and 15 matched controls without knee OA. In that study, no correlation between IPFP volume and BMI or weight was observed.[22]

However, the small sample size of this study likely renders the study to be underpowered to detect a relation between IPFP volume and anthropometric variables.

Recently, a cross-sectional study among participants of the Osteoarthritis Initiative healthy reference cohort found a correlation between IPFP size and body weight ($r = 0.34$ in men and 0.50 in women, $p<0.05$).[123] However, associations between the IPFP volume and BMI or body composition were not studied , also because the healthy reference cohort participants had a normal weight by definition.[123]

The findings of the current study are in agreement with observations in mice that longitudinal change in weight (i.e. high-fat feeding) induced modification of the IPFP volume.[24] In this mouse model, these changes in IPFP volume were observed along with an almost 3-fold increase in subcutaneous fat and approximately 4.6-fold increase in visceral fat, suggesting that the IPFP is responsive to changes in weight and BMI.[24]

The E intervention led to a significant decrease in IPFP volume without considerable body weight loss. This could be potentially the result of reduced inflammation and edema or improved circulation within the substance of the IPFP due to exercise applied in this sedentary and overweight or obese population. However, exercise was shown to reduce intermuscular fat of the thigh without substantial body weight loss and a reduction of both subcutaneous and intermuscular fat, as well as an increase in muscle mass, this being observed after strength and endurance training in subjects with low baseline cardiovascular fitness.[124] Yet, contrary to intermuscular fat, the IPFP is not closely related to the musculature involved in exercise training, rendering it unlikely to serve as a local energy source. Nevertheless, there are signs of metabolic activity of the IPFP, especially in advanced knee OA.[17] Thus, a reduction of the adipose tissue of the IPFP in response to an overall weight loss is plausible and may be associated with a lesser production of adipokines and hence a reduction in “low grade” inflammation, supported by lower IL-6 levels observed in the D and D+E group of IDEA study participants.[13] However, to reveal the actual mechanistic link between IPFP volume changes and dietary or exercise interventions, further studies are needed that include metabolic variables, inflammatory markers taken from synovium and specific signs of IPFP inflammation or edema.

In the IDEA trial, participants of all intervention groups yielded modest clinical improvements in WOMAC pain and functions scores as well as mobility.[13] The D+E intervention achieved a statistically significantly better clinical outcome than E or D alone.[13] The IPFP may contribute to the sensation of pain in knee OA, since it is known to be extensively innervated, as reviewed by Clockaerts and collegues.[66] Recently, greater pain in knee OA was found to be associated to larger IPFP volume.[23,117] Likewise, the reduction in IPFP volume observed in our current study could partially explain the improvements in WOMAC pain scores observed in the IDEA population by reduced pain sensation in addition to reduction in “low grade”

inflammation. The greater effect size of the IPFP volume reduction in D+E compared to E could, for example, be reflected in the differences between the same groups in the improvements of WOMAC pain scores. It is therefore of great interest to study whether a correlation between IPFP volume change and WOMAC pain or overall disability exists.

7. CONCLUSION

In summary, in the current randomized controlled trial the IPFP is shown to be responsive to diet-induced weight loss and to exercise in sedentary and overweight or obese patients with knee OA, while diet in combination with exercise appeared to be more effective in reducing IPFP volume than exercise alone. Further, volume changes of the IPFP were positively correlated with changes in body and thigh fat mass. The IPFP has been described as a potential source of inflammatory mediators contributing to the incidence and progression of knee OA;[15–17] this motivates further exploration of the relationship between IPFP volume change, improvement in clinical outcomes, and their relationship with levels of markers for inflammation and catabolic processes in the synovial fluid of the knee joint.

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Comment

The results of the current thesis will be presented in the poster session of the OARSI Congress, Seattle 2015

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