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THE RELATION BETWEEN TYPE 2 DIABETES MELLITUS, KNEE OSTEOARTHRITIS AND ULTRASONOGRAPHIC MEASUREMENT OF FEMORAL CARTILAGE THICKNESS

TİP 2 DİYABET, DİZ OSTEOARTRİTİ VE FEMORAL KARTİLAJ KALINLIĞININ ULTRASONOGRAFİK ÖLÇÜMÜ ARASINDAKİ İLİŞKİ

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ABSTRACT

Aim: The aims of this study are: 1-to determine the relation between knee osteoarthritis, ultrasonographic measurement of femoral cartilage thicknesses and type 2 diabetes,2-to investigate the effect of the related factors such as body mass index, abdominal waist circumference, HbA1c on this relationship.

Methods: A total of 126 female patients were divided into two groups: 1-Diabetes Group, 2-Control Group. Variables were age, HbA1c, body mass index, waist circumference, visual analog scale, gait speed, short form-36, Kellgren Lawrance Scale and ultrasonographic measurements of distal femoral cartilage thicknesses.

Results: The mean age was 56.26±8.05 in diabetes group, it was 58.12±7.57 in control group. There was no significant difference between groups according to ultrasonography parameters which are correlated with nor HbA1c, nor body mass index and waist circumference in both groups. Both body mass index(r=0.422) and waist circumference(r=0.423) were moderately correlated with Kellgren scores in Control Group. In Diabetes group, HbA1c(r=0.404) and body mass index(r=0.696) were moderately correlated with Kellgren scores, moreover waist circumference(r=0.791) was strongly correlated with Kellgren-scores.

Conclusion: There was found a strong relation between type 2 diabetes mellitus and knee osteoarthritis, however there was found no relation between type 2 diabetes and ultrasonographic femoral cartilage thicknesses measurement. Furthermore abdominal obesity seems to contribute to this relation between type 2 diabetes and knee osteoarthritis more than HbA1c and body mass index.

Key Words: Abdominal obesity, Diabetes mellitus, Femoral cartilage thickness, Osteoarthritis, Quality of life

ÖZET

Giriş: Bu çalışmanın amacı 1- tip 2 diyabet ile femoral kartilaj kalınlığı ve diz osteoartriti arasındaki ilişkiyi belirlemek, 2- bu ilişki üzerine beden kitle indeksi, abdominal bel çevresi, HbA1c gibi faktörlerin etkisini araştırmaktır.

Yöntem: Bu çalışmaya toplam 126 kadın hasta kabul edilerek, hastalar diyabet varlığı (Diyabet grubu) ve yokluğuna (Kontrol grubu) göre iki gruba ayrıldı. Yaş, HbA1c, beden kitle indeksi, abdominal bel çevresi, vizüel analog skala, yürüme hızı, Kısa Form-36, Kellgren Lawrance Skalası ve ultrasonografik distal femoral kartilaj kalınlık ölçümü çalışmanın değişkenleri idi.

Bulgular: İki grup arasında femoral kartilaj kalınlığı arasında bir fark saptanmadı, ne HbA1c ne de vücut kitle indeksi ve bel çevresi değerleri her 2 grupta da femoral kartilaj kalınlığı ile korelasyon göstermedi. Kontrol grubunda hem beden kitle indeksi(r=0.422) hem de bel çevresi(r=0.423) Kellgren skorları ile korelasyon gösterdi. Diyabet grubunda ise hem HbA1c(r=0.404), hem de beden kitle indeksi(r=0.696) ile Kellgren skorları arasında korelasyon saptanmakla birlikte, abdominal bel çevresi (r=0.791) ile Kellgren skorları arasındaki korelasyon daha güçlü düzeyde idi.

Sonuç: Tip 2 diyabet ve diz osteoartriti arasında güçlü bir ilişki saptanmıştır ancak tip 2 diyabet ile ultrasonografik femoral kartilaj kalınlığı ölçümü arasında bir ilişki saptanmamıştır. Ayrıca tip 2 diyabet ve osteartritin arasındaki ilişkiye, abdominal obezite, HbA1c ve beden kitle indeksinden daha fazla katkı yapıyor görünmektedir.

Anahtar Kelimeler: Abdominal obezite, Diyabetes Mellitus, Femoral kartilaj kalınlık, Osteoartrit, Yaşam kalitesi

INTRODUCTION

Musculoskeletal pain is known to be more prevalent in patients with diabetes mellitus (DM) (1). Some of the studies showed that diabetes may predispose to knee osteoarthritis (OA) (2,3) but some studies showed no relation between them (4,5).

While evaluating the relation between diabetes and osteoarthritis, it is necessary to consider the effects of diabetes on articular cartilage. The loss of cartilage thickness is known to be associated with knee pain and OA progression (6). MRI (Magnetic Resonance Imaging) based studies reported that patients with diabetes had increased degeneration in articular cartilage in comparison to subjects without diabetes (2,3). Advanced glycation endproducts can accumulate in diabetic cartilage in early periods and disrupt biomechanics (7). On the other hand there is evidence, diabetes alter cartilage extracellular matrix (ECM), also animal studies showed that diabetes leads to decreased collagen production (8) and increased proteoglycan catabolism (9). Furthermore, there is an increasing recognition that inflammation is the key role between DM and OA. Hyperglycemia increases reactive

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oxygen species, inflammatory cytokines contributing to tissue damage (10).

Osteoarthritis and diabetes share risk factors including both obesity and abdominal obesity. In many studies, both obesity and abdominal obesity was found to be strongly related with knee OA (11,12). Possible mechanisms; 1- Each additional kilogram increases the mechanical loads on knee joints and induces cartilage degeneration, contributing to knee OA (13,14). 2- Inflammation is the other possible mechanism. The location of adipose tissue is more important than total amount of adipose tissue, in the development of inflammation. Therefore, OA is more found in patients with abdominal obesity due to the inflammatory mediators originating from adipose tissue. And these mediators has many effects not only on synovial tissue, but also on cartilage and bone (15). Also in a recent article, the resistin levels were found to be associated with knee OA and adiposity measures (16). Moreover in previous studies in patients with knee OA a significant relationship was shown between glycosaminoglycan content and body mass index (17).

Even though there are many studies investigating the relation between DM and OA, however the exact role of diabetes in osteoarthritis and femoral cartilage thickness is still unclear. It is also unclear that this relationship is more associated with diabetes itself or the underlying obesity and abdominal obesity. This study investigates the relation between type 2 DM, knee OA and ultrasonographic measurement of femoral cartilage thicknesses.

Considering all the above, this study is conducted; 1-to determine the relation between knee osteoarthritis, ultrasonographic measurement of femoral cartilage thicknesses and type 2 diabetes mellitus, 2-to investigate the effect of the related factors such as body mass index, abdominal waist circumference, HbA1c on this relationship.

METHODS

This cross-sectional study was designed as a single centre study in September and October 2020 with 126 female patients who admitted to the physical medicine and rehabilitation outpatient clinic with knee pain. The inclusion criteria were being postmenopausal, aged lower than 70. Patients with any chronic diseases, inflammatory arthritis, knee surgery, trauma, bone mass or cancer, impaired cognition, immobilized patients, type 1 diabetes mellitus were excluded from the study. Patients who met inclusion and exclusion criteria were divided into two groups: Diabetes group and Control group.

The presence and the absence of diabetes mellitus was accepted as self reported and it was confirmed from the patient files. All diabetes patients were using one or more medication (insulin / oral anti-diabetic medication). Fasting blood glucose values of all patients were evaluated retrospectively from the patient files. All control patients had fasting glucose values lower than 100 mg/dl and had never use diabetes medication. Also, the HbA1c values of patients in the last 6 months were recorded retrospectively from the patient files.

An anamnesis was about the age, smoking, education, working. After the anamnesis, an examine was made by a physiatrist to identify knee pain. Chronic constant knee pain was accepted as having persisting pain for more than ¼ years (18). Intermittent knee pain was described as having a history of recurrent knee pain. Visual analog scale (assessed from 0 to 10) was used for measuring pain severity (no pain to worst possible pain) (19). Physical performance was assessed with “gait speed”. Patients walked 5 meters with a normal pace, starting and ending section of fifty cantimeters was not evaluated, only 4 meters gait speed evaluated (20).

The weight of each patient was measured with a digital medical scale in light clothes and socks (a standard right-angle device and a fixed measurement tape without shoes). Before the measurement, the scale was calibrated to the zero level.

Abdominal obesity was defined as the abdominal waist circumference was more than 88 cantimeters in female (21). Quality of life assessment was done using Short Form 36 (SF-36), with 36 items (22). Knee radiographs which were taken in the last one year, were interpreted by two physiatrists for Kellgren-Lawrance (K-L) Scale. (23).

All ultrasonographic measurements were performed using a 5-10 MHz linear probe (Arietta V60, Hitachi Aloka Medical Systems, Tokyo, Japon) as single blind. The evaluation of distal femoral cartilage (for both knees) was performed while lying in a supine position with maximal knee flexion. The transducer was placed axially, over the patellar outer edge. The measurement of distal femoral cartilage thickness were marked from the mid-points of:1- the medial femoral condyle (MFC), 2- intercondylar area (IA) and 3- the lateral femoral condyle (LFC). The distal cartilage thickness was measured according to the distance between the thin hyperechoic line at the cartilage - synovial interface and the sharp hyperechoic line at the bone - cartilage interface (24). Knee measurement were recorded seperately for each knee, the mean of both knees were not recorded.

Written, informed consent was obtained from all participants.

This trial was performed in the ethics standarts as laid down in the 1964 Declaration of Helsinki. Ethics committee approval was received from Eskişehir Osmangazi University ethics committee (16/06/20-37 :E-25403353-050.99-68877).

Statistical analysis

The distribution of each continuous variable was

Tablo 1. Comparison of demographic characteristics and laboratory parameters between patients with and without diabetes mellitus.

	Diabetes group (n=56) median (25-75%)	Control group (n=57) median (25-75%)	*P value*
Age (years)	59 (52-64)	56 (49-62)	0.169*
HbA1c (%)	6.7 (6.1-8.6)	5.5 (5.1-5.8)	**<0.001***
Fasting glucose levels (mg/dl)	150 (124-204)	92 (81-95)	**<0.001***
Body mass Index (kg/m²) (mean **±** SD)	31.4 ± 5.2	28.5 ± 4.1	**0.001****
Abdominal waist circumference (cm)* (mean **±** SD)	99.0 ± 12.7	89.7 ± 9.9	**<0.001****
Working status			0.053***
Working n (%)	6 (10.7%)	15 (26.3%)	
Not working n (%)	41 (73.2%)	38 (66.7%)	
Retired n (%)	9 (16.1%)	4 (7%)	
Educational status			**0.003*****
Primary school and lower n (%)	49 (87.5%)	36 (63.1%)	
High school and higher n (%)	7 (12.5%)	21 (36.9%)	
Smoking n (%)	8 (14.3%)	9 (15.8%)	>0.05***

(*Mann Whitney U Test, **t-test, *** chi-square test)

Tablo 2. Comparison of clinical parameters between diabetes and control group.

	Diabetes Group (n=56) median (25-75%)	Control group (n=57) median (25-75%)	*P value*
Gait speed (m/s) (mean**±**SD)	0.9 ± 0.2	1.0 ± 0.2	**0.006****
Visual Analog Scale (n)	6 (4-8)	5 (2-7)	**0.036***
SF-36 subgroups (n)			
Physical function (mean**±**SD)	45.8 ± 26.5	69.2 ± 19.9	**<0.001****
Role physical	0 (0-50)	50 (25-100)	**<0.001***
Role emotional	33.3 (0-100)	33.3 (33,3-100)	**0.043***
Bodily pain	45 (22.5-67.5)	55 (38.7-77.5)	**0.015***
Energy	40 (25-53.7)	40 (25-55)	0.516*
Emotional wellbeing	60 (48-68)	60 (42-78)	0.449*
General health (mean**±**SD)	47.6 ± 17.3	54.1 ± 15.3	**0.039****
Social function	50 (25-87.5)	87.5 (62.5-100)	**<0.001***

(*Mann Whitney U Test, **t-test) (SF-36: Short Form-36)

tested for normality using the Shapiro-Wilk test. Normally distributed variables were performed using the t test and are expressed as mean ± standard deviation (SD). Non-normally distributed variables were performed using the Mann Whitney U and are expressed as median value (25%-75%). The categorical variables are expressed in frequencies and percentages. The chi-square tests were used to compare categorical variables. $p < 0.05$ was considered significant. The Spearman correlation coefficient was used as the correlation analysis (a coefficient of <0.1: negligible correlation, 0.1-0.39: weak correlation, 0.4-0.69: moderate correlation, 0.7-0.89: strong correlation, ≥0.9: very strong). All analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 126 patients with knee pain were admitted to our study. 8 (6 .3%) patients were excluded due to cardiac disease, 3 (2.3%) patients were excluded due to chronic obstructive pulmonary disease, 1 (0.7%) patient was excluded due to rheumatoid arthritis, 1 patient was excluded due to dermatomyositis. 221 knee of 113 patients (with the mean age of 57,1±7,84) were evaluated. Only one knee of five patients was evaluated due to artroplasthy in the other knee. 113 patients were divided into two groups: 57 (50.4%) patients in Control Group, 56 (49.6%) patients in Diabetes Group. The median HbA1c value of patients with diabetes was 6,7 (50mmol/mol) (6.1 [43mmol/mol] - 8.65 [71mmol/mol]) and 11 of 56 (19.6%) patients with diabetes were using insulin. Comparison of demographic characteristics and laboratory parameters between patients with and without diabetes mellitus is shown in Table 1.

All clinical parameters (except SF-36 subgroups: energy and emotional wellbeing) were found significantly different between patients with diabetes and without diabetes. Gait speed (p=0.006) and SF-36 subgroups (physical function, role physical, social function: p<0.001, role emotional: p=0.043, bodily pain: p=0.015, general health: p=0.039) were significantly lower, VAS score (p=0.036) was significantly higher in diabetes group (Table 2). However, there was no significant difference between groups according to ultrasonographic parameters, on the other hand Kellgren-Lawrance scores were significantly better in patients without diabetes (Table 3).

Correlation analysis in Diabetes Group showed that, there was found a moderate correlation between Kellgren Scores and age (p<0.001, r=0.603), HbA1c (p<0.037, r=0.404) and BMI (p<0.001, r=0.696). A strong correlation was found between only Kellgren Scores and waist circumference (p<0.001, r=0.761). However, there was found no correlation between femoral cartilage thicknesses and age, BMI and waist circumference (Table 4).

Correlation analysis in Control Group showed that, there was found a moderate correlation between Kellgren scores and age (p<0.001, r=0.602), BMI (p=0.014, r= 0.422) and waist circumference (p=0.014, r= 0.423). However, there was found no correlation between

Tablo 3. Comparison of ultrasonographic and radiographic parameters between diabetes and control group.

	Diabetes Group (n=56) Mean ± SD	Control group (n=57) Mean ± SD	*P value*
Femoral Cartilage Thickness (mm)			
Right MFC	1.5 ± 0.3	1.5 ± 0.3	0.933**
Right IA	1.7 ± 0.3	1.6 ± 0.3	0.421**
Right LFC	1.7 ± 0.3	1.6 ± 0.2	0.076**
Left MFC	1.5 ± 0.4	1.5 ± 0.3	0.805**
Left IA	1.7 ± 0.3	1.6 ± 0.3	0.184**
Left LFC	1.7 ± 0.3	1.6 ± 0.3	0.144**
Kellgren Lawrance Scale (n) median (25-75%)	2 (1-3)	1 (1-2)	**0.001***

(*Mann Whitney U Test, **t-test) (mm: millimeters, MFC: the medial femoral condyle, ICA: intercondylar area, LFC: the lateral femoral condyle)

Tablo 4. Correlations of ultrasonographic and radiographic parameters with age, body mass index, abdominal waist circumference and HbA1c in diabetes group.

	Age (years)	BMI (kg/m²)	Abdominal waist circumference (cm)	HbA1c (%)
Femoral Cartilage Thickness (mm)				
Right MFC	-0.006[a] 0.966*	-0.072[a] 0.602*	-0.032[a] 0.814*	-0.023[a] 0.883*
Right IA	-0.002[a] 0.989*	0.114[a] 0.407*	0.025[a] 0.855*	0.170[a] 0.269*
Right LFC	-0.051[a] 0.710*	0.093[a] 0.499*	0.036[a] 0.793*	0.020[a] 0.897*
Left MFC	-0.051[a] 0.714*	0.022[a] 0.873*	-0.015[a] 0.914*	-0.009[a] 0.955*
Left IA	-0.033[a] 0.815*	0.157[a] 0.255*	0.067[a] 0.631*	0.079[a] 0.614*
Left LFC	-0.160[a] 0.249*	0.049[a] 0.723*	0.067[a] 0.631*	-0.007[a] 0.964*
Kellgren Lawrance Scale (n)	**0.603[a] <0.001***	**0.696[a] <0.001***	**0.761[a] <0.001***	**0.404[a] 0.037***

([a]: r values, *: p values. All p and r values: The Spearman correlation coefficient) (BMI: Body mass index, MFC: the medial femoral condyle, IA: intercondylar area, LFC: the lateral femoral condyle)

femoral cartilage thicknesses and age, BMI and waist circumference (Table 5).

Tablo 5. Correlations of ultrasonographic and radiographic parameters with age, body mass index and abdominal waist circumference in control group.

	Age (years)	BMI (kg/m²)	Abdominal waist circumference (cm)
Femoral Cartilage Thickness (mm)			
Right MFC	-0.142[a] 0.295*	-0.135[a] 0.321*	-0.174[a] 0.199*
Right IA	-0.125[a] 0.358*	-0.201[a] 0.138*	-0.022[a] 0.871*
Right LFC	0.152[a] 0.262*	-0.042[a] 0.760*	-0.053[a] 0.699*
Left MFC	0.062[a] 0.650*	-0.134[a] 0.326*	-0.067[a] 0.626*
Left IA	0.092[a] 0.499*	-0.168[a] 0.217*	-0.026[a] 0.847*
Left LFC	0.246[a] 0.071*	-0.099[a] 0.472*	-0.045[a] 0.745*
Kellgren Lawrance Scale (n)	**0.602[a] <0.001***	**0.422[a] 0.014***	**0.423[a] 0.014***

([a]: r values, *: p values. All p and r values: The Spearman correlation coefficient) (MFC: the medial femoral condyle, IA: intercondylar area, LFC: the lateral femoral condyle)

DISCUSSION

Our study results showed that type 2 diabetes mellitus is related with increased severity of knee OA and decreased physical performance and quality of life in female patients with knee OA. And waist circumference contributes to this relation more than HbA1c and body mass index. However, there was not found any relation between ultrasonographic measurement of femoral cartilage thickness and type 2 diabetes.

In literature there are a few studies which investigates the relation between diabetes, knee osteoarthritis and obesity, not abdominal obesity (3,25). Similar to our study, a recent metaanalysis reported that diabetes is not an independent risk factor for OA, BMI is more important (4). Different from our study, in Taiwan, Dubey et al. reported a dry-to-wet laboratory study results and significant association between knee OA and DM was reported in both obese and non obese patients (25). Also, Neumann et al. reported an altered tissue composition and accelerated knee cartilage matrix degeneration at MRI in patients with diabetes, independent of body mass index (3). These studies showed that diabetes itself was a risk factor for knee osteoarthritis independent of obesity. Obesity and abdominal obesity are different from each other; both of them have mechanic load on weight bearing joints however abdominal obesity is known to be more related with inflammation (15). Our results showed that both obesity and abdominal obesity are related with radiographic severity of knee OA in patients with and without diabetes. However, in diabetes patients, waist circumference was found to be strongly correlated with severity of radiographic knee OA. The relation between abdominal obesity and knee OA is already known. This relationship has been imputed to mechanical overload on knees. Furthermore, extra one kilogram corresponds to six kilograms of overload on two knees, that leads to

mechanical stress on knee joints (13). On the other hand not only weight bearing joints, but also non-load bearing joints of obese patients has been shown to have much degeneration. It has been suggested that proinflammatory cytokines, systemic mediators and adipokines are released from visseral adipose tissue and they seem to be related with the development of knee osteoarthritis (26). Abdominal obesity and diabetes seem to be acting together in reducing mobility and radiographic severity in knee OA. The mechanisms; mechanic load and inflammation, seem to be additive insulin resistance in type 2 diabetes as a result of abdominal obesity and diabetes acting together.

Although MRI-based studies have shown that patients with diabetes have increased degeneration in articular cartilage in comparison to subjects without diabetes (3,4). In our study there was not found any association between femoral cartilage thickness and type 2 DM. Also there was no found any correlation between femoral cartilage thickness and BMI, abdominal waist circumference and HbA1c. The thickness of femoral cartilage was measured with ultrasonography which has previously been shown to be a valid and reliable method for measuring the femoral cartilage (24). Similar to our study, another study in which cartilage thickness was evaluated with ultrasonography in patients without osteoarthritis, reported no relation in cartilage thickness between good glysemic controlled DM patients and healthy controls (27). Considering the mechanisms of diabetes in cartilage such as: advanced glycation endproducts (7), altered cartilage ECM (8), inflammation, thinner cartilage was expected in diabetes patients compared to patients without diabetes. However in our study, diabetes group consist of mostly good glisemic controlled patients, like other ultrasound study. In good glysemic control, the lack of increased reactive oxygen species and inflammatory cytokines that contribute to tissue damage (10), may be the reason why cartilage thicknesses are similar to patients without diabetes.

It is well known that both DM leads to poor quality of life (28). In our study, quality of life was found lower in diabetes patients. Diabetes mellitus was found to related with poor quality of life. Similar to our study results, after total knee replacement surgery, patients with diabetes were found to exhibit poor quality life scores than patients without diabetes (29). Patients with diabetes usually reacts with aggression predisposition which leads to loss of social support, furthermore sleep disorders and mental comorbidity are associated with lower quality of life in patients with diabetes (30).

Limitations of the study

The diabetes group consisting of mostly good glycemic control, not taking into account the mean level of HbA1c in the last five years, not investigating the duration of type 2 DM also not excluding prediabetes patients from control group are the limitations of our study. Further studies are needed which investigates the cartilage thickness and knee osteoarthritis in prediabetes patients. This study showed the relationship between type 2 DM, knee OA and ultrasonographic measurement of femoral cartilage thickness, this is the strength of our study.

CONCLUSION

Type 2 diabetes mellitus is related with both radiographic and symptomatic knee OA in female patients, and abdominal obesity seems to be an important contributor to this relationship. However there was not found any relation between type 2 diabetes mellitus and ultrasonographic measurement of the femoral cartilage thickness.

Additional information: Availability of data and material, The protocol of this trial is registered to www.clinicaltrials.gov, Date:02.03.21, Number: NCT04779164)

Ethics Committee Approval: This trial was performed in the ethics standarts as laid down in the 1964 Declaration of Helsinki. Ethics committee approval was received from Eskişehir Osmangazi University ethics committee (16/06/20-37 :E-25403353-050.99-68877).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions: Idea/Concept: FB, Design: FB, BO, FŞM, BMÖ, Supervision: FŞM, Data Collection or Processing: FB, BO, FŞM, BMÖ, Analysis or Interpretation: FŞM, FB, Literature Search: FB, Writing: FB, Critical Review: FB, BO, FŞM, BMÖ, References And Fundings: -, Materials: FB, BO, FŞM, BMÖ.

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