Bone Quality in Elderly Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic diseases worldwide and it is associated with an increased risk of osteoporosis and fragility fractures. Our purpose was to analyse microstructural and bone mechanics from femoral heads, markers of bone turnover and bone mineral density in T2DM patients with or without recent fragility fractures. To identify the factors that influence this risk and elucidate diabetes-induced alterations in trabecular bone microarchitecture and bone turnover markers.

Methods: The studied population consisted of 28 patients, divided in 4 groups: 6 subjects with hip fracture (OP) without T2DM, 8 patients with hip fracture and T2DM (OP-T2DM), 7 patients with osteoarthritis (OA) without T2DM and 7 patients OA and with T2DM (OA-T2DM). Bone markers, bone mineral density, FRAX score, microstructural and bone material strength from femoral heads and were assessed.

Results: The group with hip fracture presented lower BMD values than OA ($p < 0.05$). The OP, OP-T2DM and OA-T2DM groups showed a decrease in bone volume fraction (BV/TV); trabecular number (Tb.N); trabecular thickness (Tb.Th) and increase of the structural model index (SMI) and trabecular bone pattern factor (Tb.Pf), as microstructure results and Young's modulus or elastic modulus; toughness; ultimate stress; ultimate load; extrinsic stiffness and work to failure, as biomechanical results, regarding OA patients ($p < 0.05$).

Conclusion: Our results show the negative effect of Type 2 Diabetes Mellitus on trabecular bone structure and mechanical properties. These results emphasize the importance of evaluating diabetic bones using not only bone markers and bone mass, but also bone quality parameters. Therefore, diabetes should be included as a risk factor for osteoporotic fracture in daily clinical practice and in the FRAX tool.

Background

Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic diseases worldwide. T2DM patients exhibit an increased risk of suffering further complications of the disease, which are mainly due to complex and interconnected mechanisms, such as hyperglycaemia, insulin-resistance, low-grade inflammation and accelerated atherogenesis [1]. In addition, these chronic complications adversely affect multiple organ systems including bones, which have been widely associated with an increased risk of osteoporosis and fragility fractures [2, 3].

Osteoporosis (OP) is a metabolic bone disease that is characterized by low bone mineral density (BMD) and microarchitectural deterioration in the bone structure, with a higher risk of fragility fractures [4]. Osteoarthritis (OA) is a metabolically active and dynamic process that involves all joint tissues. OA can lead to mechanical failure, pain and surgical joint replacement with a prosthesis [5]. Clinical and epidemiological studies suggest that OP and OA may coexist in the same patient. BMD values are usually normal or elevated in OA patients at any age, in contrast to OP [6].

T2DM is also very frequent in elderly people, and it exhibits high morbidity and mortality. Furthermore, various lifestyle factors contribute to the increased incidence of T2DM, OA and OP [7, 8]. On the other hand, patients with T2DM are at significant risk for fragility fractures at skeletal sites, such as the hip, spine and forearm, although these patients often have normal or increased BMD [9, 10]. A published meta-analysis showed that T2DM patients exhibit a relative risk of 1.7 (95% CI: 1.3 to 2.2) for hip fracture, and surprisingly, BMD was generally higher in patients with T2DM [11]. The low cortical bone strength and poor bone quality, due to the glycation of bone proteins, may also underlie increased fracture risk in diabetes [12].

The greater risk of an osteoporotic fracture despite normal or high BMD [13] makes necessary to identify the factors that influence this risk and elucidate diabetes-induced alterations in trabecular bone microarchitecture and bone turnover markers.

The goal of this study is to analyze trabecular microstructural and mechanical properties from femoral heads using micro-CT, BMD and bone turnover markers (BTM) in patients with T2DM with or without recent fragility fractures in order to examine skeletal outcomes related to this disease and to establish a relative risk assessment method in the clinical setting. In this regard, we hypothesized that Diabetic patients have higher BMD values than expected, and T- score and FRAX can predict fracture but underestimate risk, therefore skeletal properties must be altered in these patients.

Methods

Study design and subjects

The study was designed as a cross-sectional study. Subjects were included in a consecutive manner (October 2019 to July 2020). We calculated the sample size with the Granmo sample size and power calculator (v.7.12, IMIM,Spain) (https://www.imim.es/ofertadeserveis/software-public/granmo/), in order to detect a significant standardized mean difference of 0.5 (one size average effect) in BV/TV with a type I error rate of 5% (alpha = .05) and a 90% power (1-beta = .90), we required 7 subjects in each group.

The studied population consisted of 31 patients (aged 65–93), the cases group constituted the 14 patients with hip osteoporotic fracture (OP group) undergoing prosthetic hip replacement and the control group constituted the 14 patients with hip osteoarthritis (OA group) but not having any osteoporotic fracture along their life, undergoing total hip arthroplasty. Both groups were subdivided according to the criteria of whether the patient had T2DM. Then the case group was subdivided into OP without T2DM (6 patients) and OP-T2DM (8 patients). Like the control group that was divided into OA without T2DM (7 patients) and OA-T2DM (7 patients) (Fig. 1). 3 patients were excluded, 2 in OP group because not had a normal kidney function and 1 subject in OA group because not had osteoporosis criteria.

The inclusion criterion for the OP patients was to have a current frailty hip fracture (a fall from less than the patient's height without an acceleration mechanism). OA patients could not have been previously

diagnosed with osteoporosis or have a history of frailty fracture since the age of 50 nor could they have congenital or acquired dysplasia or avascular necrosis.

The medical history of all patients was checked and the diagnosis of T2DM for more than 5 years was confirmed for the diabetic patients and discarded for the rest of them. All of the T2DM patients have been treated with metformin.

The exclusion criteria for all the groups included malignant diseases, hyperthyroidism, hyperparathyroidism, multiple myeloma, rheumatoid arthritis, osteomalacia, secondary OP due to corticosteroids or those who were treated with osteoporosis drugs. In addition, patients with congenital or acquired dysplasia or avascular necrosis were excluded from the OA and OA-T2DM groups. In both group of patients had a normal kidney function.

Standardized interviews were used to obtain the following information: age (years), weight (kg), height (cm), body mass index or BMI (kg/m2), use of calcium and vitamin D supplements (none vs. any), use of medication and family history of hip fracture.

We estimated the 10-year risk of major osteoporotic fracture (clinical spine, hip, forearm, or humerus fracture) and the 10-year risk of hip fracture for each patient by the FRAX® tool, calibrated for Spain (www.shef.ac.uk/FRAX/index.htm). The criteria of the Scientific Advisory Council of Osteoporosis in Canada was used to classify the FRAX® scores [14].

The study was approved by the Ethical Review Board of Seville (internal references 2147) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent were obtained from all participants. All patients included in the study agreed to donate their bone samples. Arthroplasty was performed in the Orthopaedics & Traumatology Department of the “Virgen Macarena” University Hospital (Seville, Spain). Because of the difficulty to obtain healthy hip bone donors, the osteoarthritic samples (OA) were considered the reference group since the BMD values classified them as non-osteoporotic.

Biochemical measurements

Fasting morning blood was drawn and stored at -80ºC. We assessed carboxy-terminal telopeptide of type I collagen (CTX), aminoterminal propeptide of type I procollagen (PINP), parathyroid hormone (PTH) and 25-hydroxyvitamin D (25(OH)D), insuline-like growth factor I (IGF-I) and glycated haemoglobin (HbA1c).

PTH, CTX and P1NP were analyzed by immunoassay by an autoanalyzer COBAS 601 (Roche, Spain); inter-assay CV < 5.8%, < 7.6% and < 4.2% respectively.

25(OH)D were analyzed by direct competitive immunoassay by an autoanalyzer LIAISON (DiaSorin, Italy); inter-assay CV < 5.5%. IGF-I was determined using a chemiluminescence immunoassay (CLIA) by an autoanalyzer (IMMULITE 2000, Siemens); inter-assay CV was 6.9%. HbA1c was measured using an autoanalyzer (ADVIA 2400, Siemens; inter-assay CVs was 1%). In all cases, the intra-assay CV was < 5%.

Bone mineral density

BMD of the total hip and femoral neck was measured using a Dual-energy X-ray absorptiometry using the Hologic Discovery W densitometer (Hologic, Inc, Waltham, MA) using the APEX 3.1.1 software. In vivo CV was 2.4% (femoral neck) and 1.1% (total hip).

Microstructural and bone material strength

Femoral heads were stored frozen in phosphate-buffered saline (PBS, Lonza) at -20 °C until processing. A cylinder of trabecular bone was extracted from each femoral head and processed as previously optimized and described by our laboratory[15]. The bone cores were analyzed without further preparation by micro-CT (Skyscan 1172, Bruker micro-CT NV, Kontich, Belgium). The following histomorphometry parameters were measured: bone volume fraction (BV/TV; %), bone surface density (BS/TV; 1/mm), trabecular thickness (Tb.Th; mm), trabecular separation (Tb.Sp; mm), trabecular number (Tb.N; 1/mm), structural model index (SMI) and trabecular bone pattern factor (Tb.Pf; 1/mm).

To visualize material failure on a microstructural level, compression tests of the bone cores were performed using a micro-mechanical testing device (Material Testing Stage, Bruker micro-CT NV, Kontich, Belgium). The following mechanical parameters were measured: ultimate load (Fult; N), extrinsic stiffness (S; N/mm); work to failure (U; mJ); and intrinsic or material mechanical properties: ultimate stress (σult; MPa); Young's modulus (E; MPa); and toughness (u; MPa).

Statistical analysis

Continuous variables are presented as the mean and standard deviation (SD). To compare continuous variables with a normal distribution, ANOVA was used with more than two samples, and Student's t-test with two samples; if the distribution was not normal, the Kruskal-Wallis test or the Mann-Whitney U test was used. Normality testing was performed using a combination of the Kolmogorov-Smirnov test. An adjustment for age, analysis of covariance (ANCOVA), was applied in OA group when needed (to compare microstructural and bone material strength parameters). Correlations between variables were examined using the Spearman correlation, which is appropriate for smaller sample sizes with more robust potential outliers. All hypotheses were two-tailed, and a p value < 0.05 was considered statistically significant. Statistical package SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

In order to check whether type 2 diabetes mellitus has a related effect on bone fragility and risk of fracture we compared the microstructural and biomechanical parameters among osteoporotic patients (OP) with type 2 diabetes mellitus (OP-T2DM group) or without T2DM (OP group) with recent fragility fractures, and we also compared between the OA and OA-T2DM group patients. Because of the difficulty in using bone samples from heathy donors, osteoarthritis patients (OA group) were used as non-osteoporotic control as in other studies they have been used [15]. In Tables 1 and 2 we observe the anthropometric characteristics, BMD and biochemistry of all the groups. We did not find any significant

difference between the values by gender, so we performed the statistical analysis with the total means of the group.

Table 1
Patient characteristics (total and by gender) and analyzed parameters.

	OA	OA-T2DM	p
Gender (Male/Female)	3/4	2/4	
Age (years)	**73.0 ± 5.3**	**76.7 ± 2.2**	n.s
Male	73.7 ± 7.5	76.0 ± 2.8	
Female	72.5 ± 4.4	77.0 ± 2.1	
BMI (kg/m2)	**33.9 ± 3.9**	**30.1 ± 4.0**	n.s
Male	34.2 ± 5.6	25.8 ± 3.2	
Female	32.1 ± 2.7	31.2 ± 3.6	
10-year risk of major fracture (FRAX® tool)	**5.7 ± 4.6**	**8.2 ± 5.4**	n.s.
Male	2.7 ± 1.8	3.5 ± 1.8	
Female	7.9 ± 5.0	10.4 ± 5.1	
10-year risk of hip fracture (FRAX® tool)	**2.6 ± 3.6**	**7.3 ± 11.2**	n.s
Male	1.4 ± 1.8	1.9 ± 1.2	
Female	5.5 ± 5.5	7.9 ± 5.1	
Femoral neck BMD (gHA/cm2)	**0.700 ± 0.09**	**0.688 ± 0.14**	n.s.
Male	0.760 ± .015	0.744 ± 0.25	
Female	0.673 ± 0.06	0.64 ± 0.12	
Hip BMD (gHA/cm2)	**0.858 ± 0.15**	**0.930 ± 0.18**	n.s.
Male	0.99 ± 0.19	1.15 ± 0.12	
Female	0.80 ± 0.10	0.86 ± 0.13	
25-hydroxyvitamin D (ng/mL)	14.2 ± 5.8	12.8 ± 6.8	n.s
PTH (pg/mL)	48.0 ± 20.1	53.4 ± 40.1	n.s
β-CrossLaps (µg/mL)	0.45 ± 0.20	0.32 ± 0.15	n.s
P1NP (ng/mL)	50.7 ± 25.0	37.6 ± 11.5	n.s
IGF-1 (ng/mL)	57.1 ± 16.5	77.0 ± 39.0	n.s
HbA1c (%)	5.4 ± 0.3	7.0 ± 1.3	0.019

Values are shown as the means ± standard deviation (SD). n.s. not statistically significant p values

Table 2
Patient characteristics (total and by gender) and analyzed parameters.

	OP	OP-T2DM	p
Gender (Male/Female)	2/4	2/6	
Age (years)	**83.7 ± 6.2**	**79.4 ± 6.9**	n.s
Male	83.0 ± 5.2	74.5 ± 2.2	
Female	84.2 ± 7.6	81.0 ± 7.3	
BMI (kg/m2)	**28.5 ± 5.2**	**28.47 ± 4.8**	n.s
Male	24.8 ± 3.5	26.9 ± 5.0	
Female	31.3 ± 4.7	29.0 ± 5.0	
10-year risk of major fracture (FRAX® tool)	**20.2 ± 9.6**	**20.3 ± 7.0**	n.s.
Male	13.7 ± 5.9	24.0 ± 4.5	
Female	25.0 ± 9.4	19,7 ± 7.4	
10-year risk of hip fracture (FRAX® tool)	**13.2 ± 8.8**	**13.0 ± 7.9**	n.s
Male	9.5 ± 5.9	21.0 ± 3.8	
Female	16.0 ± 10.1	19.7 ± 7.4	
Femoral neck BMD (gHA/cm2)	**0.493 ± 0.06**	**0.437 ± 0.06**	n.s.
Male	0.538 ± 1.2	0.354 ± 0.03	
Female	0.471 ± 0.1	0.453 ± 0.05	
Hip BMD (gHA/cm2)	0.712 ± 0.10	0.608 ± 0.10	n.s.
Male	0.813 ± 0.04	0.517 ± 0.04	
Female	0.662 ± 0.09	0.625 ± 0.09	
25-hydroxyvitamin D (ng/mL)	13.5 ± 7.8	12.8 ± 9.9	n.s
PTH (pg/mL)	49.0 ± 33.1	77.0 ± 34.8	n.s
β-CrossLaps (µg/mL)	0.75 ± 0.34	0.58 ± 0.53	n.s
P1NP (ng/mL)	63.6 ± 23.6	46.1 ± 31.9	n.s
IGF-1 (ng/mL)	73.0 ± 45.4	63.8 ± 40.0	n.s
HbA1c (%)	5.4 ± 0.3	6.4 ± 1.3	n.s
Values are shown as the means ± typical deviation (SD). n.s. is not statistically significant p values			

(insert in the text Table 1 and 2*)*

Due to OA patients were younger (73.0 ± 5.4 years) than the other groups, an adjustment for age was applied to the successive statistical analyses. No significant differences were found in weight, height, or BMI between the study groups (Table 1y 2). Densitometric parameters were higher in the OA and OA-T2DM groups. We observed significant differences in BMD at the femoral neck and total hip between OA vs OP-T2DM ($p = 0.000$; $p = 0.008$) and between OA-T2DM vs OP-T2DM ($p = 0.032$; $p = 0.007$). While between OA and OP there are significant differences at femoral neck BMD ($p = 0.001$). This indicates that fracture patients have worse BMD values, both at total hip and femoral neck, and OA patients, regardless of whether they have T2DM, their BMD is in normal ranges. The FRAX® 10-year risk of major or hip fracture was higher in OP and OP-T2D patients than OA patients ($p = 0.004$; $p = 0.001$) and with T2DM ($p = 0.005$). The FRAX® 10-year risk of major and hip fracture between the OP and OP-T2DM groups and the OA and OA-T2DM patients were statistically not significant.

The serum levels of the bone turnover markers were also analyzed in all groups. CTX and P1NP were lower in the OA-T2DM patients than the other groups and the highest levels were observed in OP group no significant difference. Vitamin D levels were below 20 ng/mL in all groups of patients, without significant differences between groups (Tables 1 and 2).

Three-dimensional reconstruction and micro-CT images were shown in Fig. 2. We can observe how the samples of the OA group show a higher BMD than the other groups and how the effect of the T2DM produces a significant deterioration at the macroscopic level in the trabecular bone structure.

Microstructural indices showed differences in cancellous bone microarchitecture between groups. Most of the studied parameters in osteoporotic subjects, with and without T2DM, and OA-T2DM subjects showed significant differences compared to control group (OA group) (Fig. 3). The OP, OP-T2DM and OA-T2DM bone samples had smaller BV/TV compared to OA bone biopsies (-53%, $p = 0.001$; -36%, $p = 0.01$; -53%, $p = 0.001$). At the trabecular level, the OP group, OP-T2DM and OA-T2DM, show a lower number of trabeculae, TbN (-33%, $p = 0.0013$; -32%, $p = 0.233$; -14% $p = 0.016$) and less width of the trabeculae Tb.Th (-37%, $p = 0.001$; -35%, $p = 0.001$; -27%, $p = 0.000$). There are no significant differences with the separation of the trabeculae, although the tendency is to be less in all of them compared to the OA group, Tb.Sp (-10%, -15% and – 5%). Furthermore, these three groups also had higher Tb.Pf (in all groups almost 6 times more $p < 0.02$). Among OP group vs OP-T2DM, we found significant differences in SMI parameter (OP: 1.7 ± 0.16; OP-T2DM 1.1 ± 0.16, $p = 0.015$), the other microstructural indices were no significant differences. These results show that the OA-T2DM patients had similar microstructural characteristics to patients OP and OP-T2DM in trabecular bone characteristics, which indicates that the diabetic disease maintains BMD but the microarchitecture is of poor quality and more fragile.

In order to test whether the strength of the trabecular bone is lower in the T2DM patients (OA-T2DM and OP-T2DM) and OP compared with OA patients, different biomechanical parameters were studied (Fig. 4).

The OA-T2DM, OP-T2DM and OP samples showed lower stiffness because of the structural features and material properties of bone: Young's modulus (-59%, -38% and – 51%, respectively; $p < 0.022$) and ultimate stress (-61%, -46% and – 68%; $p < 0.001$). Toughness (-34%, -51% and – 80%, respectively; $p = 0.021$), work to failure (-61%, -54% and – 80%, respectively; $p = 0.005$), extrinsic stiffness (– 58%, -38% and-49%, respectively) and ultimate load (-65%, -49% and – 68%, respectively; $p < 0.001$) were lower in T2DM groups and the OP group compared with the OA group. The OA-T2DM patients exhibited similar biomechanical parameters to patients with osteoporotic hip fracture (OP) in the trabecular bone, while the OP-T2DM group showed the most impacted values in biomechanical parameters. The statistical power for significant differences ($p < 0.05$) for each of the variables studied was calculated, and we always found a higher statistical power of 88% (beta error < 12%).

Finally, we found no statistically significant correlations between duration of T2DM or serum levels of HbA1c with microstructural values.

Discussion

It is widely accepted by the scientific community that T2DM impairs bone metabolism [8, 16], and the risk of fragility fractures is increased in these patients [9, 10]. The mechanisms by which the risk of fracture is increased, and this impairment occurs are not clear. In addition, BMD measurements or FRAX® tool cannot predict these risks. Therefore, there is a need to establish a relative risk assessment method in the clinical setting in patients with T2DM to predict possible impacts on bone fracture related to the disease. The purpose of our analysis was to study the impact in the microstructural and bone mechanics in T2DM patients with or without recent fragility fractures and the relationship of these fractures with type 2 diabetes mellitus.

To verify the influence of T2DM on quantity and quality of trabecular bone tissue from 28 patients, we have assessed BMD, microarchitecture and biomechanical properties of femoral heads from 4 patient groups: OA, OP, OA-T2DM and OP-T2DM. The control group is made up of patients with osteoarthritis, these patients tend to have a localized increase of bone density and/or sclerosis in subchondral bone of the femoral head, but minimal differences in bone density of the femoral neck [17], where we obtained the samples by micro-CT. Moreover, both our diabetic and non-diabetic subjects were undergoing total hip replacement, and therefore the groups should be comparable. Thus, we do not believe presence of osteoarthritis negatively affected our ability to draw conclusions about diabetes vs. non-diabetes. As expected, osteoporotic patients with hip fractures had lower BMD values than osteoarthritic patients, but no differences between osteoporotic patients with and without T2DM were found and neither between the OA group and OA-T2DM. Previous data demonstrated that T2DM patients have normal or increased BMD values [18–20], even when this variable was normalized by the BMI [21]. Although it can be prevalent in juveniles, T2DM is very common in the elderly, and it frequently coexists with age-related bone loss [18]. Therefore, the establishment of risk factors for fragility fractures during ageing should be identified since

these factors can contribute to fracture risk in older diabetic patients. In our case, OP-T2DM and OP patients showed BMD values lower than − 2.5T (T-score score < -2.5) at all hip sites, which is consistent with the stablished World Health Organization Definitions. We found no differences in BMD between osteoarthritic groups with and without T2DM, and the values of BMD were considered normal or healthy by T-score in these groups. As our BMD values shown, clinical and epidemiological studies suggested an inverse relationship between many parameters studied in OP and OA patients [6, 22–25]. The increased BMD may minimize the expected negative effects on bone metabolism caused by diabetes.

The more relevant data obtained in the present study is based on decrease of the values observed of the bone microarchitecture and biomechanical properties that we tested in the trabecular hip bone of patients with both osteoarthritis and T2DM compared with non-diabetic osteoarthritic patients. Both groups of osteoarthritic patients were similar in terms of age, weight, lifestyle and evolutionary stage of degenerative disease. However, bone strength in the T2DM group was importantly damaged, and it was in a similar range in patients with osteoporotic hip fracture. These results show the negative effect of T2DM on trabecular bone structure and mechanical properties. Our findings are also broadly consistent with reports of lower bone material strength index in patients with T2D compared to non-diabetic controls [19, 26]. Conversely, improved properties of trabecular bone were noted in subjects with T2DM compared with controls; however, compromised cortical bone microarchitecture (e.g., increased cortical porosity) [26, 27] was observed. Cortical bone characteristics were not evaluated in this study, but we demonstrated damage in bone microstructure and the mechanics, which are important elements in trabecular bone quality in these subjects with T2DM [28, 29]. We also demonstrated a significant deterioration in these parameters in hip fracture patients. However, a lower quality of trabecular bone was not observed in OP-T2DM patients compared to non-diabetics. Patsch et al. showed similar results in younger people with diabetes using HR-pQCT of the ultradistal and distal radius and tibia [30]. These data note that diabetic disease is a key factor that is directly involved in the deterioration of bone quality, which is likely responsible for the increased risk of fragility fractures.

We found no correlation between microstructure parameters and mechanical values with bone turnover markers. OP subjects exhibited more active bone remodeling, primarily because of bone resorption, as evidenced by the significantly higher levels of β-CrossLaps, which is consistent with a previous study [15]. However, a trend of a reduced bone remodeling activity was observed in T2DM patients, which was demonstrated by the lower levels of formation and resorption markers than the respective controls [19, 20, 31, 32]. Some authors reported defects in bone formation that were produced by a decrease in osteoblast differentiation and an increase in apoptosis in these cells [33]. These changes may lead to an imbalance between bone resorption and bone formation [32, 34].

Considerable evidence suggests that specific factors, such as poor glycemic control and T2DM duration (e.g., a glycated haemoglobin level ≥ 7.5%) [35] exacerbate risk factors in T2DM patients, although this relationship has not been established unequivocally [36]. In the present study, both groups of diabetic patients were fairly well controlled. The average glycated haemoglobin level was lower than the previously mentioned average [35], and it was not associated with mechanical or microstructural

parameters. We did not find a correlation among these values and the duration of diabetic disease, remaining very similar in OP-T2DM and OA-T2DM groups, which is consistent with a previous study [19].

The FRAX tool revealed that the OP and OP-T2DM subjects showed moderate to high risk. However, OA-T2DM patients of similar age showed low risk probability for both types of fracture, but mechanical and microstructure indicated the opposite risk. These results suggest that effective intervention thresholds for fracture prevention in patients with T2DM might be different than those that are effective for non-diabetic patients, as discussed recently [30, 37].

Despite the potential of the present entered data obtained from hip bone human samples, our study had several limitations. Our sample size was relatively small although with sufficient power to obtain significant differences between the differences found. Therefore, our results should be eventually confirmed. The lack of cortical bone microarchitecture and histomorphometry indices of the samples is an additional concern. Nevertheless, this study includes BMD, BTM, trabecular bone microarchitecture and mechanical strength measures in T2DM patients with and without recently suffered fragility hip fracture, thus allowing for establishment a relationship between osteoporotic fracture and diabetes.

Conclusions

Our findings are the first demonstration of compromised trabecular bone microarchitecture and material properties using measurements of human bone biopsies from hip with and without fragility fracture in T2DM subjects. In conclusion, our results show the potential detrimental effects of diabetic disease on bone quality. Furthermore, our results in OA-T2DM subjects confirm that diabetes does not affect BMD, so T2DM affects quality and not bone quantity. These findings emphasize the importance of evaluating diabetic patient using bone markers and bone quality parameters. Therefore, diabetes should be included as a risk factor for osteoporotic fracture in daily clinical practice.

Abbreviations

T2DM: Type 2 Diabetes Mellitus; OP: osteoporosis; OA: osteoarthritis; BMD: bone mineral density; BTM: bone turnover markers; BV/TV: bone volume fraction; Tb.N: trabecular number; Tb.Th; trabecular thickness; SMI: structural model index; Tb.Pf: trabecular bone pattern factor; BMI: body mass index; Fult: ultimate load; S: extrinsic stiffness; U: work to failure; σult: ultimate stress; E: Young's modulus; u: toughness; CTX: carboxy-terminal telopeptide of type I collagen; PINP: aminoterminal propeptide of type I procollagen (PINP); PTH: parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D (25(OH)D; IGF-1: insuline-like growth factor I; Hba1C: glycated haemoglobin; CV: confident interval.

Declarations

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Availability of data and material: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate: All patients gave informed and written consent to participate in the study. The study has been approved by the Ethical Review Board of Hospital Universitario Virgen Macarena (2147) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Competing interests: The authors declare that they have no competing interests.

Consent for publication

Not applicable

Competing interests

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Figures

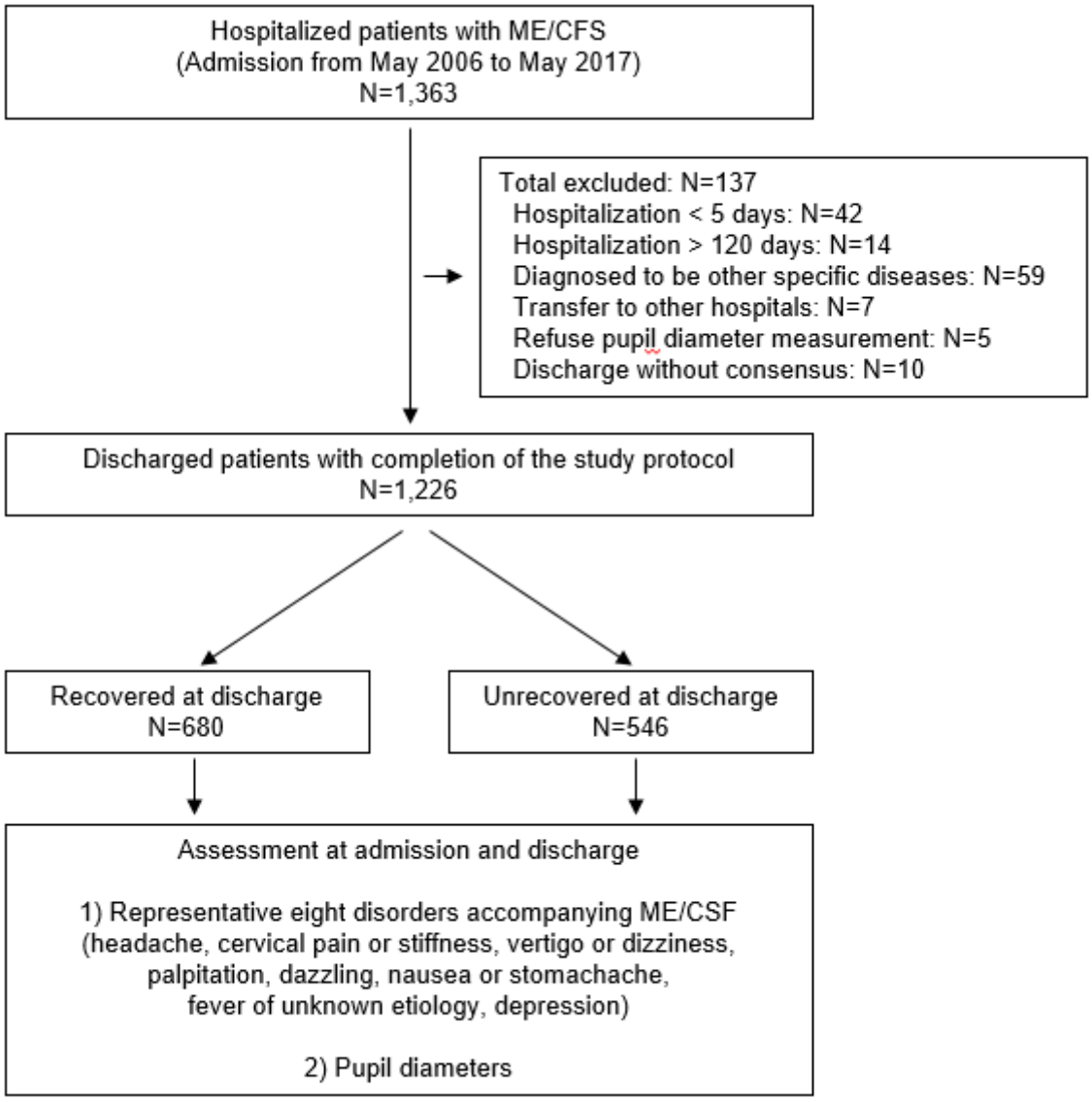
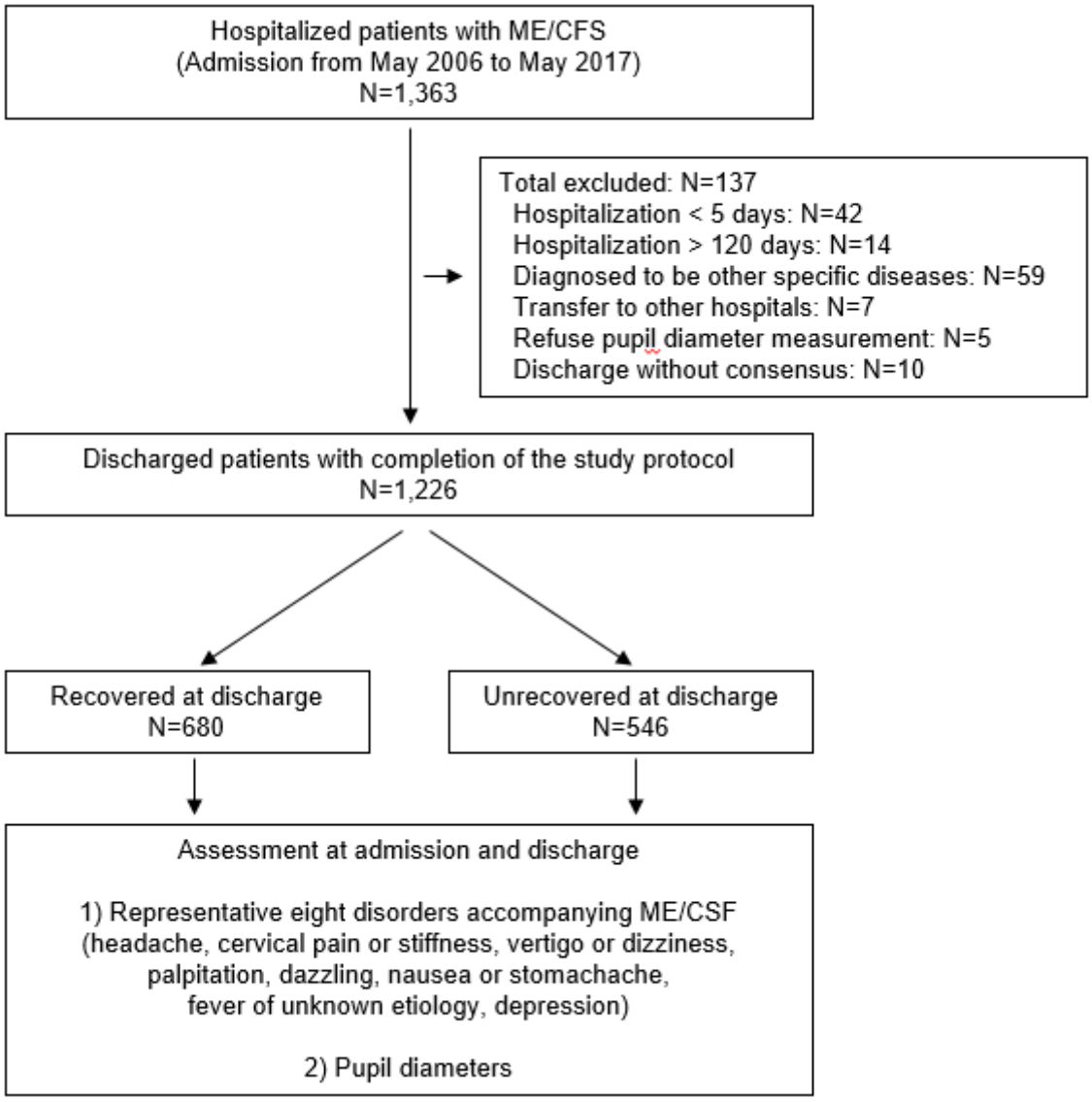


Figure 1

Outline of patient selection and study groups



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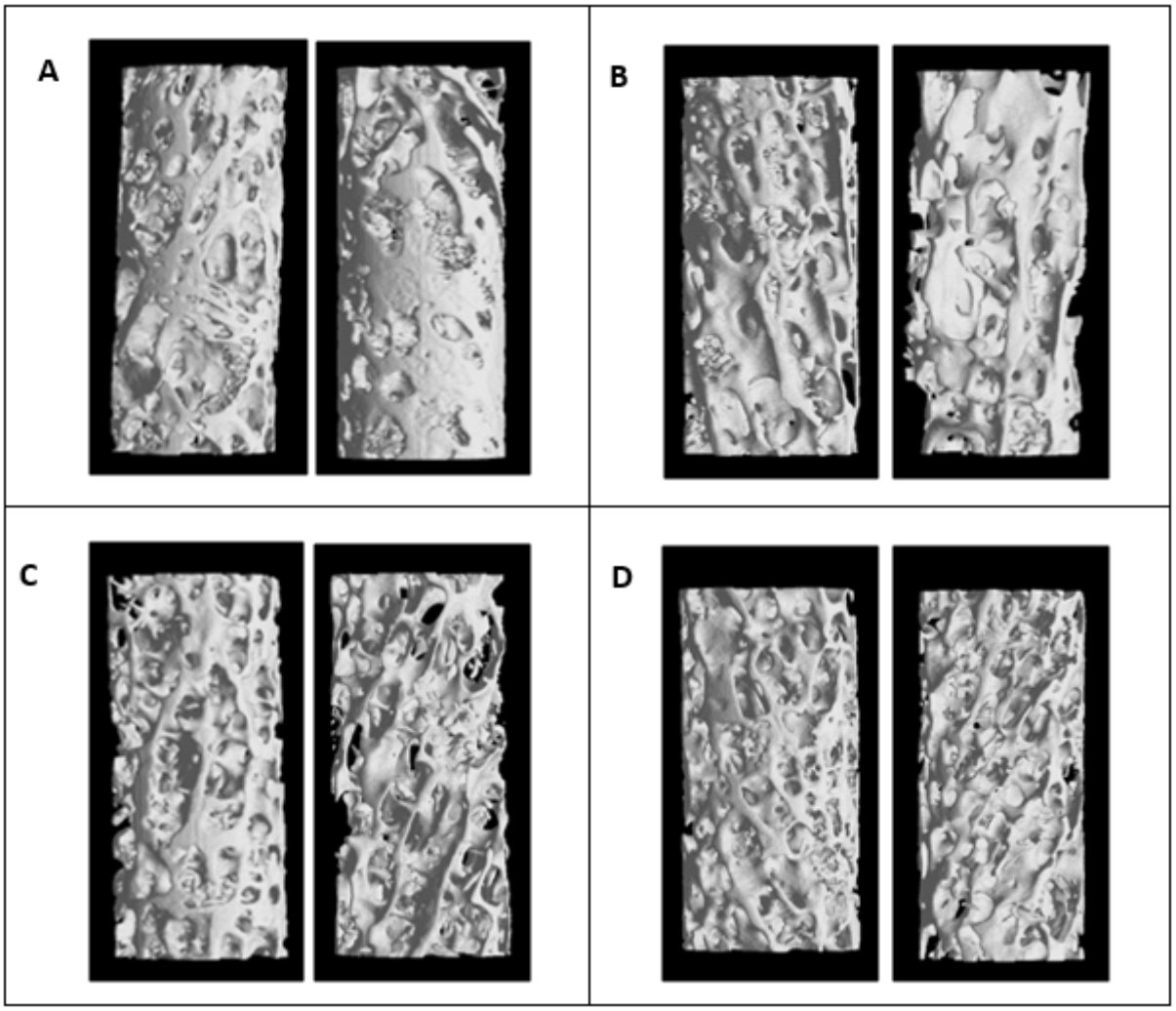
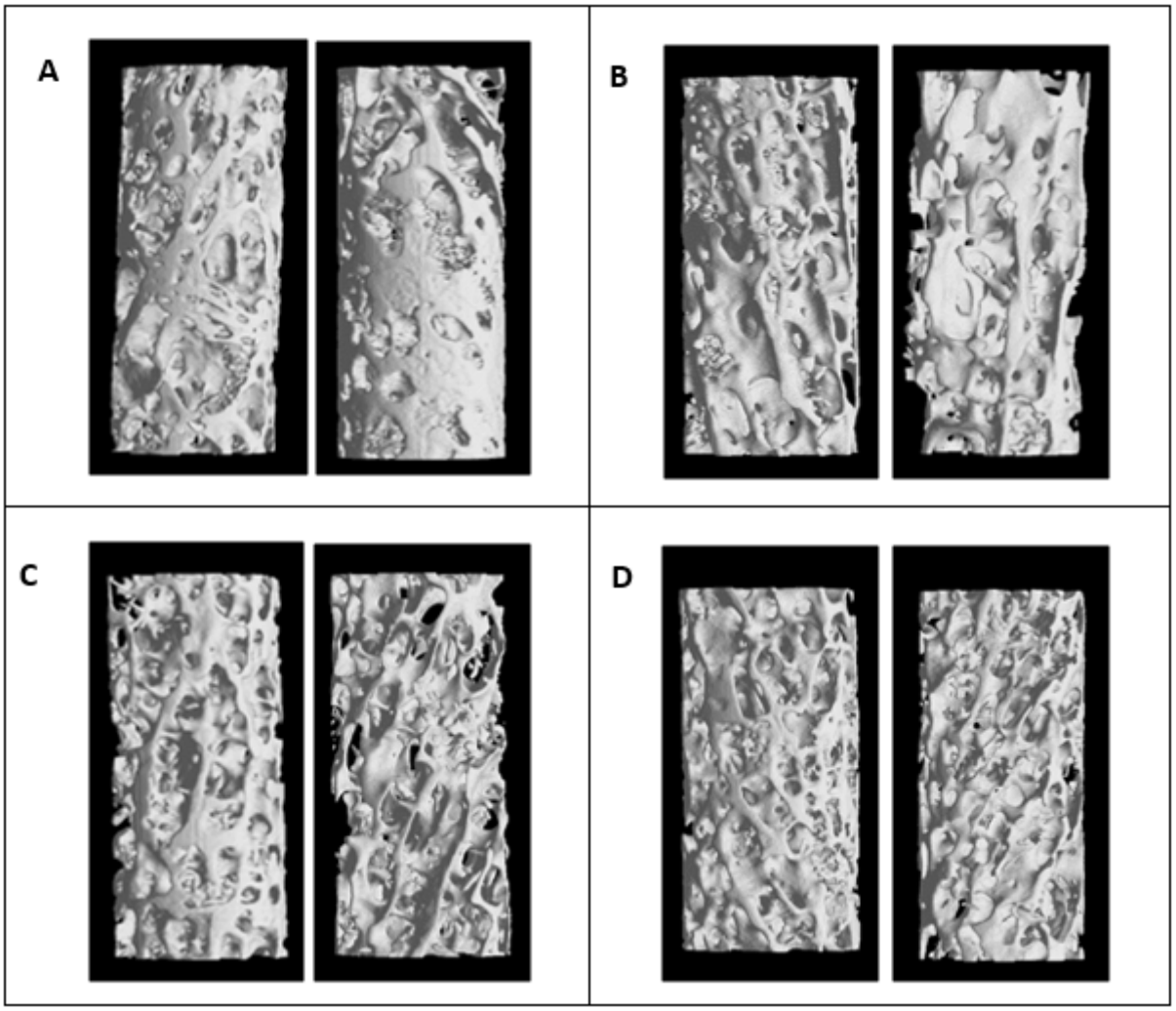


Figure 2

Three-dimensional reconstruction and micro-CT images of bone trabecular from femoral heads in the four groups. Two different samples from: (A) OA group; (B) OA-T2DM; (C) OP; (D) OP-T2DM.



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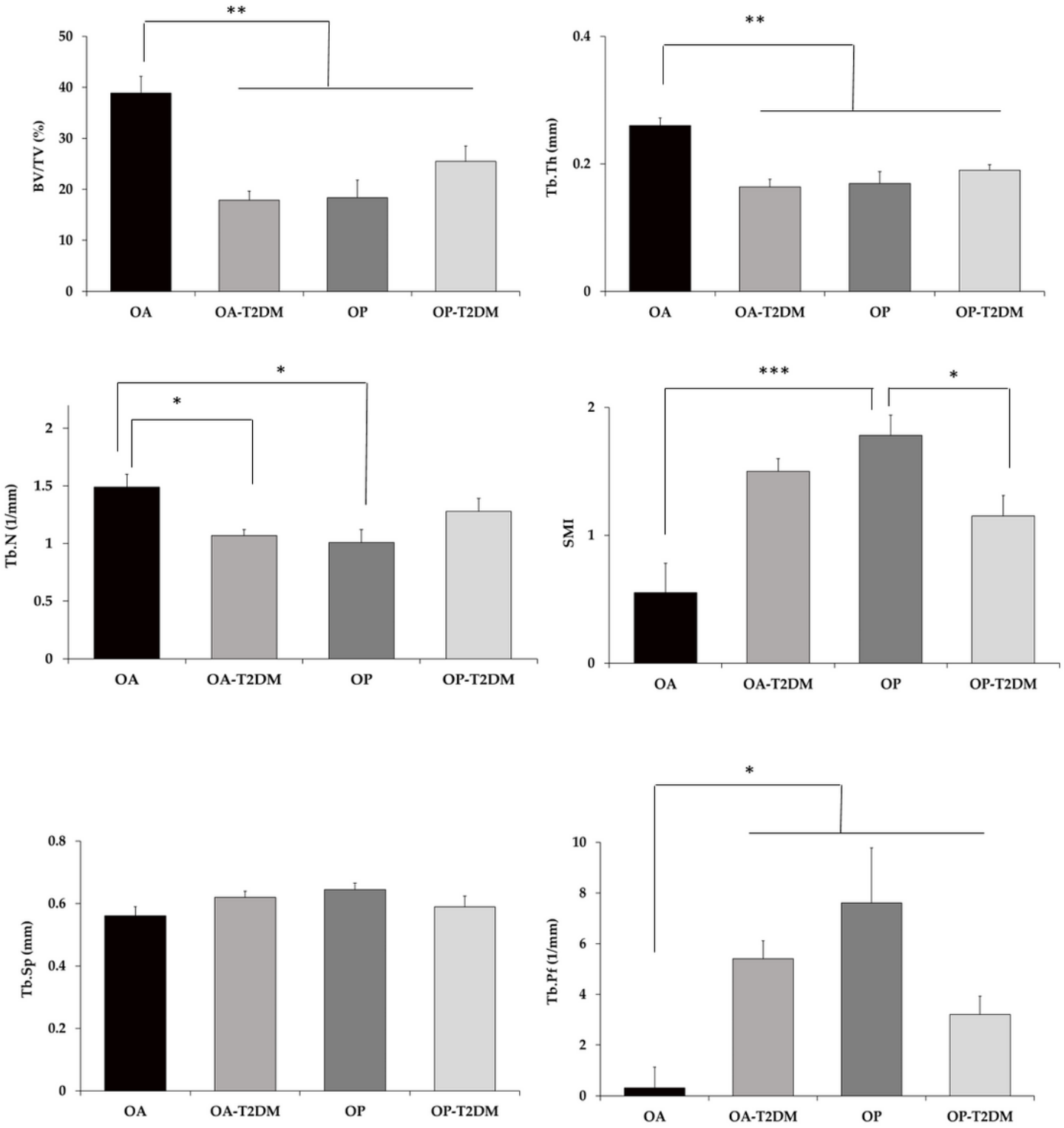
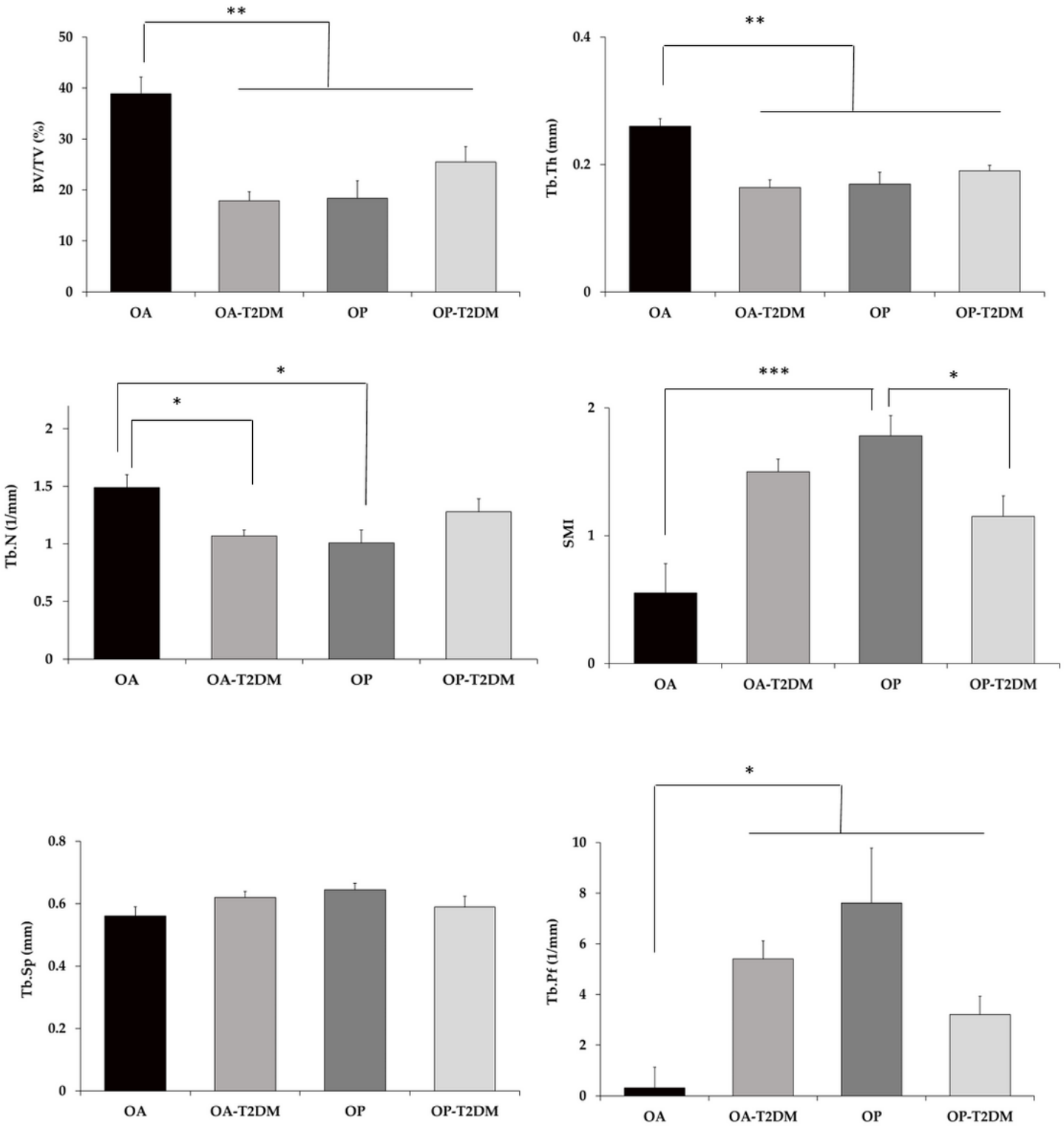


Figure 3

Comparisons of structural parameters between patients with OA and OP with or without T2DM. BV/TV, bone volume fraction; SMI, structural model index; Tb.Pf, trabecular bone pattern factor; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Values are expressed as the means ± SEM. * p< 0.05, ** p<0.01 and *** p< 0.001 statistically significant.



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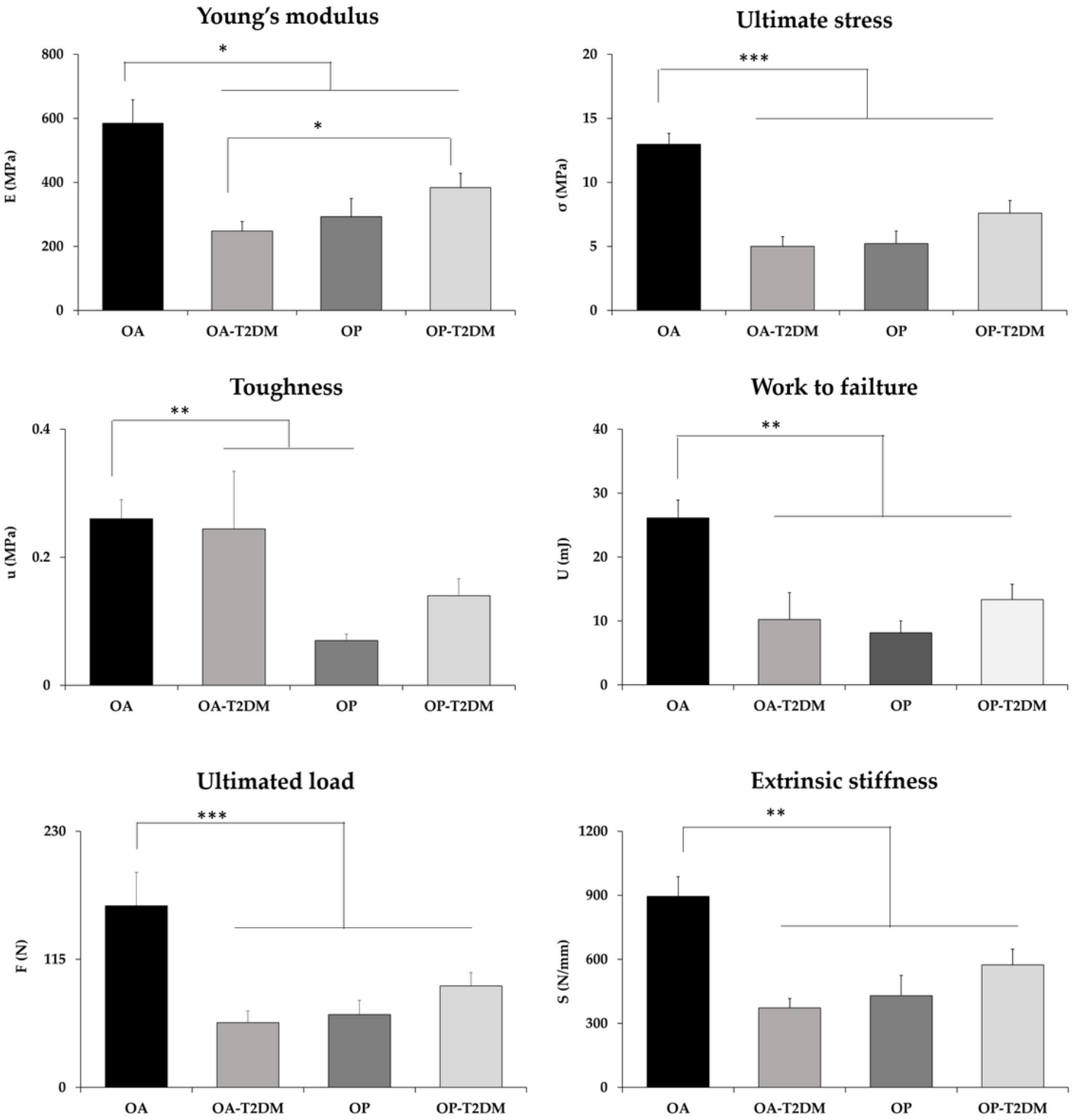
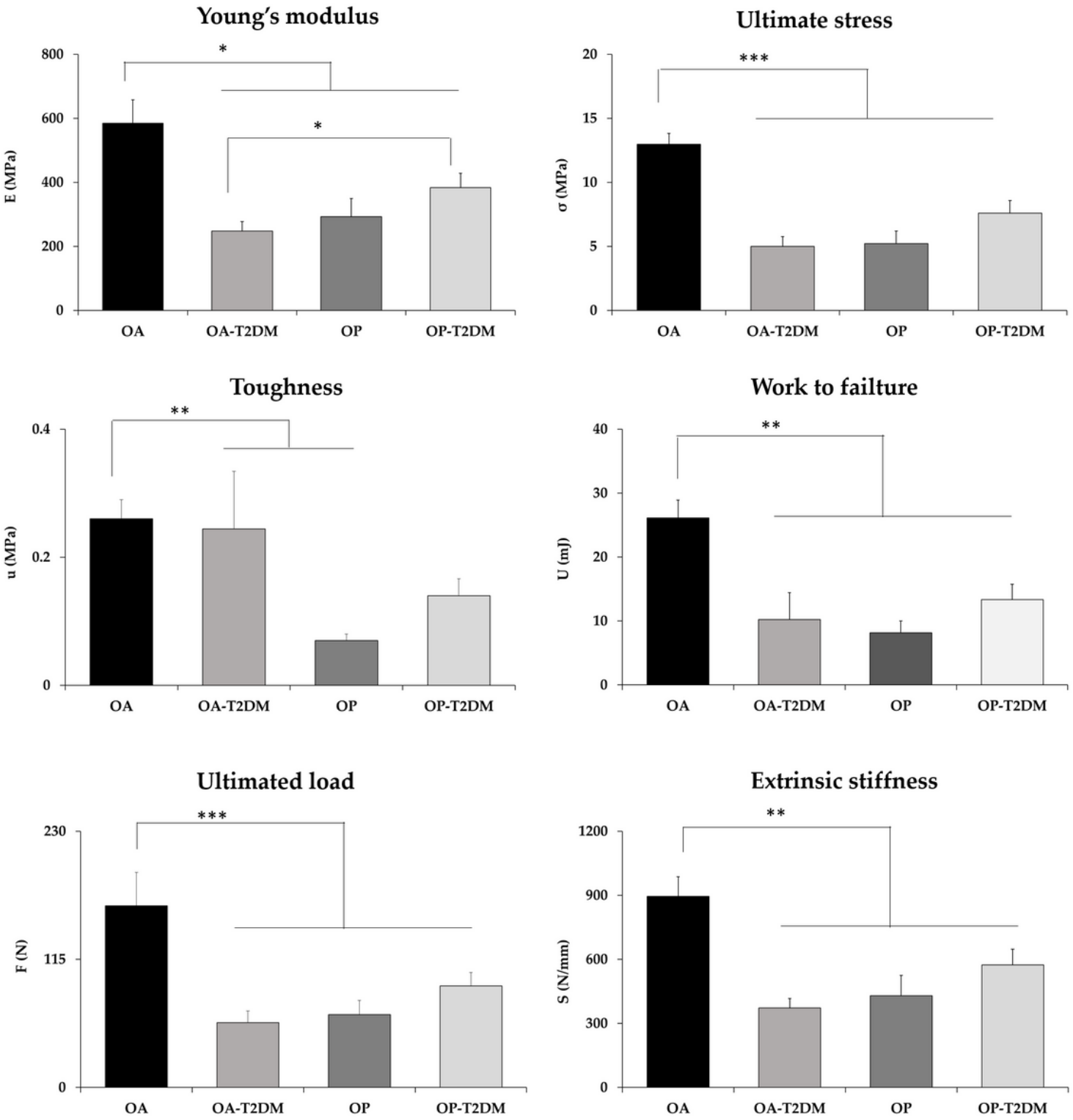


Figure 4

Comparisons of biomechanical parameters between patients with OA and OP. E, Young's modulus or elastic modulus; u, toughness; σult, ultimate stress; Fult, ultimate load; S, extrinsic stiffness; U, work to failure. Values are expressed as the means ± SEM. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ statistically significant.



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