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ORIGINAL ARTICLE

The Triangle that can Improve Postmenopausal Women's Quality of Life: Insulin, Bone Mineral Density, and Fracture Risk

Ayşegül Gülbahar, Seda Akgün Kavurmacı

Department of Obstetrics and Gynecology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

Abstract

Introduction: Women spend most of their life in the postmenopausal period. This period brings along many metabolic problems with the decrease in estrogen production. Our aim was to evaluate the effectiveness of bone mineral density (BMD) on fracture risk assessment tool (FRAX) between groups with and without insulin resistance and also to investigate the importance of new risk factors in FRAX identification and to facilitate early prevention, diagnosis, and treatment of women with fractures risk.

Methods: Sixty-eight patients who were admitted to our clinic with diagnosis of impaired glucose tolerance during postmenopausal period were included in this study retrospectively. Those who had their routine biochemical parameters, insulin, and BMD measured were included in the study. Fracture risk analyses were performed with the FRAX score. Body mass index and homeostasis model assessment-insulin resistance of the patients were calculated.

Results: In the group with insulin resistance, high-density lipoprotein cholesterol value was low (p=0.014), and triglyceride level was high (p<0.0001). When 25(OH)Vit-D3 values were examined between the groups, the mean values were 22.8±13.6 and 15.7±11.8 ng/ml, respectively (p=0.026). When femoral and lumbar T-score BMD values between the groups were examined, the bone density of the patients with insulin resistance was significantly higher than the other group (p=0.039).

Discussion and Conclusion: To summarize, we believe that low bone quality is caused by slowing bone cycle due to long-term impaired glucose levels and long-term estrogen hormone deficiency caused by menopause. This suggests that BMD value is not specific enough for determining bone fractures. The conclusion to be drawn here is to accurately establish the relation between DM or impaired glucose tolerance and osteoporosis; to constitute a guide for further prospective and large-scale studies that use different diagnostic and follow-up parameters; and to investigate the significance of new risk factors in FRAX identification for early prevention, diagnosis, and treatment of women who are at a risk of fractures.

Keywords: Insulin; menopause; osteoporosis; women.

Despite the increase in average human life expectancy, menopause age has remained unchanged over the past century. As a result, women spend a large part of their life in the postmenopausal period in which they face metabolic problems such as insulin resistance and diabetes with decreasing estrogen production. In this period initially, bone loss acceleration progresses asymptomatically, followed by the increase in osteoporosis that is accompanied by pain, kyphosis, pathological fracture, and mortality.

Osteoporosis affects 200 million and osteoporotic fracture affects approximately 8.9 million women per year across the world[1,2]. Approximately 10% loss of lumbar bone mass doubles the risk of vertebral fractures, whereas 10% loss of hip bone mass increases the fracture risk 2.5 fold[3]. Accord-

Correspondence (İletişim): Ayşegül Gülbahar, M.D. Izmir Katip Celebi Universitesi, Ataturk Egitim ve Arastirma Hastanesi, Kadin Hastaliklari ve Dogum Klinigi, Izmir, Turkey
Phone (Telefon): +90 505 355 83 40 **E-mail (E-posta):** draysegulgulbahar@gmail.com
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ing to a study conducted in 11 countries, postmenopausal women do not have enough information about risk factors, early diagnosis, and treatment of osteoporosis before experiencing first fracture[4]. All this information shows us that osteoporosis is a worldwide public health problem.

The relation of osteoporosis with the current insulin level is controversial. While the anabolic effect of increased insulin level is still present, demographic characteristics, body mass index (BMI), and biochemical parameters (lipid profile and Vitamin D levels) should be noted when evaluating this condition. Ultimately, fracture risk is an important problem, and it is impossible to predict only with bone mineral density (BMD). It should be examined along with other risk factors.

The WHO's fracture risk assessment tool (FRAX) is used to calculate the 10-year probability of a fracture in men and women using details such as BMD and various risk factors[5,6]. However, the possibility to get the same level of performance in menopausal women is uncertain.

Our aim of this study was to examine patients with impaired glucose tolerance in postmenopausal period, regardless of risk factors, to evaluate the effectiveness of BMD on FRAX between groups with and without insulin resistance and to investigate the importance of new risk factors in FRAX identification.

Materials and Methods

Sixty-eight patients who were admitted to the obstetrics and gynecology outpatient clinic between 2017 and 2019 with a diagnosis of impaired glucose tolerance during postmenopausal period were included in this study retrospectively. The research started after the approval of the ethics committee (approval no: 881, September 17, 2020).

Patients with follicle-stimulating hormone (FSH) values >40 mIU/mL, estradiol (E2) values <25 mIU/ml, over 40 years of age, and not having menstruation for more than 1 year were included in the study. The patients were analyzed in terms of age, menopausal age and menopause year, previous operations, medications used, diseases history, smoking, and alcohol use. Patients with a known history of diseases (such as coronary artery disease, hyperlipidemia, hypertension, and DM) or diseases that could cause secondary osteoporosis (such as thyroid dysfunction, hypogonadism, hyperparathyroidism, DM, Cushing's syndrome, malnutrition, malabsorption, chronic renal failure, and liver disorders) were excluded from the study. In addition, patients who received hormone replacement therapy, calcium, Vitamin D supplements, osteoporosis therapy, antiepileptic, chemotherapeutic, anticoagulant, corticosteroid, smoking, and alcohol use history were not included in the study.

The anamnesis of postmenopausal patients who applied to the outpatient clinic for routine control were examined; and those who had their routine biochemical parameters of FSH, estradiol (E2), 25 (OH)Vit-D3, lipid profile (total cholesterol; low-density lipoprotein cholesterol; and triglyceride [TG]), fasting blood glucose (FBG), postprandial blood glucose, insulin, and BMD measured were included in the study. Femur T-score, lumbar T-score, lumbar BMD (g/cm^2), femur total BMD (g/cm^2), and femur neck BMD (g/cm^2) values were used in the study. BMD measurements were calculated according to the osteoporosis diagnostic criteria of the WHO, and patients were categorized into three groups as osteoporosis (T-score <−2.5), osteopenia (−1> T-score >−2.5), and normal (T-score >−1). Fracture risk analyses were performed using the FRAX score that made available as a fracture risk assessment tool in 2008 (www.shef.ac.uk/FRAX) by the WHO. The FRAX scoring has been developed to calculate the 10-year risk of hip fractures and the possible 10-year total risk of fractures (vertebrae, hip, forearm, and humerus). The calculation is performed based on the ethnicity of individuals. Before the analysis, all patients were individually called for the risk assessment and their age, weight, height, fracture history, drug use history, smoking, alcohol use, and rheumatoid arthritis history were questioned again. Femur neck BMDs in g/cm^2 is used to calculate the total fracture risk and the risk of hip fracture percentages.

BMIs of the patients were calculated by dividing their weights (kg) by their height (m) in square meter (kg/m^2).

Insulin resistance was determined by calculating current fasting insulin, FBG values, and homeostasis model assessment-insulin resistance (HOMA-IR) indices[7].

HOMA-IR Measurement: Fasting insulin x FBG (mmol/L)/22.5 formula.

According to the HOMA-IR threshold, two groups have been formed based on insulin resistance: The group with insulin resistance of ≥2.5 and without insulin resistance of <2.5.

Statistical Analysis

All analyzes were done using SPSS V22.0 software (IBM®, NY, USA). Categorical data are indicated as numbers and percentages (%), whereas numerical data are given as arithmetic mean±standard deviation (minimum-maximum). Chi-square test was used to compare categorical data. Analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) were used to test the normality distribution of the variables. The t-test was used to compare the two groups (HOMA <2.5 and HOMA >2.5) in terms of numerical data. P <0.05 was considered statistically significant.

Table 1. Demographic, BMI, biochemical, BMD, and FRAX risk parameters of patients

	HOMA <2.5 group (n=30)	HOMA ≥2.5 group (n=38)	p
Age	53.6±6.0	53.5±4.3	0.916
Age at menopause	48.8±3.4	48.7±3.2	0.887
Duration of menopause	4.9±4.0	4.9±3.2	0.981
BMI kg/m^2	27.0±2.4	33.7±4.2	<0.0001*
Biochemical parameters			
Total-C mg/dl	214.6±44.3	202.7±39.6	0.247
HDL-C mg/dl	58.0±15.5	49.8±9.2	0.014*
LDL-C mg/dl	143.3±40.1	131.9±34.6	0.214
TG mg/dl	106.3±35.1	188.4±94.3	<0.0001*
FSH mIU/mL	70.7±30.1	59.9±15.5	0.081
E2 pg/ml	14.7±7.0	15.6±6.5	0.622
25(OH)Vit-D3 (µg/L=ng/ml)	22.8±13.6	15.7±11.8	0.026*
Insulin fasting µu/ml	6.0±1.8	15.6±8.6	<0.0001*
FBG mg/dl	94.9±9.5	104.6±13.3	<0.001*
PBG mg/dl	104.0±16.2	132.5±30.6	<0.0001*
BMD			
Lumbar BMD g/cm^2	1.1±0.3	1.1±0.2	0.538
Femur total BMD g/cm^2	0.9±0.1	1.0±0.1	0.144
Femur neck BMD g/cm^2	0.9±0.2	0.9±0.1	0.904
Femur T-score BMD	−0.6±1.0	0.2±0.8	<0.0001*
Lumbar T-score BMD	−0.6±1.1	−0.3±1.1	0.039*
FRAX major osteoporosis	4.4±1.3	4.2±1.5	0.683
FRAX hip fracture risk, %	0.5±0.5	0.3±0.5	0.146

*: P<0.05; values are means±SD; n (%); HOMA: Homeostatic model assessment; FSH: Follicle-stimulating hormone; E2: Estradiol; FBG: Fasting blood glucose; PBG: Postprandial blood glucose; Total-C: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; BMD: Bone mineral density; FRAX: Fracture risk assessment tool.

Results

Sixty-eight patients were included in the study. The patients participating in the study were divided into two groups according to the HOMA index; 30 (44.1%) of the patients were HOMA <2.5; 38 (55.9%) of them were in the HOMA ≥2.5 group.

The mean values of HOMA index between groups were HOMA <2.5; (1.4±0.5), HOMA ≥2.5; (4.1±2.7) and statistically significant (p<0.0001).

Demographic characteristics of all patients were examined, age, menopausal age, and mean time of menopause is 53.6±5.1, 48.7±3.3, and 4.9±3.6, respectively. When both patient groups were examined, no statistically significant difference was observed between these parameters (p>0.05) (Table 1). The mean FSH and E2 values of all patients were 64.7±23.6 and 15.2±6.7, respectively, and no statistically significant difference was observed between the groups (p>0.05) (Table 1). The mean BMI value of the study group was 30.8±4.8 kg/m^2. When the BMI values between the groups were examined, the BMI (33.7±4.2 kg/m^2) of the group with HOMA ≥2.5 was found to be higher and statistically significant (p<0.0001) (Table 1).

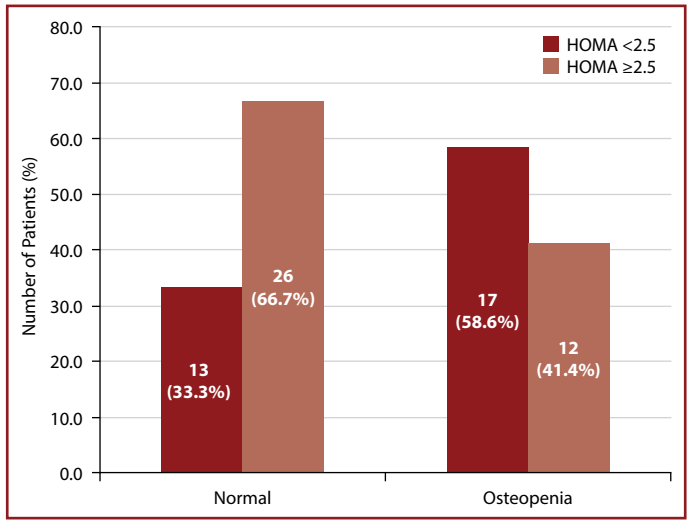

Figure 1. The distribution of patients, identified with BMD, by HOMA index.

BMD: Bone mineral density, HOMA: Homeostasis model assessment.

Distribution of anthropometric, biochemical, hormonal parameters, BMD, and FRAX risk scores according to the groups is given in Table 1. When HDL, TG values between groups were examined. In the group with insulin resistance (HOMA ≥2.5), HDL cholesterol value (49.8±9.2 mg/dl) was low (p=0.014), and TG level (188.4±94.3) was high and statistically significant (p<0.0001). When 25(OH)Vit-D3 values were examined between the groups (HOMA of <2.5 and HOMA of ≥2.5), the mean values were 22.8±13.6 and 15.7±11.8 ng/ml, respectively, and there was a statistically significant difference (p=0.026). It was observed that Vitamin D values among patients who have insulin resistance were low according to the cutoff value of 20 ng/ml.

When the femoral T-score BMD and lumbar T-score BMD values between the groups were examined, the bone density of the patients with insulin resistance was significantly higher than the other group (p<0.0001 and p=0.039).

There was no statistically significant difference between the groups according to the FRAX risk score.

When BMD values of all patients were examined, 39 (57.3%) of the patients were normal and 29 (42.7%) had osteopenia. There were no patients with osteoporosis in the study group. The distribution of these patients according to the HOMA index is presented in Figure 1. Accordingly, the ma-

jority of patients with osteopenia (n=17, 58.6%) were in the group with HOMA of <2.5.

Discussion

In our study, it was found that isolated, impaired glucose tolerance has a positive effect on BMD. In addition, BMD and insulin resistance were not affecting the FRAX result alone and the risk factors other than BMD and insulin resistance in FRAX evaluation were considered to be important.

Studies have shown that, in obese individuals, the release of pro-inflammatory cytokines from adipocytes and low serum adiponectin levels can cause chronic low-grade systemic inflammation and eventually lead to insulin resistance and development of diabetes[8-10]. This is also supported by our study and mean BMI values of patients with insulin resistance were in the obesity range and significantly higher than the other group.

It is noted that Vitamin D has a major role in the development of obesity and many chronic diseases, whereas its deficiency may be a risk factor for Type 2 DM and insulin resistance[11,12]. In addition, Vitamin D is also said to be low in patients who are considered overweight and obese based on BMI. From another point of view, the group with Vitamin D deficiency is considered to have increased obesity due to sedentary life and thus increased metabolic conditions such as insulin resistance[13,14].

In our study, although Vitamin D levels were low in both groups, the level in the group with insulin resistance was significantly deficient. Our opinion is that changing dietary habits and paying attention to quality of nutrition and life can support a decrease in BMI level, loss or absence of insulin resistance, and maintain healthy Vitamin D level.

Osteoporosis is less common among patients, who have impaired glucose tolerance, although both insulin and BMI values are high[15]. In our study, femur and lumbar T-score values between the groups were statistically significant. It was observed that insulin has a protective effect on bone mass.

When BMD increases in obese individuals, the risk of fracture decreases[16]. In addition to mechanical effects of increased weight, increase of BMD, in bones without load, shifts the focus onto adiposity function and conversion of androgens into estrogen[15]. In our study, due to adiposity function, TG levels are higher in the group with insulin resistance than the other group and this relation is found statistically significant which is an expected result.

In the Rotterdam study, BMD values were found higher and no change in fracture risk was detected in patients who have impaired glucose tolerance when compared to the healthy group[17]. In our study, the difference between the groups in terms of FRAX major risk and FRAX hip fracture risk percentages was not significant. We believe that the FRAX risk score was low due to our patient exclusion criteria.

Increased glucose levels cause an increase in reabsorption. Insufficient glycemic control and prolonged course of the disease with microvascular complications also lead to a decrease in BMD[18]. Negative effects of increased insulin levels for a prolonged period have been reported on bone quality, whereas bone cycle is significantly decreased compared with healthy postmenopausal women[19]. Therefore, not only BMD value but also poor bone quality examination should be considered to assess the fracture risk and bone health.

The limitations of our study include its retrospective design, small sample size, and lack of long-term follow-up of the patients. A prospective study with a large number of patients will help to better interpret the results. We believe that long-term follow-up of the study group will provide us with more information to validate our findings.

To summarize, although the risk of fractures in the groups was low according to the FRAX scoring, in the long term, due to the decrease in bone quality, this risk will increase. We believe that low bone quality is caused by a slowing bone cycle due to long-term impaired glucose levels and long-term estrogen hormone deficiency caused by menopause. This suggests that the BMD value is not specific enough for determining bone fractures.

Conclusion

The conclusion to be drawn here is to accurately establish the relation between DM or impaired glucose tolerance and osteoporosis; to constitute a guide for further prospective and large-scale studies that use different diagnostic and follow-up parameters; and to investigate the significance of new risk factors in FRAX identification for early prevention, diagnosis, and treatment of women who are at a risk of fractures.

Ethics Committee Approval: Ethical approval for the study was obtained from The Izmir Katip Celebi University Ethics Committee (date: 17.09.2020 number: 881).

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