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RESEARCH ARTICLE

Bone mass and microarchitecture in T2DM patients and corticosteroids therapy: the Bushehr Elderly Health program

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Abstract

Purpose Our study examined whether T2DM and glucocorticoids treatment affect bone quality and quantity that are measured by Bone Mineral Density (BMD) and Trabecular Bone Score (TBS).

Materials & methods Participants in this study were 2294 women and men aged over 60 years who participated in stage II of the Bushehr Elderly Health (BEH) program. Patients with T2DM and those who received glucocorticoids were included. BMD was detected using the DXA method and the TBS of L1-L4 was evaluated by TBS iNsight® software. To evaluate the correlation between TBS and BMD levels with diabetes and taking corticosteroids sex-specific multivariable linear regression models were appplied.

Results TBS and BMD were not significantly different in those who had received glucocorticoids versus those who did not. T2DM revealed a significant association with both BMD and TBS in men (beta = 0.12, $p < 0.001$ and beta = 0.063, $p = 0.03$, respectively). BMD values were significantly higher in diabetic women (beta = 0.073, $p < 0.01$). BMI had a significant association with both TBS and BMD but in an opposite direction, in women and men (BMD: beta = -0.22, -0.24, and regarding TBS: beta = 0.37, 0.25, all p-values < 0.001).

Conclusion Our findings showed that T2DM had major effects on BMD in both men and women. However, T2DM only affects TBS in men. Furthermore, neither BMD nor TBS were affected by GC intake in men or women.Based on the variable importance of covariates, BMI was the most influential factor on both BMD and TBS, although in opposite directions, in both sexes.

Keywords Type 2 diabetes mellitus · Glucocorticoids · Bone Mineral Density · And Trabecular bone score · Elderly · Iran

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Introduction

Osteoporosis is one of the world's most common types of bone disease. It is characterized by low bone mineral density (BMD) and structural degradation that increases the likelihood of osteoporotic fractures and fragility of bones. [1–3]. Ageing populations and lifestyle changes in recent decades have contributed significantly to the increase in osteoporosis and fractures it causes [4]. Osteoporosis-related fractures lead to adverse effects such as mortality, morbidity and also place a significant economic burden on individuals and healthcare systems [5, 6]. Factors such as age, sex, race, smoking, and corticosteroid use can increase the risk for osteoporotic fractures. [7]. Studies have demonstrated that diabetes mellitus and osteoporosis are related health problems [8]. Therefore, as the burden of osteoporosis and diabetes grows [9, 10] more effective and less costly approaches are needed to detect and treat patients at risk for fractures.

Dual x-ray absorptiometry (DXA) is a gold standard tool for detecting and monitoring osteoporosis, in which is measured BMD [8, 9]. While BMD is considered the most common bone fracture risk index, it has been reported that the BMD score could not accurately discriminate between people with and without fractures [10–12].

Osteoporotic fractures are more common among people with diabetes [13–15]. In patients with diabetes, BMD can increase [12], decrease [16], or remain normal [17]. T2DM has also been linked with hip [18, 19], wrist [20], vertebral [21, 22], and overall fractures [23–25]. On the other hand, glucocorticoids (GCs), are one of the most important influencial factor on bone health. The use of GCs for the treatment of inflammatory disorders may harm bone quality because they suppress bone formation and cause bone resorption, so the most prevalent cause of secondary osteoporosis is GC-induced osteoporosis [26, 27].

Since BMD plays a critical role in risk prediction of bone fragility, this controversy is further aggravated by the lack of sufficient tools to identify patients with diabetes and GC intake who are at increased risk of fracture. DXA is hindered by several drawbacks, such as the ability to obtain only quantitative information from scans, as well as obtaining no qualitative information about bone structures. As a result, besides bone mineral density, other factors need to be considered such as cortical bone macrogeometry, trabecular bone microarchitecture, and turnover markers [12, 28, 29].

As a novel imaging technology, the trabecular bone score (TBS) evaluates the variation of pixel gray-level in lumbar spine DXA images. TBS is strongly associated with bone micro-architecture and fracture risk and providing information independent of BMD [8, 30]. As well as predicting fractures related to osteoporosis, [31, 32], TBS is able to classify individuals who fall outside of the range of osteoporosis [8, 33]. It has been shown that TBS can be used to determine fracture risk in patients with diabetes mellitus and hypercortisolism [12, 34]. despite a high BMD score in diabetic patients, the risk of osteoporosis-related fractures has also increased [35, 36], So, in terms of predicting microstructural changes in these patients, TBS or a combination of TBS and BMD have been shown to be more effective.The present study aims to determine if T2DM and GC therapy affect bone quality and quantity through measurements of BMD and TBS in Iranian elderly patients. BMD and TBS were measured in elderly patients with and without T2DM as well as those receiving GC therapy or not.

Materials and methods

Study design

This study is part of the Bushehr Elderly Health (BEH) program that was initiated in Bushehr, the capital of a province in the south of Iran. The design of the BEH program has already been defined elsewhere, and its description and methodology applied to the current process, are clarified here. The goal of this cohort project is, in short, to investigate the prevalence and risk factors of non-communicable diseases within a representative elderly population [37]. Stage II of the BEH program started in October 2015 [38]; In this phase, 2426 individuals aged ≥ 60 years were included to determine the prevalence of musculoskeletal disorders such as osteoporosis and their risk factors.

To this end a standardized questionnaire was designed for evaluating physical activity level, in which 9 different metabolic equivalents of task (MET) levels were ranged on a scale from sleep/rest to high-intensity physical activities [39, 40].

Additionally, demographic information was gathered from respondents, including education level, history of fracture, vitamin D supplement use, calcium supplement use, normal calcium consumption, hypertension, years after menopause, and osteoporosis.Using the Global Physical Activity Questionnaire (QPAG) and the brief Tobacco Questionnaire the physical activity and smoking status were measured, respectively. In addition, anthropometric measures including height, weight, body mass index (BMI) and waist circumference were measured based on the NHANES III anthropometric measurement protocol [37]. This study approved by the Research Ethics Committee of both Bushehr University of Medical Sciences and Endocrinology and Metabolism Research Institute.

Assessment of BMD and TBS

BMD was measured using DXA scanner (Discovery WI, Hologic, Bedford, Virginia, USA) by the same instrument and trained operators. The aBMD of femoral neck (FN) and lumbar spine (LS) (L1–L4) were measured following the International Society for Clinical Densitometry (ISCD) guidelines [25]. TBS iNsight software (version 2.2; Medimaps Group, Plan-les-Ouates, Switzerland) was applied to quantify trabecular pattern of LS (L1–L4) [41–43].

Participants of the study

In total, 2294 people of the 2426 studied were assessed; 25 people with a cancer history, 6 people with chronic liver disease, and 107 people with missing information regarding corticosteroids and/or diabetes were excluded.

Definition of terms

In the present study according to the highest educational level question completed by participants, education was defined as less than high school/ high school graduate and some college or more. The BMI was calculated as weight in kg divided by the square of height in meters. History of corticosteroids consumption was considered positive if the participants had received oral corticosteroids for more than three months. Moreover, a history of fragility fracture defined as a previous fracture either spontaneously or after minor trauma.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or current use of antihypertensive drugs [44]. T2DM was defined as HbA1c ≥ 6.5% (≥ 48 mmol/mol), FPG ≥ 126 mg/dl (≥ 7.0 mmol/L), and/or taking medication for T2DM [45].

According to physical activity level, four lifestyle categories are defined: sedentary: 1–1.39 MET-minutes/week, low active: 1.4–1.59 MET-minutes/week, active: 1.6–1.89 MET-minutes/week, very active: 1.9–2.5 MET-minutes/week [46]. We divided the study population into two categories; low physical activity (sedentary and low active) and high physical activity (active and very active). Daily food intake of calcium was categorized into three groups—low (< 500 mg/day), moderate(≥ 500 and < 1000 mg/day) and high (≥ 1000 mg/day). Calcium and vitamin D supplement intake were defined according to the questions inquired about dietary supplements.

Statistical analysis

Quantitative data were described as mean ± SD for normally distributed data, based on the Shapiro–Wilk test, while non-normal variables were presented as median (interquartile range: P25-P75). Group comparison was made with independent t-test.

Using the linear regression, sex-specific outcome (BMD and TBS) models were adjusted for the potential effects of main exposures (T2DM and GC use), age, BMI, education level (illiterate as reference category), smoking status (nonsmokers as reference), history of fracture, low physical activity, taking a supplement of calcium, taking a supplement of vitamin D, daily calcium intake level (> 1000 mg/day as reference), hypertension, and years since menopause (in women), standardized beta and effect size partial eta-squared were reported.

One of the main challenges in the modeling is to select the "best" subset of determinants. There are several statistical methods proposing different methodologies for selecting the covariates from a set of candidates and estimating regression coefficients [47]. One of the most popular classes of selection methods is regularization and penalization models. Ridge regression, LASSO (least absolute shrinkage and selection operator), and elastic net (ENET) are the methods of this class [48, 49]. Although the lasso has shown success in many situations, it has some limitations such as instability with high-dimensional data and inability to handle highly-correlated variables [50]. The ENET is an extension of the lasso that is robust to extreme correlations among the predictors. Real-world data and a simulation study showed good performance of the elastic net and its superiority over the lasso [51]. So, we used an elastic net to select the optimum set of covariates. A separated variable selection process has been done for each outcome in both set via the elastic net algorithm; so that the final set of variables in each model was different. All statistical analyses were performed with STATA Statistical Software Release 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.). P-values < 0.05 were considered as statistically significant.

Results

The study involved 2294 participants with a mean age of 69.3 ± 6.3, of which 1182 (51.5%) were female. The baseline characteristics of study participants, including physical activity, smoking, educational status, history of fracture, vitamin D supplementation, calcium supplementation, normal calcium intake, hypertension, years after menopause, BMD, TBS, and osteoporosis medications, are illustrated in Table 1. Women were statistically more likely to have T2DM and to take GC, and the prevalence of both conditions was higher among them (regarding diabetes, 34% of women compared to 28% of men; taking GC, 52% compared to 30% of men). TBS did not statistically differ in either exposure; BMDL1-L4 levels for diabetic women were higher (0.79*0.14 g/cm2 vs. 0.84*0.14 g/cm2) than those

Table 1 Baseline Characteristics of Study Participants

	T2DM			GC		
	No(n = 770)	Yes(n = 412)	p-value	No(n = 561)	Yes(n = 621)	p-value
Female						
Age	69.3 ± 6.6	68.5 ± 5.5	**0.03**	69.6 ± 6.6	68.6 ± 5.8	**< 0.01**
BMI	28.4 ± 5.2	29.5 ± 5.4	**< 0.01**	27.8 ± 5.2	29.6 ± 5.3	**< 0.0001**
Smoking			0.19			0.89
No(ref)	374(48.5)	183(44.4)		265(47.2)	292(47.0)	
Past	251(32.6)	156(37.8)		190(33.8)	217(34.9)	
Current	145(18.8)	73(17.7)		106(18.9)	112(18.0)	
Education			0.73			0.41
Illiterate	349(45.3)	198(48.0)		250(44.5)	297(47.8)	
Primary school	241(31.3)	132(32.0)		183(32.6)	190(30.6)	
Secondary school	91(11.8)	40(9.7)		60(10.7)	71(11.4)	
High-school	72(9.3)	34(8.2)		58(10.3)	48(7.7)	
University degree	17(2.2)	8(1.9)		10(1.8)	15(2.4)	
Low Physical activity	704(92.4)	393(96.1)	**0.01**	523(93.5)	36(6.4)	0.87
History of Fracture	340(82.9)	70(17.0)	0.07	490(79.0)	130(20.1)	0.33
Supplement of Vitamin D	109(14.1)	42(10.2)	0.05	56(9.9)	95(15.3)	**< 0.01**
Supplement of Calcium	360(87.4)	52(12.6)	0.18	511(82.3)	110(17.71)	**< 0.01**
Daily intake of Calcium			0.39			0.38
High	22(2.8)	18(4.4)		19(3.4)	21(3.4)	
Moderate	253(33.0)	134(32.7)		195(34.9)	192(31.2)	
Low	490(64.0)	257(62.8)		344(61.6)	403(65.4)	
Hypertension(yes/no)	74(17.9)	338(82.0)	**< 0.001**	156(25.1)	465(74.9)	0.72
Years since menopause	22.5 ± 8.5	20.9 ± 7.7	**< 0.01**	22.6 ± 8.6	21.4 ± 8.0	**0.01**
Osteoporosis drugs	34(4.4)	8(1.9)	**0.03**	14(2.5)	28(4.5)	0.06
BMDL1L4	0.79 ± 0.14	0.84 ± 0.14	**< 0.001**	0.80 ± 0.14	0.82 ± 0.14	**< 0.01**
TBSL1L4	1.24 ± 0.08	1.23 ± 0.09	0.08	1.24 ± 0.09	1.24 ± 0.08	0.88
Male	**(n = 798)**	**(n = 314)**		**(n = 778)**	**(n = 334)**	
Age	69.8 ± 6.6	68.8 ± 5.9	**0.02**	69.7 ± 6.6	69.1 ± 5.9	0.17
BMI	25.9 ± 4.0	27.1 ± 4.0	**< 0.001**	26.1 ± 3.9	26.5 ± 4.1	0.12
Smoking			**0.01**			**0.05**
No(ref)	322(40.3)	142(45.2)		340(43.7)	124(37.1)	
Past	270(33.8)	117(37.2)		254(32.6)	133(39.8)	
Current	206(25.8)	55(17.5)		184(23.6)	77(23.0)	
Education			0.63			0.10
Illiterate	152(19.0)	52(16.6)		139(17.8)	65(19.4)	
Primary school	210(26.3)	89(23.3)		203(26.1)	96(28.7)	
Secondary school	154(19.3)	60(19.11)		141(18.1)	73(21.8)	
High-school	164(20.5)	73(23.2)		181(23.2)	56(16.7)	
University degree	118(14.8)	40(12.7)		114(14.65)	44(13.1)	
Low Physical activity	718(91.1)	286(91.9)	0.65	696(90.51)	73(9.4)	0.12
History of Fracture	299(95.8)	13(4.1)	0.40	315(94.3)	19(5.7)	0.52
Supplement of Vitamin D	28(3.5)	12(3.8)	0.80	25(3.2)	15(4.5)	0.29
Supplement of Calcium	300(95.5)	14(4.4)	0.88	310(92.8)	24(7.2)	**< 0.01**
Daily intake of Calcium			0.79			0.92
High	73(9.23)	30(9.7)		72(9.3)	31(9.3)	
Moderate	384(48.5)	143(46.3)		365(47.5)	162(48.8)	
Low	334(42.2)	136(44.0)		331(43.1)	139(41.8)	
Hypertension(yes/no)	77(24.5)	237(75.5)	**0.02**	104(31.1)	230(68.8)	0.46
Osteoporosis drugs	3(0.3)	0(0.0)	0.5*	0(0.0)	3(0.90)	**0.03***
BMDL1L4	0.97 ± 0.17	1.03 ± 0.16	**< 0.001**	0.98 ± 0.17	0.99 ± 0.17	0.35
TBSL1L4	1.35 ± 0.08	1.36 ± 0.09	0.08	1.34 ± 0.09	1.35 ± 0.09	0.94

*Fisher's Exact

The bold value represent the overal effect size of the variable and for each of the levels of the variable(compared to the refernce category) we present the related p-values

of non-diabetic women; BMDL1-L4 levels of participants taking GC were higher than those of people not taking GC (0.80 ± 0.14 g/cm2 vs. 0.82 ± 0.14 g/cm2). In diabetic men, BMDL1-L4 was higher compared to non-diabetic individuals (1.03 ± 0.16 g/cm^2 vs 0.97 ± 0.17 g/cm^2, p < 0.001). Results of multiple linear regression analysis for factors associated with BMD are presented in Table 2. Taking GC was not associated with altering BMD in men or women. In contrast, T2DM was positively associated with both sexes, although the effect was greater in men (standardized beta: 0.120 vs. 0.073, both p-values < 0.01). In both sexes, a positive history of fractures and low calcium intake were associated with lower BMD; in this case, the average reduction fell between -0.112 and -0.159 for men and women, respectively. According to BMD, the average of low calcium intake levels among men and women was -0.104 and -0.301 respectively. In addition, those with higher BMI have a higher BMD, where elevation averages were 0.252/0.378 in men and women, respectively. After menopause, BMD decreases by 0.14 percent annually.

Table 3 shows the results for the linear regression of TBS with potentially related factors. Similar to BMD, taking GC did not show a significant association with T2DM. T2DM was only associated with men. (beta = 0.06, p-value = 0.03). In both sexes, BMI was significantly correlated with both TBS and BMD, but in an opposite direction.A positive history of fracture and low daily calcium intake negatively associated with TBS, reduction averages between -0.111 and -0.058 for the history of fracture in men and women, respectively.

Discussion

In the present study, we evaluated the effects of diabetes and GC consumption on osteoporosis index, TBS, and BMD in elderly patients. According to regression analysis, diabetic patients showed higher BMD levels in both sexes in comparison with non-diabetics, however, in models of TBS, diabetes only had a significant effect on men.In line

Table 2 Multiple Linear regression of Diabetes and Corticosteroids on Bone Mineral Density (BMD), by sex

	Women			*Men*		
	Effect Size*	Standardized beta	p-value	Effect Size	Standardized beta	p-value
T2DM	**0.007**	**0.073**	**< 0.01**	**0.016**	**0.120**	**< 0.001**
GC	0.000	0.012	0.54	0.001	0.030	0.28
Age	0.003	-0.073	0.05	0.004	0.066	0.03
BMI	**0.149**	**0.378**	**< 0.001**	**0.052**	**0.252**	**< 0.001**
Smoking	0.002			0.013		
No(ref)						
Past		-0.06	0.32		-0.050	0.10
Current		0.057	0.48		**-0.118**	**< 0.001**
Education	**0.015**			0.006		
Illiterate(ref)						
Primary school		**0.124**	**0.05**		-0.031	0.39
Secondary school		**0.260**	**< 0.01**		0.046	0.21
High-school		**0.341**	**< 0.01**		0.015	0.69
University degree		0.242	0.16		0.034	0.33
Low Physical activity				0.005	-0.077	0.02
History of Fracture	**0.007**	**-0.159**	**< 0.01**	**0.014**	**-0.112**	**< 0.001**
Supplement of Calcium				0.000	0.018	0.52
Daily intake of Calcium	**0.007**			0.004		
High(ref)						
Moderate		-0.221	0.09		-0.087	0.08
Low		**-0.301**	**0.01**		**-0.104**	**0.04**
Hypertension(yes/no)	**0.011**	**0.207**	< 0.01	0.003	0.056	0.05
Years since menopause	**0.012**	**-0.146**	< 0.01			

*Partial Eta-Squared, The highlighted variables are not included in the model

The bold value represent the overal effect size of the variable and for each of the levels of the variable(compared to the refernce category) we present the related p-values

Table 3 Multiple Linear regression of Diabetes and Corticosteroids on Trabecular Bone Score (TBS), by sex

	Women			*Men*		
	Effect Size	Standardized beta	p-value	Effect Size	Standardized beta	p-value
T2DM	0.002	-0.044	0.12	0.004	**0.063**	**0.03**
GC	0.001	0.031	0.27	0.000	0.026	0.35
Age				0.003	**-0.062**	**0.04**
BMI	**0.042**	**-0.227**	**< 0.001**	**0.048**	**-0.247**	**< 0.001**
Smoking	0.004			0.020		
No(ref)						
Past		-0.066	0.03		-0.070	0.02
Current		**-0.012**	0.69		**-0.153**	**< 0.001**
Education	0.039			0.020		
Illiterate(ref)						
Primary school		**0.095**	**< 0.01**		-0.003	0.93
Secondary school		**0.148**	**< 0.001**		**0.091**	**0.01**
High-school		**0.174**	**< 0.001**		**0.094**	**0.01**
University degree		**0.046**	**0.10**		**0.133**	**< 0.001**
Low Physical activity	0.006	-0.088	< 0.01	0.001	-0.048	0.15
History of Fracture	0.004	**-0.058**	**0.03**	0.013	**-0.111**	**< 0.001**
Supplement of Vitamin D	0.000	-0.021	0.46			
Daily intake of Calcium	0.008			0.002		
High(ref)						
Moderate		-0.124	0.28		-0.035	0.49
Low		**-0.187**	**0.01**		-0.071	0.17
Hypertension(yes/no)	0.001	0.031	0.28			
Years since menopause	0.023	-0.156	< 0.001			
Osteoporosis drugs(yes/no)	0.000	0.013	0.65			

*The highlighted variables are not included in the model

The bold value represent the overal effect size of the variable and for each of the levels of the variable(compared to the refernce category) we present the related p-values

with univariable analysis, taking GC showed no significant effect on TBS in both sexes; while women with positive history of GC had higher BMD in univariable analysis.

Several studies have shown controversial evidence on the relationship between T2DM and bone status, concerning the vital role of glucose in bone health [25]. It is becoming clearer that BMD values in T2DM could increase [12], decrease [16], or remain normal [17]. Furthermore, in some studies, a strong association between T2DM and risk of the hip [18, 19], wrist [20], vertebral [21, 22], and overall fractures [23–25] has been found; despite this, other studies found no distinct association between T2DM and the risk of regional or overal fractures [52, 53].

These studies have suggested that bone quality rather than bone mass influences fracture resistance in T2DM patients, such as increased cortical porosity [61] and reduced bone resistance [62]Many other factors [54]) in diabetic patients can also lead to poor bone quality, such as a rise in the incidence of falling, neurological and cognitive disability, microvascular disease [55], mild chronic inflammatory state [56], elevated levels of cytokines [57], and aging [58].In the absence of a comprehensive understanding of the mechanisms of diabetic bone dysfunction, it is difficult to establish reliable methods for measuring fracture risk.

At this point, there are no clear cutoffs and single approaches that can accurately predict all fracture outcomes in T2DM patients. The risk factors and history of fractures should be evaluated in elderly T2DM patients, and the measurement of BMD is recommendedEven when considering BMD values, we observed no differences in the history of fracture between diabetics and non-diabetics.As s result, TBS is suggested to improve the diagnosis risk of fractures. Leslie et al. showed that TBS can predict osteoporotic fractures independent of the glycemic status [12]. Generally, the mean of TBS was lower in T2DM compared to non-diabeticindividuals. Our findings showed that T2DM had major effects on BMD in both sexes and TBS in men, and BMD and TBS in both women and men was not affected by GC intake. Further research

is therefore needed to clarify exactly which properties affect the lumbar spine of the TBS in T2DM.

GC is known as a significant factor in bone loss, predominantly affecting bone quality, and increases the likelihood of osteoporosis. It has been shown that GC inhibits bone formation through prolong osteoclast life span and induces apoptosis of osteoblast and osteocyte [1]. This is not consistent with the results of our study; Regression analysis showed taking GC didn't affect BMD score. This discrepancy might be related to the fact that adverse effects of GC on bone quality are mainly dose-dependent on daily intake which has not been documented in the data of BEH study, The GC variable in our study was actually a history of taking GC and we did not access to the dosage and duration of it.

BMI is linked to T2DM and bone health as a potential risk factor [59–61], in previous studies, obesity and hyperinsulinemia have been mentioned as bone protectors in T2DM. Based on Elizabeth Barrett-Connor's studies, insulin significantly influenced the bone density of the radius and spine.Fat accumulation, especially visceral fat, induces inflammatory cytokine secretion despite increasing BMD, which may stimulate bone resorption and decrease bone strength [62]. In this way, our findings showed that in both women and men, BMI had a strong correlation with BMD. But TBS is inversely related to BMI and abdominal fat.

Last but not least, known and unknown factors such as diabetic medication, lifestyle, physical activity, smoking may influence the results differently. This research could provide sufficient information on the impact of T2DM and GC drugs on bone health, according to an evaluation of BMD and TBS in the elderly population.

Conclusion

In comparison with non-diabetics, diabetic patients had higher BMD levels in both sexes, however diabetes had a significant effect only in men in TBS modeling.Concerning standardized beta, a measure of covariates' relative importance, BMI was the most influential factor on both BMD and TBS but in an opposite direction, in both sexes.

Limitation

Diabetes control status, as well as the dose of GC, was not evaluated in this study. Therefore, to better understand the role of these exposures on bone health, it would be valuable to consider the dosage and the control group.

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Declarations

Ethics approval and consent to participate This study approved by the Research Ethics Committee of both Bushehr University of Medical Sciences and Endocrinology and Metabolism Research Institute.

Consent for publication All of the authors consent for publication.

Conflict of Interest None.

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