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Clinical Application of FRAX: A Practical Tool for Assessment of the Accuracy of Osteoporosis Fracture Risk

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Abstract

Background: Osteoporosis is a chronic systemic skeletal disorder marked by a reduction in bone mineral density and structural deterioration of bone tissue, resulting in a substantially increased risk of fragility fractures.

Objective: To assess the accuracy and reliability of the FRAX tool in predicting the 10-year risk of osteoporosis-related fractures, and to determine its potential utility in guiding clinical decisions for fracture prevention and patient management.

Method: This case-control study included 100 adult women aged between 40 ≥ 60 years. Participants were grouped by menopausal status (pre- and postmenopausal) and type 2 diabetes status, as well as a healthy control group, resulting in five distinct groups. Measured variables included fasting blood glucose, fasting blood insulin, and HOMA-IR. Bone mineral density (BMD) was assessed for all participants using dual-energy X-ray absorptiometry (DEXA). Additionally, the FRAX tool was employed to estimate the 10-year probability of major osteoporotic and hip fractures.

Results: Significant differences were observed among study groups in age, BMI, waist-to-hip ratio, BMD, and FRAX scores ($p < 0.05$). Diabetic and postmenopausal groups showed higher risks of major osteoporotic and hip fractures. Reduced BMD was significantly associated with higher HbA1c levels and increased insulin resistance. ROC analysis showed that fasting blood glucose (AUC = 0.941) and HOMA-IR (AUC = 0.879) had the highest diagnostic performance.

Conclusion: FRAX is significantly associated with clinical and metabolic risk factors; however, its predictive accuracy may be influenced by metabolic disturbances, especially in type 2 diabetes mellitus. Insulin resistance and poor glycemic control are strongly associated with reduced bone mineral density, underscoring the importance of including metabolic parameters in fracture risk assessment.

التطبيق السريري لأداة :FRAXأداة عملية لتقييم دقة تقدير خطر كسور هشاشة العظام.

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الملخص

المقدمة: هشاشة العظام هي اضطراب عظمي هيكلي مزمن يتميز بانخفاض كثافة المعادن في العظام وتدهور بنية النسيج العظمي، مما يؤدي إلى زيادة كبيرة في خطر حدوث الكسور الهشّة.

الهدف: تقييم دقة وموثوقية أداة FRAX في التنبؤ بخطر الكسور المرتبطة بهشاشة العظام خلال 10 سنوات، وتحديد إمكانية استخدامها في توجيه القرارات السريرية للوقاية من الكسور وإدارة المرضى.

الطريقة: شملت هذه الدراسة ذات تصميم الحالات والشواهد 100 امرأة بالغة تتراوح أعمارهن بين 40 سنة و60 سنة فأكثر، تم تصنيف المشاركات حسب حالة انقطاع الطمث (قبل وبعد انقطاع الطمث) وحالة الإصابة بداء السكري من النوع الثاني، إضافة إلى مجموعة سيطرة سليمة، مما أدى إلى تكوين خمس مجموعات متميزة. شملت المتغيرات المقاسة سكر الدم الصائم، والأنسولين الصائم، ومؤشر مقاومة الأنسولين .HOMA-IRكما تم تقييم كثافة المعادن في العظام BMDلجميع المشاركات باستخدام جهاز قياس امتصاص الأشعة السينية ثنائي الطاقة .DEXAبالإضافة إلى ذلك، تم استخدام أداة FRAX لتقدير احتمال حدوث كسور هشاشة العظام الرئيسية وكسور الورك خلال 10 سنوات.

النتائج: أظهرت النتائج وجود فروقات معنوية بين المجموعات في العمر، ومؤشر كتلة الجسم BMI ونسبة الخصر إلى الورك، وكثافة العظام BMD، ودرجات .($p < 0.05$) FRAXكما أظهرت مجموعات مرضى السكري وبعد انقطاع الطمث ارتفاعًا في خطر الكسور الرئيسية وكسور الورك. وكان انخفاض BMD مرتبطًا بشكل معنوي بارتفاع HbA1c وزيادة مقاومة الأنسولين. أظهر تحليل منحنى ROC أن سكر الدم الصائم (AUC = 0.941)ومؤشر (AUC = 0.879) HOMA-IR حققا أعلى أداء تشخيصي.

الاستنتاج: ترتبط أداة FRAX بشكل معنوي مع العوامل السريرية والتمثيل الغذائي، إلا أن دقتها التنبؤية قد تتأثر بالاضطرابات الأيضية، خصوصًا في داء السكري من النوع الثاني. كما أن مقاومة الأنسولين وضعف السيطرة على سكر الدم يرتبطان بقوة بانخفاض كثافة العظام، مما يؤكد أهمية إدخال المؤشرات الأيضية ضمن تقييم خطر الكسور.

1. Introduction

Osteoporosis is a common metabolic bone disorder marked by a progressive reduction in bone mass and structural deterioration of the skeleton, resulting in increased vulnerability to fractures, often occurring with minimal trauma. This condition imposes substantial health and economic burdens worldwide, particularly among postmenopausal and middle-aged women (Tański *et al.,* 2021). Patients with type 2 diabetes often have normal or high BMD but increased fracture risk. Bone microarchitecture changes and diabetes-specific factors reduce bone quality beyond BMD. FRAX does not include diabetes-related markers, limiting its accuracy. Therefore, research integrating these factors is needed to improve fracture prediction (Öz *et al*., 2026). Diabetes Mellitus (DM) is a chronic metabolic condition characterized by impaired insulin production, action, or both, leading to disturbances in glucose homeostasis and metabolic processes within key tissues such as the liver, muscle, and fat *(*Sanyaolu *et al.,* 2023). Globally, DM affects over 589 million adults, with Type 2 Diabetes Mellitus (T2DM) accounting for more than 90% of cases, and the number of affected individuals is projected to reach 853 million by 2050 (Ong *et al.,* 2023). The disease is associated with substantial morbidity and mortality, including cardiovascular and renal complications, with a growing burden particularly in low- and middle-income countries(Hossain *et al.,* 2024). Epidemiological evidence indicates that individuals with T2DM have an elevated risk of fractures, although data on bone mineral density (BMD) remain inconsistent (Care & Suppl, 2025). Regional studies further highlight the influence of lifestyle-related risk factors, underscoring DM as a critical public health challenge (Saado & Hussein, 2024). The Fracture Risk Assessment Tool (FRAX) was developed to estimate an individual's 10-year probability of sustaining a fracture by integrating multiple clinical risk factors, including age, sex, history of prior fractures, parental history of hip fracture, lifestyle factors such as smoking and alcohol consumption, exposure to glucocorticoids, and comorbid conditions including rheumatoid arthritis and secondary causes of osteoporosis (Anupama *et al.*, 2025). The model also allows for the inclusion of femoral neck BMD measurements to enhance predictive accuracy (Kanis, J. A., 2025). This study aims to estimate the 10-year probability of fractures and classify participants into low, moderate, and high-risk groups, thereby facilitating the identification of individuals with elevated fracture susceptibility and supporting targeted clinical interventions.

2. Materials and Methods

This case-control study included 100 women aged 40 ≥ 60 years who attended Imam Hassan Al-Mujtaba Hospital in Karbala from October 2025 to April 2026. Bone mineral density (BMD) at the lumbar spine and femoral neck was measured using DEXA by a rheumatology specialist. The FRAX tool was used to estimate the 10-year risk of major osteoporotic and hip fractures in all participants.., which integrates clinical data including age, sex, history of previous fractures, parental hip fracture, smoking, long-term glucocorticoid use, rheumatoid arthritis, secondary causes of osteoporosis, and alcohol consumption with BMD and Body mass index (BMI) was calculated for all participants using the standard formula (Shanks *et al*., 2025):

2.1. BMI $= \frac{\textbf{Weight (kg)}}{\textbf{Height } (\text{m}^2)}$ BMI serves as an important input in the FRAX algorithm for fracture risk estimation. BMI is an important input to the FRAX algorithm for estimating fracture risk.

Additional demographic and clinical data were collected, including menopausal status, medication history, medical and family history, lifestyle factors, and waist and hip circumferences. Exclusion criteria included chronic diseases affecting bone health, such as liver disease, chronic kidney disease, malignancies, rheumatoid arthritis, and lupus; use of medications that influence bone metabolism, including long-term corticosteroids, hormonal

therapies, and osteoporosis drugs; recent fractures or significant bone disorders; and pregnancy or breastfeeding. For laboratory analysis, venous blood samples (5 mL) were collected following skin disinfection (Al-Fatlawi, Khudair, *et al*., 2025). A portion of each sample was placed in a plain gel tube, allowed to clot, and centrifuged at 4000 rpm for 15 minutes to obtain serum. The remaining sample was collected in an EDTA tube for HbA1c measurement. The separated serum was stored in sterile Eppendorf tubes at −18 °C until analysis. Fasting insulin was measured in serum using the Sandwich-ELISA method, and fasting glucose was measured using the Trinder method. Insulin resistance was calculated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula (Ocakli, 2025):

$$\textbf{2.2 HOMA-IR} = \frac{\textbf{Fasting Glucose (mg/dL) x Fasting Insulin (}\mu\textbf{U/mL)}}{405}$$ Glycated hemoglobin (HbA1c) was used to reflect average blood glucose levels over the previous three months (Salman *et al.*, 2025).

2.3.Statistical Analysis

Statistical analysis was performed using SPSS version 26. The normality of data distribution was assessed using the Shapiro–Wilk test, which indicated that the data were normally distributed. Accordingly, the one-way ANOVA test was applied, after confirming its underlying assumptions, to compare means across multiple groups for continuous variables. The Chi-square test was used to evaluate associations between categorical variables. A p-value of less than 0.05 was considered statistically significant.

3. Results

The comparison of demographic and clinical variables among the study groups revealed statistically significant differences across all assessed parameters. Age varied significantly between groups (p = 0.001), with the highest mean observed in the postmenopausal diabetic group. Body mass index (BMI) was significantly elevated in all patient groups compared to controls (p = 0.004). In addition, the waist-to-hip ratio was significantly higher in the study groups (p = 0.045), reflecting increased central adiposity. Regarding bone mineral density, both T-scores and Z-scores were significantly lower in-patient groups than in controls (p = 0.001), indicating reduced bone mass. Moreover, FRAX scores for major osteoporotic fractures and hip fractures were significantly higher in the patient groups than in controls (p = 0.001 and p = 0.011, respectively), suggesting an increased risk of fractures in the patient groups Table1.

Table1: Demographic Comparison Between Study Groups

Parameters	Control		Post with D.M	Post without D.M	Pre with D.M	Pre without D.M	p-value
	Mean ±SD		Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
Age (years)	51.40 ±8.04		60.28 ±3.18	58.20 ± 4.08	49.00 ±5.29	48.60 ±6.80	0.001
BMI kg/m²	22.52 ±0.87		29.63 ±5.25	29.57 ±4.90	30.17 ±7.20	30.38 ±5.83	0.004
Waist –to-hip ratio	0.84 ±0.01		0.93 ±0.15	0.90 ±0.07	0.96 ±0.09	0.94 0.06	0.045
T -score	-	-	-3.22 ±0.66	-3.37 ±0.80	-2.85 ±0.30	-2.93 ±0.43	0.001
Z -score	-	-	-1.84 ±0.79	-1.99 ±0.90	-2.04 ±0.50	-2.16 ±0.75	0.001
FRAX major osteoporotic	-	-	0.17 ±0.13	0.22 ±0.15	0.12 ±0.04	0.14 ±0.05	0.001
FRAX hip fractures	-	-	0.10 ±0.12	0.14 ±0.16	0.06 ±0.03	0.07 ±0.05	0.011

*P-value is considered statistically significant when it is below 0.05
*An empty cell indicates that no participants (0.0%) were included in this category; therefore, No statistical comparison could be conducted.

The results showed that the distribution of bone mineral density (BMD) categories differed significantly among the study groups ($p < 0.001$). All individuals in the control group exhibited normal BMD (100%), whereas reduced BMD was evident across all patient groups. The premenopausal diabetic group showed the highest proportion of severely reduced BMD (60%), while the premenopausal non-diabetic group had the highest proportion of mildly reduced BMD (53.3%). Overall, both the premenopausal and postmenopausal groups showed a clear trend toward lower BMD than in controls, as shown in Table2.

Table2: Distribution of Bone Mineral Density (BMD) Categories Across Study Groups

Parameters	Groups	Control	Post with DM	Post without DM	Pre with DM	Pre without DM	p-value
Bone Mineral Density	Normal	100.0%	8.0%	16.0%	0.0%	0.0%	<0.001
	Mildly Low	0.0%	48.0%	36.0%	40.0%	53.3%	
	Severely low	0.0%	44.0%	48.0%	60.0%	46.7%	

* P-value is considered statistically significant when it is below 0.05
*Pre: Premenopausal group
*Post: Postmenopausal group
*D.M: Diabetes Mellitus
*S. D: Standard Deviation

Shown in Table3, HbA1c levels differed significantly among the groups ($p < 0.001$), with higher values observed in participants with more severe reductions in BMD. Fasting blood glucose also showed a significant difference ($p = 0.030$), with higher levels generally observed in patient groups compared to controls. In contrast, fasting insulin levels did not differ significantly between groups ($p > 0.05$). However, HOMA-IR values were significantly elevated in groups with reduced BMD ($p = 0.04$), suggesting an association between insulin resistance and reduced bone density.

Table3: Comparison Between Metabolic Parameters Based on the Bone Mineral Density

Parameters	Z-Score Categories	Control	Post with DM	Post without DM	Pre with DM	Pre without DM	P-value
		Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
HBA1c %	Normal	5.48 ±0.47	7.55 ±1.48	5.50 ±0.72			**0.004**
	Mildly Low		7.25 ±0.71	5.49 ±0.36	6.88 ±0.61	5.17 ±0.62	**<0.001**
	Sever low		7.66 ±0.93	5.60 ±.35	7.08 ±1.03	4.96 ±0.46	**<0.001**
	P-value		0.522	0.799	0.684	0.465	
Fasting blood glucose mg/dL	Normal	98.58±17.37	143.13±21.71	164.08±72.01			**0.030**
	Mildly Low		154.20±36.04	168.00±54.74	176.40±31.54	203.05±53.83	0.148
	Severely low		145.21±36.59	160.46±36.05	151.24±44.26	178.01±54.50	0.420
	P-value		0.809	0.942	0.252	0.388	
Fasting blood insulin µIU/mL	Normal	1.04 ±.40	2.34 ±1.50	2.10 ±1.50			0.080
	Mildly Low		2.02 ±1.20	1.76 ±1.00	1.49 ±0.96	1.69 ±1.05	0.789
	severely low		1.65 ±0.99	2.16 ±1.35	2.33 ±1.32	2.03 ±1.23	0.638
	P-value		0.629	0.756	0.206	0.573	
HOMA-IR	Normal	26 ±0.13	0.87 ±0.65	0.79 ±0.66			0.04
	Mildly Low		0.82 ±0.60	0.63 ±0.29	0.67 ±0.49	0.76 ±0.37	0.800

	Sever low		0.54 ±0.25	0.86 ±0.56	0.82 ±0.42	0.85 ±0.54	0.316
	P-value		0.341	0.559	0.539	0.689	

*P-value is considered statistically significant when it is below 0.05
*Pre: Premenopausal group
*Post: Postmenopausal group
*DM: Diabetes Mellitus
*SD: Standard Deviation

The results of the correlation analysis revealed significant associations among some metabolic variables. HbA1c was positively and significantly correlated with fasting blood glucose ($r = 0.518$, $p = 0.004$), while no significant relationship was found between HbA1c and either fasting insulin or HOMA-IR ($p > 0.05$). Fasting blood glucose also showed a significant positive correlation with HOMA-IR ($r = 0.396$, $p < 0.001$), indicating that elevated glucose levels are associated with increased insulin resistance. Additionally, a strong positive correlation was found between fasting insulin and HOMA-IR ($r = 0.890$, $p < 0.001$), confirming the close relationship between insulin and insulin resistance Table4.

Table4: The Correlation Analysis Between Metabolic Parameters in All Patients

Parameters		**HBA1c %**	**FBS mg/dL**	**FBI µIU/mL**	**HOMA-IR**
HBA1c %	**R-value**	1	0.518**	0.054	-0.079
	P-value		0.004	0.634	0.488
Fasting blood glucose (FBS) mg/dL	**R-value**		1	-0.014	0.396**
	P-value			0.9	<0.001
Fasting blood insulin (FBI) µIU/mL	**R-value**			1	0.890**
	P-value				<0.001
HOMA-IR	**R-value**				1
	P-value				

*P-value is considered statistically significant when it is below 0.05
*Pre: Premenopausal group
*Post: Postmenopausal group
*DM: Diabetes Mellitus
*SD: Standard Deviation

The results of Table5 and Fig.1 showed that all the studied metabolic indicators have varying diagnostic abilities in detecting bone density disorders. Fasting blood glucose recorded the highest diagnostic performance (AUC = 0.941), with a sensitivity of 84%, specificity of 100%, and diagnostic accuracy of 85.6%, indicating its high efficiency as a metabolic marker. HOMA-IR also showed good diagnostic ability (AUC = 0.879), while the diagnostic ability of both HbA1c and fasting insulin was lower compared to the other indicators. These results suggest that fasting blood glucose and HOMA-IR represent more effective indicators in assessing metabolic disorders associated with decreased bone density.

Table 5 Receiver Operating Characteristic (ROC) Curve for Metabolic Parameters

Metrics		HBA1c %	Fasting blood glucose mg/dL	Fasting blood insulin µIU/mL	HOMA-IR
Std. Error		0.061	0.026	0.076	0.049
Asymptotic Sig.		0.021	<0.001	0.012	<0.001
Asymptotic 95% Confidence Interval	**Lower Bound**	0.605	0.890	0.596	**Asymptotic 95% Confidence Interval**
	Upper Bound	0.843	0.993	0.892	0.975
Area Under Curve (AUC)		0.724	0.941	0.744	0.879
Cutt-off point		6.07	117.491	1.59	0.42
Accuracy		57%	85.6%	52%	73%
Specificity		100%	100%	100%	90%
Sensitivity		52%	84%	46%	71%

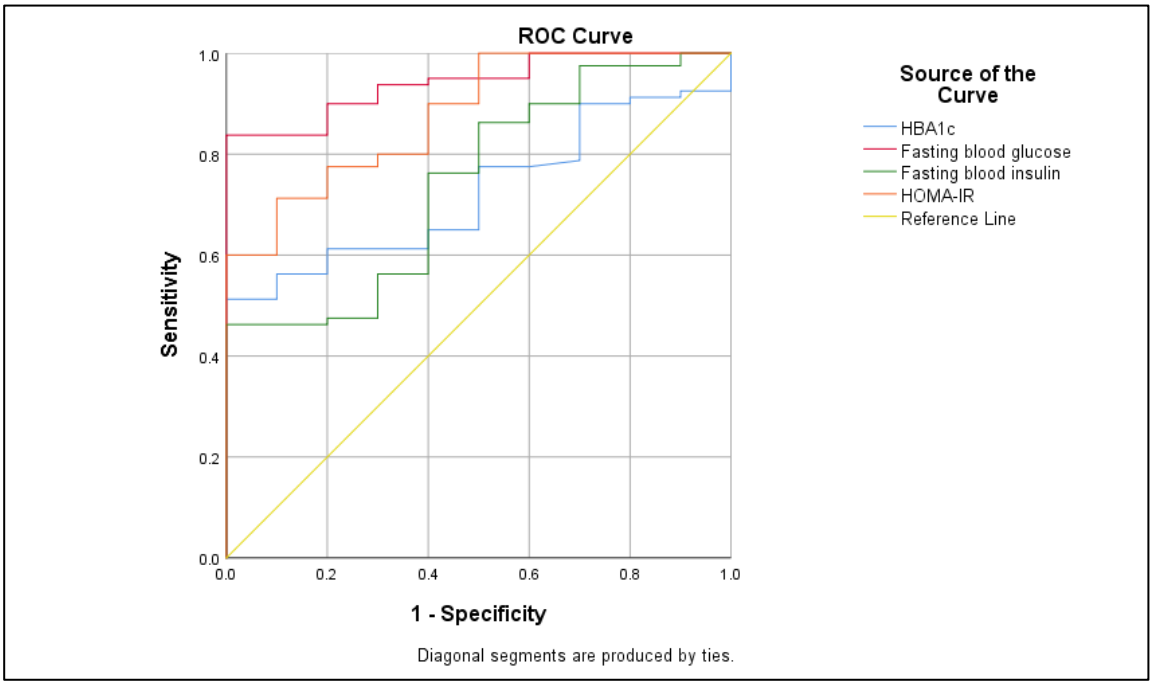

Figure:1 ROC Curve Showing the Diagnostic Accuracy of the Metabolic Parameters.

4. Discussion

The findings of the present study indicate a clear relationship between metabolic disturbances, menopausal status, and impaired bone health, as evidenced by reduced bone mineral density (BMD) and increased fracture risk estimated by FRAX. Advancing age and estrogen deficiency remain fundamental contributors to osteoporosis, particularly in postmenopausal women, where decreased estrogen levels accelerate bone resorption through increased osteoclast activity and disruption of bone remodeling processes (Cai *et al*., 2025). An increase in body mass index (BMI) was observed across all patient groups. Although higher BMI has traditionally been considered beneficial for bone due to increased mechanical loading, emerging evidence suggests that metabolic abnormalities may offset this protective effect. Specifically, obesity accompanied by insulin resistance and chronic low-grade inflammation may negatively influence bone quality, indicating that BMI alone cannot be relied upon as a protective indicator in such populations (Sima *et al*., 2025).

In addition, central obesity, as indicated by an elevated waist-to-hip ratio, was significantly associated with reduced BMD (Al-Fatlawi, Khaleel, *et al*., 2025). Visceral fat is known to be metabolically active and capable of producing pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to increased osteoclast genesis and bone resorption. This supports the concept that metabolic alterations linked to adiposity play a direct role in skeletal deterioration (Nagendra *et al*., 2023).

A notable observation in this study is the marked reduction in BMD among individuals with type 2 diabetes mellitus and those in the postmenopausal stage. It is well established that T2DM affects bone integrity primarily through alterations in bone quality rather than bone mass. Chronic hyperglycemia leads to the formation of advanced glycation end-products (AGEs), which interfere with collagen structure and reduce bone strength, thereby increasing susceptibility to fractures even when BMD values appear relatively preserved (Vashishth *et al*., 2026). The analysis also revealed significantly elevated FRAX scores among diabetic and postmenopausal participants, indicating a higher estimated probability of fractures over 10 years. However, it is important to recognize that the FRAX model does not explicitly include diabetes as an independent variable, which may result in an underestimation of fracture risk in individuals with T2DM. This limitation has been highlighted in recent literature and suggests the need for cautious interpretation when applying FRAX in metabolically complex populations (Patel *et al*., 2024). Metabolic markers were significantly associated with bone health parameters. Higher HbA1c and fasting blood glucose levels were associated with lower BMD, suggesting that prolonged hyperglycemia may impair bone remodeling through oxidative stress and inflammation. In contrast, fasting insulin levels alone were not significantly associated with BMD, whereas insulin resistance, as measured by HOMA-IR, showed a stronger relationship. This finding indicates that insulin resistance, rather than insulin concentration per se, may be a more relevant factor influencing bone metabolism. In addition, the results showed that dysregulation of blood sugar and insulin resistance clearly contribute to declines in bone health. Despite the significant increase in HbA1c levels in groups with greater decreases in bone density, its diagnostic efficiency was lower than that of fasting blood sugar and HOMA-IR, suggesting that HbA1c is less effective for early detection of metabolic effects on bones. In contrast, both fasting blood sugar and HOMA-IR showed higher diagnostic capability, reflecting the more influential role of hyperglycemia and insulin resistance in bone metabolism disorders. These data suggest that insulin resistance may be a more accurate and reliable indicator than insulin levels alone for evaluating osteoporosis risk (Yang *et al*., 2024). Correlation analysis further supported the central role of metabolic dysfunction, showing strong associations between fasting glucose and insulin resistance, and between fasting insulin and HOMA-IR. The relatively weak association between HbA1c and other metabolic indicators may reflect variations in disease duration, treatment regimens, and overall glycemic control among participants (Chuang *et al*., 2024). Furthermore, ROC curve analysis demonstrated that fasting blood glucose and HOMA-IR had superior diagnostic performance compared with HbA1c and fasting insulin. These findings emphasize the importance of insulin resistance and acute glycemic status as key indicators for identifying individuals at higher risk of metabolic and skeletal abnormalities (Jain *et al.*, 2025). Taken together, the results of this study suggest that osteoporosis in this population arises from a complex interplay between hormonal changes, metabolic dysregulation, and inflammatory processes. Additionally, the findings highlight the limitations of relying solely on FRAX in patients with type 2 diabetes and support the need to incorporate metabolic parameters into fracture risk assessment models to improve predictive accuracy.

Conclusion

This study concludes that aging, menopause, and increased adiposity are significantly associated with reduced bone mineral density and higher fracture risk. Poor glycemic control and insulin resistance are strongly associated with bone loss, suggesting that metabolic dysfunction adversely affects bone health. Among the studied markers, insulin resistance (HOMA-IR) and fasting blood glucose showed the strongest diagnostic value, while HbA1c and insulin were less effective. Overall, the findings highlight a strong interaction between metabolic disorders and osteoporosis risk, emphasizing the importance of early detection and metabolic control.

Ethical statement

The Ethics Committee approved the conduct of this study at the College of Applied Medical Sciences, Department of Pathological Analysis, University of Karbala. CLAMSKY/20.

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