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The dysfunctional Impacts of Diabetic Nephropathy Associated With Bone Metabolic Disorder

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Abstract
Background*:** Diabetic nephropathy is one of diabetic complication approximately affecting 40% of diabetic patients that leads significantly to morbidity and mortality. impaired kidney function in patients with diabetic nephropathy disrupts mineral metabolism leading to imbalance of hormones and altered in bone remodeling processes. Osteopenia and osteoporosis are bone diseases in which bone mineral density loss has occurred at a significant level**.** This aimed to show the association between diabetic nephropathy and disorder of bone metabolism with an emphasis on osteopenia and osteoporosis. ***Patients and Methods: A case-control study was proceeding on 55 volunteers including 25 DN patients and 30 healthy controls, aged 41–81 years. all participants were diagnosed with diabetic nephropathy by the physicians at Al-Zahraa Teaching Hospital and some private clinics in Wasit province, Iraq. Bone mineral density (BMD) was detected using dual energy X- ray absorptiometry (DEXA). Serum level of RANKL, sclerostin, FGF23 and PTH were estimated using ELISA assay according to the procedure provided by the manufacturer's instructions, Biont Co., Germany. Also, serum levels of phosphate, calcium and vitamin D were determined automatically using automated Roche cobas c111 immunoassay platform. Multi-statistical testses were used in this study (Independent sample t-test, one way (ANOVA), Kruskal-Wallis and Chi-square at significant level ($P \leq 0.05$). ***Results***: The serum RANKL, sclerostin, FGF23 and PTH levels showed a higher significant ($P < 0.05$) with significantly reduced of serum Vit. D3 levels in DN patients with osteoporosis left femur than normal left femur and osteopenia left femur. While, serum levels of Ca^{+2} and Pi observed a non-significant difference ($P \geq 0.05$) in both DN patients (normal left femur, patients with osteopenia left femur and osteoporosis left femur) and also, in healthy groups with osteopenia left compare to patients with normal left femur. ***Conclusion***: This study confirms that DN induced disrupts in phosphate and vitamin D homeostasis that leading to elevate FGF23 and PTH, which drive bone resorption via RANKL and sclerostin pathways. These findings may underscore the multifactorial pathogenesis of DN-related osteoporosis and osteopenia as a renal dysfunction to reinforce its role as a risk factor to accelerate bone loss through dysregulated mineral metabolism and osteoclast activation

Keywords: *Diabetic nephropathy (DN), Osteoporosis (OP), Osteopenia, Bone disorder biomarkers, RANKL, Sclerostin, FGF23.*

INTRODUCTION

Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD) is one of the main kidney related disorders **(Luo et al., 2024)**. Basically. the kidney plays an essential role in maintaining vitamin D activation (calcitriol). **(Ростока et al., 2021).** Also, the bone, an important part of the body, can also secrete bone-derived proteins or peptides that act on distal organs. As an organ with high metabolism, the kidney is responsible for signal and material exchange with other organs at any time through circulation **(Yang et al., 2022).** So**,** the research indicates that bone metabolism disorders may be a risk factor for the development of kidney complications in T2DM **(Winiarska et al., 2021).**

Bone mineral density (BMD) is one of the most important factor to measure bone quantity **(Docaj & Carriero, 2024).** Osteopenia (low bone mass) is a clinical term used to describe bone mineral density

characterized by decreased bone mass, density, and mineral content **(Teng et al., 2021)**. It can be considered as a precursor to osteoporosis due to a lowered BMD and can diagnosed before an osteoporosis diagnosis **(Munnikhuysen, 2022)**. Besides, osteoporosis (OP) is a progressive bone disorder characterized by decreased bone mass, bone mineral density, mineral content and destruction of the microarchitecture of the bone**(Srivastava, 2024).** Roughly every ten years, the entire adult skeleton is replaced by remodeling, osteoporosis occurs when there is an imbalance between the bone formation of osteoblasts and bone resorption of osteoclasts, when bone resorption exceeds bone formation that leads to increased bone fragility**(D. Wu et al., 2021) .**

Osteocyte, osteoclasts , osteoblast and bone lining cell are cellular compounds responsible for the synthesis and mineralization of bone during both initial bone formation and later bone remodeling, these cells secreted many of biomarkers and receptors take part in bone turnover **(Šromová et al., 2023)**. FGF23 is a bone- and bone marrow-derived hormone and is principally synthesized by osteoblasts and osteocytes**(Portales-Castillo & Simic, 2022)**,but under pathological conditions, FGF23 can be secreted by the heart, liver, kidney, macrophages, or bone marrow **(Zhu et al., 2024)**. The classical target organs of FGF23 are the kidney and parathyroid glands and plays a crucial role in mineral metabolism, particularly in regulating phosphate and vitamin D homeostasis **(Dastghaib et al., 2023).** Also**, r**eceptor Activator of Nuclear Factor-κappa B ligand (RANKL) is a tumour necrosis factor family cytokine produced by osteoblasts. Its target consists of the receptor activator of NF-κB (RANK (**Monti et al., 2024).** Sclerostin is a human bone tissue protein involved in the anti-anabolic processes of bone formation **(Oniszczuk et al., 2022)** and can stimulate RANKL secretion in osteocytes, osteoclastogenesis and bone resorption **(Kitaura et al., 2020)**.

On the other hand, PTH regulation is another important pathway for bone-mineral homeostasis. The suppression of PTH by FGF23 is primarily mediated by a Klotho-dependent mechanism and Klotho-independent mechanism **(Sirikul et al., 2022)**. Despite the fact that FGF23 significantly inhibits PTH production and secretion, the dominant regulators of PTH levels at circulating are free (ionized) calcium and calcitriol levels, which are monitored by the calcium-sensing receptor (CaSR) and the VDR in the parathyroid gland **(Shaker & Deftos, 2023)**.

So, the gool study to search of the relationship between osteopenia and osteoporosis impacts associated diabetic nephropathy and to attempt evaluate some related- bone disorders biomarkers to figure out the possibility dysfunctional during bone metabolic disorder.

MATERIALS AND METHODS

Subject and design study: The Case-control study was conducted on 55 of both apparently healthy, and diabetic nephropathy patients with an age range between (41-81) years. The study included 30 apparently healthy volunteer (16male and 14 female) and 25 patients with diabetic nephropathy (12 male and 13 female) diagnose by physician. Patients were recruited from Al-Zahraa Teaching Hospital, Al-Karama Teaching Hospital, and some other private clinics, Wasit, Iraq. The practical part was conducted in the private laboratories in Wasit. Clinical history was taken from each patient and their parents including: name, age, sex, duration of illness, family history of diabetic.

Blood Samples Collection: Five ml of venous blood were obtained from each subject by vein puncture discharged slowly into disposable gel test tubes without anticoagulant (gel tube) and allowed to clot at 37°C for 10 minutes, then serum was separated from whole blood using table centrifuge. Blood was centrifuged for 10 minutes at 4000 rpm at room temperature in a table centrifuge (Hettich EBA 20, Germany). Serum samples was aliquot into Eppendorf tubes for estimation of PTH and 25(OH) D and for freezing at -20°C to be used for measuring bone biomarkers (Sclerostin, RANKL and FGF23).

Laboratory Assay of Bone Biochemical - Biomarkers: FGF23, RANKL, and Sclerostin, are determined based on the sandwich ELISA principle for direct antigen detection including high affinity and specificity antibodies (enzyme labelled and biotinylated) with different and distinct epitope recognition. The quantitative determination of phosphate, vitamin D3 and calcium in human serum was done in vitro by cobas c111 system. Each test was followed by the method given in the analyzer document. Cobas c systems calculated the analyte concentration automatically of each sample in the unit mmol/L (mg/dL, mg/L).

Statistical Analysis: Numeric data were presented as mean, standard deviation after performance of Kolmogorov- Smirnov normality test and making decision about normally and non-normally distributed variables. Independent sample t-test was used to study difference in mean between any two groups provided that the variable is normally distributed, one way ANOVA test (SPSS version 26), Kruskal-Wallis test was used to study difference in median between more than two non-parametric groups and Chi-square test were used in this study (Daniel & Cross, 2018).

RESULTS

Distribution of Study Groups According to T-Score Reading.

The distribution of study groups (DN patients and control) according to T-score reading are shown in table (1). The frequency distribution of DN patients were as following: 6 was normal left femur, 12 with osteopenia left femur and 7 with osteoporosis left femur. Whereas the healthy control was as following: 19 was normal left femur, 11 with osteopenia left femur and no healthy control have osteoporosis left femur. The findings showed a significantly (P> 0.05) osteopenia in left femur among most DN patients than to healthy subjects.

Table (1): Frequency distribution of ND patients and heathy groups according to t-score reading.

Study Groups		T-score reading			P-value
		Normal	Osteopenia	Osteoporosis	
Groups	DN patients	6	12	7	0.006 * ¥
	Control	19	11	0	
Total		25	23	7	

¥: Chi-square test; *: significant at (P < 0.05)

The Serum bone biomarkers levels according to T-score reading

The serum RANKL according to T-score reading showed a higher significant (P < 0.05) mean in patients with osteoporosis left femur in comparison with both other groups (normal left femur and patients with osteopenia left femur) respectively. Whereas, in healthy sample the mean of serum RANKL was elevated significantly (P < 0.05) in osteopenia left femur than to normal left femur (table-2).

Table (2): Serum RANKL Levels (ng/L) according to T-score reading in DN patients and healthy groups.

T-score reading		Receptor Activator of Nuclear Factor-Kappa B Ligand (RANKL) (ng/L)
Diabetic nephropathy patients (DN)		
Normal	Mean ± SD	96.53 ± 13.49^{A}

Osteopenia	**Mean ± SD**	**142.75 ± 4.75^{B}**
Osteoporosis	**Mean ± SD**	**182.85± 9.72^{C}**
P-value		**0.001*** **K**
Healthy group		
Normal	**Mean ± SD**	**34.35 ± 7.46**
Osteopenia	**Mean ± SD**	**66.08 ± 3.64**
P-value		**0.001*** **†**

SD: standard deviation; †: Independent T test; K: Kruskal–Walli's test; *: significant at ($P < 0.05$)

The serum sclerostin (ng/ml) means according to T-score reading demonstrated in table (3). In DN patients, the mean of serum sclerostin was elevated significantly ($P < 0.05$) in patients with osteoporosis left femur compare to both patients with normal left femur and patients with osteopenia left femur. While, the data observed non-significant differences ($P \geq 0.05$) of serum sclerostin in DN patients with osteopenia left compare to patients with normal left femur. Besides, in healthy group the mean of serum sclerostin was increased significantly ($P < 0.05$) in osteopenia left femur than to normal left femur group.

Table (3): Serum sclerostin (SOST) (ng/ml) Levels according to T-score reading in DN patients and healthy groups.

T-score reading		**Sclerostin (SOST) (ng/ml)**
Diabetic nephropathy patients (DN)		
Normal	**Mean ± SD**	**34.75 ± 2.09^{A}**
Osteopenia	**Mean ± SD**	**58.74 ± 3.36^{A}**
Osteoporosis	**Mean ± SD**	**158.25 ± 12.85^{B}**
P-value		**0.001*** **K**
Healthy group		
Normal	**Mean ± SD**	**18.87 ± 6.05**
Osteopenia	**Mean ± SD**	**26.30 ± 2.74**
P-value		**0.001*** **†**

SD: standard deviation; †: Independent T test; K: Kruskal–Walli's test; *: significant at ($P < 0.05$)

The serum FGF23 (pg/ml) levels in diabetic nephropathy patients showed a higher significant ($P < 0.05$) higher mean in patients with osteoporosis left femur and osteopenia left femur compare to normal left femur. While, the findings observed a non-significant difference ($P \geq 0.05$) of serum FGF23 in healthy group with osteopenia left compare to patients with normal left femur.

Table (4): Serum Fibroblast Growth Factor 23 (FGF23) levels according to T-score reading in DN patients and healthy groups.

T-score reading		Fibroblast Growth Factor 23 (FGF23) (pg/ml)
Diabetic nephropathy patients (DN)		
Normal	**Mean ± SD**	**156.35 ± 21.12**^{A}
Osteopenia	**Mean ± SD**	**254.38 ± 27.13**^{B}
Osteoporosis	**Mean ± SD**	**255.47 ± 17.02**^{B}
P-value		**0.021*** **K**
Healthy group		
Normal	**Mean ± SD**	**78.01 ± 7.95**
Osteopenia	**Mean ± SD**	**93.17 ± 10.91**
P-value		**0.266** ** **†**

SD: standard deviation; †: Independent T test; K: Kruskal–Wallis test; *: significant at ($P < 0.05$); **: Non-significant at ($P \geq 0.05$).

The Serum of some biochemical levels related to bone disorder according to T-score reading

The hormonal serum of PTH levels in DN patients according to T-score reading showed a high significant ($P < 0.05$) concentrations in patients with osteoporosis left femur compare to both other groups (normal left femur and patients with osteopenia left femur) respectively. While, serum of PTH levels in healthy group the levels were elevated significantly ($P < 0.05$) in osteopenia left femur than to normal left femur. Besides, the Biochemical assay for serum Pi observed a non-significant difference ($P \geq 0.05$) in both DN patients (normal left femur, patients with osteopenia left femur and osteoporosis left femur) and also, in healthy groups with osteopenia left compare to patients with normal left femur (table -5).

Table (5): Serum parathyroid hormone (PTH) (pg/ml) and PI (mg/dl) levels according to T-score reading in DN patients and healthy groups.

T-score reading		Parathyroid hormone (PTH) (pg/ml)	Pi (mg/dl)
Diabetic nephropathy patients			
Normal	**Mean ± SD**	**74.15 ± 3.84**^{A}	**4.29 ± 0.41**
Osteopenia	**Mean ± SD**	**94.60 ± 12.33**^{B}	**4.22 ± 0.40**
Osteoporosis	**Mean ± SD**	**145.00 ± 10.51**^{C}	**4.27 ± 0.37**
P-value		**0.001*** **K**	**0.933**** **K**
Healthy group			
Normal	**Mean ± SD**	**39.82 ± 6.79**	**4.71 ± 0.74**
Osteopenia	**Mean ± SD**	**62.42 ± 9.80**	**4.47 ± 0.55**
P-value		**0.001*** **†**	**0.100** ** **†**

SD: standard deviation; †: Independent T test; K: Kruskal–Wallis test; *: significant at ($P < 0.05$); **: Non-significant at ($P \geq 0.05$).

Moreover, the serum biochemical of Ca^{+2} levels according to T-score reading showed a non-significant difference ($P \geq 0.05$) in both DN patients (normal left femur, patients with osteopenia left femur and osteoporosis left femur) and also, in healthy participations with osteopenia left compare to patients with normal left femur. However, serum Vit. D3 levels in DN patients detected a reduced significant ($P < 0.05$) concentrations in patients with osteoporosis left femur compare to both other groups (normal left femur and patients with osteopenia left femur) respectively. While, serum of Vit D3 concentration in healthy subjects were decreased significantly ($P < 0.05$) in osteopenia left femur compare to normal left femur (table-6).

Table (6): Serum parathyroid hormone Ca^{+2}(mg/dl) and Vitamin D3 (ng/dl) levels according to T-score reading in DN patients and healthy groups.

T-score reading		Ca^{+2}(mg/dl)	Vitamin D3 (ng/dl)
Diabetic nephropathy patients			
Normal	**Mean ± SD**	**9.70 ± 0.59**	**13.33** ± 0.85^{A}
Osteopenia	**Mean ± SD**	**9.44** ± 0.81	**8.91** ± 1.61^{B}
Osteoporosis	**Mean ± SD**	**9.11** ± 0.80	**6.05** ± 0.64^{C}
P-value		**0.384** ** **K**	**0.001*** **K**
Healthy group			
Normal	**Mean ± SD**	**9.22 ± 0.51**	**26.17** ± 4.14
Osteopenia	**Mean ± SD**	**9.34** ± 0.62	**15.38** ± 3.54
P-value		**0.554** ** †	**0.001*** †

SD: standard deviation; †: Independent T test; K: Kruskal–Wallis test; *: significant at ($P < 0.05$); **: Non-significant at ($P \geq 0.05$).

DISCUSSION

When kidney function is impaired, the metabolic processes of the body are also affect various body systems and related with bone mineral disorders, including osteopenia and osteoporosis (OP) which are the common complications **(Modest et al., 2022).** The elevated serum levels receptor activator of nuclear factor-κB ligand (RANKL) in diabetic nephropathy maybe due to its association with elevated inflammation, which consider as a critical factor in these conditions. These processes stimulate RANKL expression in various tissues, including the kidneys **(Darenskaya et al., 2023)**. Although, the biological effect of RANKL on bone reabsorption start when it binds to RANK on the surface of preosteoclasts, which results in osteoclast differentiation, activation, and survival **(Liang et al., 2023)** , the higher level of RANKL in osteoporotic patient with diabetic nephropathy associated with an initially increased osteoclast signaling **(Chao et al., 2020)**. So, the RANKL system initiates a signaling cascade that induce osteoclastogenesis and lead to osteoclast-related diseases such as osteoporosis **(Wu et al., 2024)** .

Additionaly, the high;y serum sclerostin level among DN patients possibly resulting from the fact that the kidney plays a role in clearing sclerostin and renal dysfunction in DN may reduce its excretion, contributing to higher circulating levels. **(C.-F. Wu et al., 2021)**. Similary, in recent study revealed that the Wnt/β-catenin pathway plays a key role in kidney fibrosis and inflammation, both of which are hallmarks of

DN, besidesm hyperglycemia and oxidative stress disrupt Wnt signaling, leading to compensatory sclerostin upregulation in DN to suppress excessive Wnt activity **(Marini et al., 2023)**.

On other hand, in the body there are three hormones that control calcium and phosphorus metabolism (FGF23; 1,25(OH)2D and PTH) that interact to form a feedback loop among the kidney, bone, gut, and parathyroid glands **(Yang et al., 2022).** Patients with diabetic nephropathy have higher levels of serum PTH, as well as FGF23, and the disorder of mineral metabolism is more serious **(Deng et al., 2021).** FGF23 level was associated with an increased risk of diabetic complications especially diabetic nephropathy that results in unmetabolized accumulation of FGF23**(Donate-Correa et al., 2019; Niţă et al., 2021).** As nephritis progresses, physiologically active substances and enzymes accumulate without being metabolized an excretion due to renal dysfunction. **(Kajiwara et al., 2021).**

In diabetic nephropathy patients explore a secondary hyperparathyroidism because of elevated serum FGF23 level which reduced renal calcitriol synthesis and subsequently decreasing active intestinal calcium transport with increase phosphate excretion by the kidney results in a reduction in blood phosphate level **(Agoro & White, 2023; Wei et al., 2024).** Hyperparathyroidism is associated with increased risk of osteoporosis and be mediated by low bone mineral density (BMD) **(Walker & Silverberg, 2018),** because FGF23 that produced by osteoblasts and osteocytes was regulates phosphate metabolism by inhibits the reabsorption of phosphate in the renal proximal tubules and increase phosphate excretion through urine**(Perumal & Padidela, 2024).** As well as, serum phosphate levels are low with hyperparathyroidism that plays an essential role in bone mineralization and calcium and phosphate homeostasis by enhancing phosphate excretion by the kidneys **(Perumal & Padidela, 2024)**. This homeostasis step leading to abnormal bone metabolism. Therefore, the structure and function of bone tissue are also altered in the diabetic kidney disease, which may lead to abnormal secretion of bone derived hormones**(Wawrzyniak & Balawender, 2022).**

Eventually, the suppress of number of functioning nephrons in DN leads to disruption of vitamin D metabolism, contributing to the development of a number of complications **(Ismoilov et al., 2024).** Several studies have indicated significant lower in osteoporosis patients, indicating that vitamin D deficiency is more prevalent in DN patients **(Hong et al., 2021; Zhao et al., 2021)**. Also, FGF23 can inhibits 1a-hydroxylase, thereby reducing the production of 1,25(OH)2D and indirectly inhibiting phosphate absorption in the intestines **(Freundlich et al., 2021).** The lowering serum concentration of vitamin D in patient with osteoporosis than other groups which revealed that development of OP that play an important role in the elevation of FGF23, which is involved in suppression of the conversion of vitamin D to the active form 1,25 dihydroxy cholecalciferol (1,25-[OH]2D) **(Masajtis-Zagajewska et al., 2021).** Theses finding may reinforce the stability of serum calcium level was within normal range despite bone disorder, this calcium homeostasis was maintained through compensatory mechanisms by elevation of FGF23 in the distal tubules, which express the calcium channel protein receptor (TRPV5) , that reabsorbs calcium from the urine **(Ho & Bergwitz, 2021)**.

CONCLUSION

The elevated serum levels of RANKL and sclerostin, FGF23 and PTH, promoting osteoclastogenesis and leading to impaired hormonal bone metabolism and induced disrupts in phosphate and vitamin D homeostasis may be leading to secondary hyperparathyroidism and loss of bone mineral density. Overall, in DN patients the alterations in kidney-bone hormone axes result in impaired bone remodeling and increased risk of osteoporosis and osteopenia, emphasizing the importance of early monitoring and management of bone disorders in DN patients.

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