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Association between leptin, lipid metabolism, and bone remodeling markers in men with type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) is associated with disturbances in bone metabolism that may increase fracture risk, even in the presence of normal or high bone mineral density (BMD). Dyslipidemia and elevated leptin levels, both common in T2DM, considered potential contributors to impaired bone remodeling, particularly in men, where skeletal responses to metabolic disturbances remain insufficiently understood.

Aim. To evaluate associations between serum leptin levels, lipid metabolism parameters, and markers of bone turnover in men with T2DM.

Materials and methods. A cross-sectional study included 62 men with T2DM (aged 50–65 years) and 58 age-matched non-diabetic controls. Laboratory assessments included HbA1c, insulin, leptin, testosterone, 25-hydroxyvitamin D (25(OH)D), parathyroid hormone, lipid profile, and bone turnover markers (P1NP, β-CTX). BMD at the lumbar spine and proximal femur was measured by dual X-ray absorptiometry (DXA). Insulin resistance was evaluated using HOMA-IR. Correlations were analyzed using Spearman's rank test.

Results. Men with T2DM had higher BMI (29.8 kg/m^2 vs. 26.7 kg/m^2, $p = 0.006$), elevated leptin (15.2 ng/mL vs. 11.2 ng/mL, $p = 0.003$), dyslipidemia (increased triglycerides and LDL-C, decreased HDL-C), and lower 25(OH)D levels (16.8 ng/mL vs. 21.6 ng/mL, $p = 0.007$) compared to controls. Bone formation marker P1NP was significantly reduced (35.4 ng/mL vs. 43.9 ng/mL, $p = 0.009$), while resorption marker β-CTX was increased (0.44 ng/mL vs. 0.37 ng/mL, $p = 0.042$) in T2DM group. BMD was significantly lower at the lumbar spine and total hip ($p < 0.05$). Leptin levels were correlated positively with BMI and HOMA-IR, while triglycerides were negatively correlated with P1NP ($r = -0.218$, $p = 0.023$).

Conclusions. This study demonstrates that men with T2DM exhibited significant associations between dyslipidemia, hyperleptinemia, and altered bone metabolism. These metabolic abnormalities were linked to reduced bone mineral density, most notably at the lumbar spine and proximal femur. The results suggest that lipid and hormonal imbalances may contribute to poor bone health in T2DM, highlighting the need for careful skeletal assessment and targeted preventive approaches in this group.

Ключові слова: цукровий діабет 2 типу, лептин, дисліпідемія, маркери кісткового ремоделювання, P1NP, β-CTX, мінеральна щільність кісткової тканини, здоров'я чоловіків.

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Зв'язок між лептином, ліпідним обміном і маркерами ремоделювання кісткової тканини у чоловіків із цукровим діабетом 2 типу

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Цукровий діабет 2 типу (ЦД2) асоціюється з порушеннями кісткового метаболізму, що може підвищувати ризик переломів, навіть при нормальній або підвищеній мінеральній щільності кісткової тканини (МЩКТ). Дисліпідемія та підвищений рівень лептину, характерні для ЦД2, визначено як потенційні чинники порушення ремоделювання кісткової тканини, особливо в чоловіків, бо кісткову відповідь на метаболічні порушення у них досі вивчено недостатньо.

Мета роботи – дослідити взаємозв'язок між рівнем лептину в сироватці крові, показниками ліпідного обміну та маркерами кісткового ремоделювання у чоловіків із цукровим діабетом 2 типу.

Матеріали і методи. Здійснили поперечне дослідження за участю 62 чоловіків віком 50–65 років із ЦД2 та 58 чоловіків такого самого віку без діабету (контрольна група). Визначали рівні HbA1c, лептину, інсуліну, тестостерону, 25-гідроксивітаміну D (25(OH)D), паратгормона крові, а також ліпідний профіль і маркери кісткового ремоделювання (P1NP, β-CTX). МЩКТ оцінювали за допомогою подвійної рентгенівської абсорбціометрії у поперековому відділі хребта та в ділянці проксимального відділу стегнової кістки. Інсулінорезистентність визначали за індексом HOMA-IR. Кореляційний аналіз виконано з використанням критерію Спірмена.

Результати. Чоловіки з ЦД2 мали вищий ІМТ (29,8 кг/м^2 проти 26,7 кг/м^2, $p = 0,006$), підвищений рівень лептину (15,2 проти 11,2 нг/мл, $p = 0,003$), дисліпідемію (підвищення рівнів тригліцеридів і ЛПНЩ, зниження ЛПВЩ) та нижчий рівень 25(OH)D (16,8 нг/мл проти 21,6 нг/мл, $p = 0,007$) порівняно з контрольною групою. Маркер кісткоутворення P1NP достовірно нижчий (35,4 нг/мл проти 43,9 нг/мл, $p = 0,009$), а маркер резорбції β-CTX – вищий (0,44 нг/мл проти 0,37 нг/мл, $p = 0,042$) у групі ЦД2. МЩКТ у поперековому відділі хребта та в ділянці стегна достовірно менша ($p < 0,05$). Рівень лептину позитивно корелював з ІМТ та HOMA-IR, а рівень P1NP негативно корелював із рівнем тригліцеридів ($r = -0,218$, $p = 0,01$).

Висновки. У чоловіків із ЦД2 виявлено значущі зв'язки між дисліпідемією, гіперлептинемією та порушенням кісткового метаболізму. Ці метаболічні відхилення асоціюються зі зниженням мінеральної щільності кісткової тканини, особливо у поперековому відділі хребта та проксимальному відділі стегнової кістки. Результати підтверджують, що порушення ліпідного та гормонального балансу можуть спричиняти зниження якості кісткової тканини при ЦД2. Доцільним є ретельне оцінювання стану скелета та впровадження профілактичних заходів у таких пацієнтів.

Type 2 diabetes mellitus (T2DM) is a widely known disorder in modern society associated with multiple systemic complications. Among its less recognized complications, however, are skeletal disorders such as diabetic osteopathy including reduced bone mineral density (BMD), osteoporosis, and fragility fractures [1,2]. Moreover, the risk of fragility fractures in T2DM patients is increased not only due to decreased BMD but also because of impaired bone quality and microarchitecture. These changes underlying diabetic bone disease are multifactorial and include chronic hyperglycemia, atherosclerosis, oxidative damage, systemic inflammation, hormonal and lipid dysregulations [3,4].

Leptin, an important adipokine produced by adipose tissue, plays a critical role in integrating energy metabolism with bone remodeling. Its concentration rises with obesity and insulin resistance. Leptin has both direct and indirect actions on bone because it generates effects through receptors located in osteoblasts and osteoclasts and influences other hormones involved in bone remodeling [5]. Nevertheless, its role in the skeleton is still unresolved as effects appear context-dependent, varying by different circulating concentrations, mechanical metabolic factors, sex, hormonal status, and age [6,7].

In women, the effects of leptin are significantly modulated by estrogen levels [8], whereas in men, the mechanisms underlying its influence on bone metabolism remain unclear. Leptin's interactions with androgens, its role in osteoclastogenesis, and its central effects in the context of insulin resistance are of particular relevance. These mechanisms are of growing clinical interest, especially given the 12–30 % increase in low-trauma fracture incidence among men with T2DM over recent decades [9]. However, current osteoporosis prevention strategies often overlook sex-specific differences in bone vulnerability.

Therefore, clarification of the relationship between serum leptin, lipid metabolism, and bone turnover markers in men with T2DM is of clinical importance, particularly considering hormonal background and insulin resistance. Such evidence could contribute to more accurate risk stratification and the development of personalized strategies for the prevention and treatment of bone complications in diabetes.

Aim

To evaluate associations between serum leptin levels, lipid metabolism parameters, and markers of bone turnover in men with type 2 diabetes mellitus.

Materials and methods

This cross-sectional study was conducted at the Clinical Center of Azerbaijan Medical University between 2020 and 2021. A total of 120 men were enrolled and assigned in two groups.

Inclusion criteria for the T2DM group were: male sex; age 50–65 years; confirmed diagnosis of T2DM based on the ADA criteria; body mass index (BMI) ≥25 kg/m^2 (overweight or obese); stable metformin monotherapy (1000–2000 mg/day); no clinical evidence of bone disease.

The control group included 58 otherwise healthy men, matched by age (56.2 vs. 57.4 years, respectively), without glucose or lipid metabolism disorders, or any bone-related diseases. The control group had a lower mean BMI than the T2DM group (26.7 kg/m^2 vs. 29.8 kg/m^2), ensuring a clear metabolic contrast.

Exclusion criteria for both groups included a history of osteoporosis or low-trauma fractures; use of medications affecting bone metabolism (e. g., glucocorticoids, bisphosphonates, hormones, anticonvulsants); alcohol abuse, smoking; comorbid endocrine disorders (e. g., thyroid dysfunction, hyperparathyroidism, hypogonadism, Cushing's syndrome); secondary causes of osteoporosis, including inflammatory gastrointestinal diseases with malabsorption syndrome (e. g., Crohn's disease, celiac disease), chronic obstructive pulmonary disease, and systemic connective tissue diseases (e. g., rheumatoid arthritis, systemic lupus erythematosus); clinically significant cardiovascular disease; liver cirrhosis; chronic kidney disease (CKD) stages 4–5; malignancy.

All participants underwent comprehensive clinical and laboratory evaluations, including anthropometric measurements. Fasting venous blood samples were laboratory analyzed for the following parameters: glycated hemoglobin (HbA1c) via high-performance liquid chromatography (Bio-Rad D-10™, USA); ionized calcium (Ca^{2+}), inorganic phosphorus (P), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) using enzymatic colorimetric assays on a Cobas c311 chemistry analyzer (Roche Diagnostics, Mannheim, Germany); serum insulin levels estimated by means of an ELISA kit (DRG Instruments GmbH, Marburg, Germany); leptin concentrations quantified with an ELISA kit (Siemens Healthcare Diagnostics, Erlangen, Germany); parathyroid hormone (PTH) and 25-hydroxyvitamin D (25(OH)D) measured using electrochemiluminescence immunoassays (Cobas e411, Roche Diagnostics); glomerular filtration rate calculated via CKD-EPI formula; insulin resistance assessed by HOMA-IR index [10].

Bone turnover markers, including procollagen type I N-terminal propeptide (P1NP) and β-C-terminal telopeptide of type I collagen (β-CTX), were measured using an automated electrochemiluminescence analyzer (Cobas e411, Roche Diagnostics). BMD was assessed by dual-energy X-ray absorptiometry (DXA, Hologic Discovery A, Bedford, MA, USA) at the lumbar spine (L1–L4), total hip, and femoral neck.

The study was conducted in accordance with the ethical standards set out in the Declaration of Helsinki. The study protocol and informed consent form were approved by the Local Independent Ethics Committee of Azerbaijan Medical University (Protocol No. 02/14, dated October 14, 2020). All participants provided written informed consent.

The findings were statistically analyzed using BioStat-Pro v6.2.2.0 (AnalystSoft Inc., USA). The Mann–Whitney U test was used for between-group comparisons with data presented as median (Me) and interquartile range (Q1; Q3). Spearman's rank correlation coefficient (r) assessed relationships between continuous variables. A p-value <0.05 was considered statistically significant.

Results

Table 1 summarizes the biochemical parameters, lipid and bone metabolism markers, and BMD values.

Table 1. Biochemical and densitometric characteristics in T2DM patients and control individuals, Me [Q1; Q3]

Parameter, units of measurement	T2DM, n = 62	Control, n = 58	p-value
Age, years	57.4 [52.3; 60.5]	56.2 [51.4; 59.7]	ns
BMI, kg/m^2	29.8 [26.4; 30.7]	26.7 [24.3; 28.5]	0.006
Duration of T2DM, years	6.1 [2.2; 8.6]	–	–
HbA1c, %	6.8 [6.2; 7.9]	4.3 [4.1; 5.0]	0.001
HOMA-IR	4.2 [1.5; 6.4]	2.9 [2.4; 3.5]	0.002
Ca^{2+}, mmol/L	1.07 [0.9; 1.1]	1.10 [1.06; 1.20]	0.04
P^{+}, mmol/L	1.49 [1.42; 1.74]	1.61 [1.52; 1.71]	ns
Glomerular filtration rate, ml/min/1.73 m^2	69.7 [54.2; 88.9]	90.4 [84.4; 95.1]	0.021
TC, mmol/L	5.08 [3.1; 5.6]	4.96 [3.2; 5.3]	0.036
TG, mmol/L	1.9 [1.6; 2.3]	1.2 [0.9; 1.7]	0.004
HDL-C, mmol/L	1.6 [0.84; 1.15]	1.8 [1.4; 2.2]	0.008
LDL-C, mmol/L	3.9 [2.6; 4.3]	1.2 [0.8; 1.7]	0.002
Leptin, ng/mL	15.2 [9.3; 21.8]	11.2 [2.9; 14.5]	0.003
PTH, pg/mL	37.04 [23.76; 45.37]	28.79 [24.46; 42.19]	0.028
25(OH)D, ng/mL	16.8 [10.4; 29.8]	21.6 [12.2; 33.4]	0.007
P1NP, ng/mL	35.41 [30.82; 49.08]	43.87 [37.49; 54.66]	0.009
β-CTX, ng/mL	0.44 [0.38; 0.49]	0.37 [0.30; 0.43]	0.042
T-score (L1-L4)	-1.09[-1.43; -0.84]	-0.64 [-1.20; -0.12]	0.007
T-score (Total Hip)	-0.75 [-1.26; -0.50]	-0.13 [-0.70; 0.40]	0.032
T-score (Femoral Neck)	-0.63 [-1.12; -0.47]	-0.48 [-0.90; 0.30]	ns

The comparative analysis showed significant differences in metabolic and bone parameters between patients with T2DM and the control group ($p < 0.05$). T2DM patients were more frequently overweight or obese, with 71.1 % having an elevated BMI, compared to 48.4 % in the control group.

Insulin resistance (HOMA-IR >2.5) was present in 83.8 % of T2DM patients, compared to 37.1 % of controls. Among T2DM patients, 28 (45.2 %) had good glycemic control (HbA1c ≤7.0 %), 12 (20 %) had suboptimal control (7.1–7.5 %), and 20 (32.3 %) had poor control (HbA1c >7.5 %). In the control group, fasting glucose and HbA1c levels remained within normal limits.

Dyslipidemia was more common in the T2DM group, with elevated TG in 69.4 %, low HDL-C in 74.2 %, and high LDL-C in 61.3 %, compared to 20–35 % in controls.

Leptin levels were elevated in 71 % of T2DM patients versus 37.1 % of controls and positively correlated with BMI ($r = 0.592$, $p = 0.006$) and HOMA-IR ($r = 0.428$, $p = 0.004$).

Bone turnover markers also differed significantly. Vitamin D deficiency (25(OH)D <20 ng/mL) was present in 80.7 % of T2DM patients, hypocalcemia in 56.4 %, and elevated PTH in 62.9 %. Among the control group, vitamin D insufficiency was observed in 51.6 %, and elevated PTH in 32.3 %. 25(OH)D levels were positively correlated with femoral BMD ($r = 0.486$, $p = 0.002$). BMI values were negatively correlated with lumbar spine BMD ($r = -0.354$, $p = 0.026$), suggesting potential metabolic or mechanical impacts of adiposity on spinal bone health.

P1NP levels were decreased in 66.7 % of T2DM patients, while control subjects had mostly normal levels. Conversely, β-CTX levels were increased in 58.1 % of T2DM patients, suggesting a predominance of bone resorption. TG levels were negatively correlated with P1NP ($r = -0.218$, $p = 0.023$) and positively with β-CTX ($r = 0.397$, $p = 0.014$). Leptin levels were positively correlated with β-CTX ($r = 0.313$, $p = 0.037$), indicating its possible role in promoting bone resorption.

DXA showed that 65.0 % of T2DM patients had osteopenia (T-score between -1.0 and -2.5) in the lumbar spine, compared to 33.8 % of control. Total femur and femoral neck osteopenia was present in 53.2 % and 22.5 % of T2DM patients, respectively. Osteoporosis (T-score < -2.5) at the lumbar spine was observed in 14.5 % of T2DM patients and 5.2 % of controls. Leptin levels were negatively correlated with lumbar spine BMD ($r = -0.266$, $p = 0.041$), further supporting the hypothesis of leptin-mediated bone metabolism dysregulation in T2DM.

Discussion

The results of this study demonstrate the combined consequences of obesity and T2DM, as reflected in significant differences in lipid metabolism, leptin levels, and markers of bone remodeling when compared to the control group. T2DM patients showed a significant reduction in P1NP and an elevation in β-CTX, suggesting an imbalance between bone formation and resorption. These alterations indicate reduced osteoblastic activity and increased osteoclastic resorption – core characteristics of diabetic osteopathy [11]. This is consistent with previously published data on the detrimental effects of chronic hyperglycemia and insulin resistance on bone cell function [12].

Lipid metabolism disorders found in T2DM patients included elevated levels of TGs and LDL-C, and decreased HDL-C. These abnormalities are considered not only as cardiometabolic risk factors but also as potential mediators of bone deterioration. Specifically, the observed negative correlation between TG levels and the bone formation marker P1NP could suggest suppressed osteoblastic activity in dyslipidemic conditions [13,14].

Hyperleptinemia, which is linked to obesity and insulin resistance, has been shown to have complex and at times ambivalent effects on bone metabolism [15,16]. Leptin can modify osteoblast and osteoclast activity via both central (hypothalamic) and peripheral pathways, demonstrating both positive and negative effects on bone remodeling [17,18]. The positive correlation between leptin and β-CTX levels found in this study supports a potential involvement of leptin in promoting bone resorption in T2DM.

Alterations in mineral metabolism, including decreased 25(OH)D levels, hypocalcemia, and compensatory increases in PTH, are hallmarks of advanced secondary hyperparathyroidism. These abnormalities worsen bone pathology in T2DM, reducing mineral density and increasing fracture risk [19,20]. The correlation between 25(OH)D levels and the proximal femur T-scores highlights the importance of vitamin D deficiency as a modifiable risk factor for osteopenia and osteoporosis.

It is noteworthy that the most pronounced declines in BMD were observed at the lumbar spine and proximal femur, while no statistically significant changes were noted at the femoral neck. Such site-specific variations may result from differences in bone microarchitecture and metabolic turnover rates [21,22]. This result underscores the necessity of an integrative strategy for evaluating bone health in T2DM, encompassing both quantitative (BMD) and qualitative characteristics of bone tissue. Overall, the results emphasize that metabolic abnormalities in T2DM lead to pronounced alterations in bone turnover, warranting an integrated approach to the detection and management of osteoporotic complications.

Study limitations. The major limitation of the study lies in the variation in BMI across the groups, which complicates the independent evaluation of obesity and diabetes. However, this profile reflects the real clinical population, where T2DM is frequently associated with excess body weight. The cross-sectional design of the study does not allow for the establishment of causal relationships between changes in the lipid profile, leptin levels and bone metabolism parameters. In addition, the small sample size constrains the generalizability of the results. Relevant lifestyle-related factors, including levels of physical activity, nutritional habits, and consumption of dietary supplements, are not included. The lack of dynamic follow-up restricts the interpretation of progressive bone changes in individuals with T2DM.

Conclusions

1. Men with type 2 diabetes mellitus exhibit significant alterations in bone metabolism, which are closely associated with dyslipidemia and hyperleptinemia. These metabolic disturbances contribute to decreased bone formation and increased resorption, indicating impaired bone turnover.

2. Patients with type 2 diabetes mellitus have been shown to have decreased bone mineral density at the lumbar spine and proximal femur.

3. Elevated leptin and triglyceride levels may serve as early indicators of impaired bone health in men with type 2 diabetes mellitus.

Prospects for future research include multicenter prospective studies to clarify the causal mechanisms underlying metabolic influences on bone tissue in men with T2DM and to develop evidence-based guidelines for early diagnosis and prevention of diabetic osteopathy.

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