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IMPAIRED OSTEOGENESIS AS A LINK IN THE CHAIN OF ATHEROSCLEROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: PATHWAYS TO OVERCOMING IT

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ABSTRACT

Cardiovascular diseases in patients with type 2 diabetes mellitus exhibit a more aggressive course compared to those without this metabolic disorder. Concurrently, shared mechanisms exist between bone tissue development and atherosclerotic arterial calcification. The aim of this study was to establish potential associations between osteocalcin levels and cardiovascular complications in patients with type 2 diabetes mellitus, as well as the impact of additional glucose-lowering therapy using glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is). Methods. A total of 99 patients with type 2 diabetes mellitus were examined, including 62 men and 37 women. The mean age of the participants was 59.18 ± 1.32 years (range: 46 to 67 years). Patients had no documented history of severe cardiovascular complications, such as myocardial infarction, stroke, or stenting/bypass of coronary, carotid, or peripheral arteries. Among them, 34 patients received GLP-1 RAs in addition to baseline therapy with metformin and sulfonylurea derivatives for one year, while 25 received SGLT2is. Osteocalcin levels were measured, and echocardiographic examinations were performed. Results. Low serum osteocalcin levels were associated with the development of diastolic dysfunction characterized by impaired relaxation, left ventricular hypertrophy, and atherosclerotic aortic wall involvement in patients without clinical signs of cardiovascular disease. This was not observed in patients with type 2 diabetes mellitus who had higher osteocalcin levels. Additional use of GLP-1 RAs with baseline glucose-lowering therapy significantly increased blood osteocalcin levels. Additional use of SGLT2is did not demonstrate changes in osteocalcin levels. Conclusion. Low serum osteocalcin levels in patients with type 2 diabetes mellitus may be considered a marker for future severe cardiovascular diseases. Additional use of GLP-1 RAs with baseline glucose-lowering therapy increases blood osteocalcin levels, indicating a positive impact on the cardiovascular system.

KEYWORDS

Diabetes, Osteocalcin, Osteogenesis, Cardiovascular Disease, Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA), Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i)

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Introduction

The prevalence and progression rate of cardiovascular diseases in patients with diabetes mellitus are significantly higher compared to those without this metabolic disorder [1]. Concurrently, shared mechanisms exist between bone tissue development and arterial calcification [2-5].

Osteocalcin is a proven marker of bone metabolism that plays a key role in the pathogenesis of cardiovascular diseases, particularly atherosclerotic arterial calcification [2, 6, 7]. According to current understandings, osteocalcin possesses cardioprotective potential, and elevated levels of this marker are associated with preventive effects against the development of cardiovascular diseases [8, 9]. Conversely, low circulating osteocalcin levels are linked to a high risk of arterial calcification, carotid artery atherosclerosis, increased carotid intima-media thickness, and progression of cardiovascular diseases [10-13].

In particular, in patients with type 2 diabetes mellitus (T2DM), osteocalcin has been identified as an independent risk factor for carotid atherosclerosis and cardiovascular diseases overall [14]. Thus, the challenge of identifying additional pathogenetic mechanisms for the development of cardiovascular diseases and their complications in the context of diabetes mellitus, as well as potential therapeutic targets, remains a pressing issue in modern medicine that requires further investigation.

According to current international guidelines, metformin is the first-line pharmacotherapy for T2DM; however, it does not always reduce the risk of diabetic complications [15]. Therefore, in the ADA and EASD recommendations, incretin-based drugs — GLP-1 RAs and SGLT2is — hold a leading position after the first-line drug metformin, especially for treating patients with T2DM complicated by cardiovascular diseases, including chronic heart failure.

Incretin hormones play an important role in bone homeostasis, in addition to their effects on insulin and glucagon secretion. GLP-1 receptors are present in osteoblasts and osteoclasts; activation of these receptors stimulates type 1 collagen synthesis and alkaline phosphatase activity, consistent with an anabolic effect. In osteoclasts, GLP-1 may inhibit resorptive activity and suppress the expression of certain markers of osteoclastic differentiation [16].

The fact that SGLT2is promote weight loss may be accompanied by bone resorption and cause orthostatic hypotension, increasing the risk of falls and fractures [17]. However, despite physiological evidence of the potential harmful effects of SGLT2is on bones, clinical evidence supporting this hypothesis is limited to data on canagliflozin from the CANVAS study. Thus, the heterogeneity of results regarding the impact of GLP-1 RAs and SGLT2is on bone tissue, with emphasis primarily on fractures in patients with diabetes mellitus, necessitates examining this issue in clinical settings. Previous evidence on the extraskeletal effects of osteocalcin, particularly its associations with the cardiovascular system, prompts the study of its levels in patients with T2DM under the influence of GLP-1 RAs and SGLT2is.

The aim of this study was to establish potential associations between osteocalcin levels and cardiovascular complications in patients with T2DM, as well as the impact of additional glucose-lowering therapy using GLP-1 RAs and SGLT2is.

Materials and Methods

A total of 99 patients with T2DM were examined, who were under observation in the Department of Age Endocrinology and Clinical Pharmacology at the State Institution "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine." The group included 62 (62.6%) men and 37 (37.4%) women. The mean age of the participants was 59.18 ± 1.32 years (range: 46 to 67 years).

The study was conducted in compliance with the fundamental provisions of the "Rules of Ethical Principles for Conducting Scientific Medical Research Involving Humans," approved by the Helsinki Declaration (1964-2013), ICH GCP (1996), EEC Directive No. 609 (dated November 24, 1986), and orders of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, No. 944 dated December 14, 2009, and No. 616 dated August 3, 2012. Patients participated in the study voluntarily, confirmed by their personal signature on the informed consent form. Each patient was personally informed about their duties and rights and the possibility of terminating the study at any time without consequences or explanation of reasons.

Blood osteocalcin levels were determined using chemiluminescent immunoassay with paramagnetic particles on the "Immulite" immunoanalyzer (Siemens, Germany) (reference range: 2.0-22.0 ng/mL). In 40 patients, echocardiographic examination was performed to assess: left ventricular diastolic function by the ratio of peak early diastolic filling velocity (E) to late diastolic filling velocity (A) (E/A), left ventricular wall stiffness (DT); systolic function by ejection fraction (EF, %); signs of left ventricular wall remodeling by left ventricular mass, left ventricular mass index, interventricular septal thickness (IVST, mm), and posterior left ventricular wall thickness (PLVWT, mm), signs of concentric or eccentric left ventricular hypertrophy; manifestations of atherosclerotic involvement of the aorta, aortic valve, and mitral valve.

Patients were divided into Group 1 (n=23) and Group 2 (n=17) based on osteocalcin levels as the primary investigated parameter, to determine the likelihood of differences between them in echocardiographic parameters. It should be noted that patients in both groups had no documented history of severe cardiovascular diseases, such as myocardial infarction, ischemic stroke, or stenting/bypass of coronary or peripheral arteries in the context of T2DM, which could confirm atherosclerotic arterial involvement.

The 59 examined patients with T2DM were divided into two groups based on the type of glucose-lowering therapy added to standard baseline therapy (metformin/sulfonylurea derivatives). Group 3 (n=34) received GLP-1 RAs in addition for one year, while Group 4 (n=25) received SGLT2is for the same period.

Statistical processing of results was performed using IBM SPSS Statistics 20 (IBM Corp.; USA). The Shapiro-Wilk test was used to check the hypothesis of conformity of the actual distribution of each studied parameter to normal distribution criteria. Since the distribution of all studied parameters differed from normal, median, first quartile (Q1), third quartile (Q3), minimum and maximum values, and 95% CI were calculated. To assess differences in parameters before and after treatment, the Wilcoxon t-test was used, with differences considered significant at $p<0.05$.

Results

Given the evidence linking osteocalcin to severe cardiovascular diseases, the question arose of determining its concentration levels in patients with T2DM who do not yet have a burdened cardiac history. To ascertain which blood osteocalcin level might predict the future occurrence of severe cardiovascular diseases, we divided the patients' indicators into two groups based on osteocalcin magnitude and compared these values with echocardiographic data from the same patients (Table 1).

Table 1. Echocardiographic parameters depending on blood osteocalcin levels in patients with type 2 diabetes mellitus without severe cardiovascular diseases, median [lower-upper quartile]

Patient Group	Osteocalcin, ng/ml	E/A	DT	EF, %	IVST, mm	PLVWT, mm
Group 1 (n=23)	1,0 [1,0-2,3]	0,65 [0,63-0,68]	163 [150 -180]	58 [52- 66]	14 [12-15]	11 [11-11]
Group 2 (n=17)	3,7 [3,2-4,3]	0,84 [0,76-0,89]	150 [150-150]	64 [58-67]	12 [11-14]	10 [9-10]
p-value	**< 0,001***	**0,003***	**0,05***	0,518	**0,02***	**0,013***

* - Significant difference between Groups 1 and 2.

The obtained results demonstrate differences in echocardiographic parameters between Group 1 patients with low osteocalcin levels, specifically below the lower limit of normal in some patients, and Group 2 with significantly higher osteocalcin values. Thus, the ratio of peak early diastolic filling velocity (E) to late diastolic filling velocity (A)—E/A — in Group 1 patients with low osteocalcin was significantly lower compared to Group 2, which may indicate existing diastolic dysfunction in patients before clinical manifestations of cardiovascular disorders. Additionally, a tendency toward increased DT values in Group 2 suggests increased left ventricular wall stiffness.

Attention is drawn to the presence of signs of left ventricular wall remodeling in Group 1 patients, determined by a significant increase in interventricular septal thickness and posterior left ventricular wall thickness due to hemodynamic overload and atherosclerotic involvement. It should be noted that among Group 1 patients, 11 (48%) had concentric left ventricular hypertrophy, and 4 (17%) had eccentric hypertrophy. Concurrently, 12 (52%) patients in this group exhibited diastolic dysfunction characterized by impaired relaxation. However, prior to possible future clinical damage to the cardiovascular system, systolic left ventricular function was not impaired in patients of both groups and did not differ between groups. Left ventricular mass and left ventricular mass index were not evaluated, as they differ between sexes, preventing division into homogeneous groups by this criterion.

In addition to quantitative echocardiographic parameters, signs of atherosclerotic aortic wall involvement were recorded, which occurred more frequently among Group 1 patients (n=18) compared to those with higher osteocalcin levels (Group 2, n=5), $p<0.05$.

Group 3 patients (n=34) received GLP-1 RAs in addition to baseline therapy with metformin and sulfonylurea derivatives for one year. Similarly, Group 4 patients (n=25) received SGLT2is in addition to baseline therapy with metformin and sulfonylurea derivatives for one year. Serum osteocalcin levels in both groups were determined before the additional use of the mentioned medications and after one year of their application. Analysis of the obtained data established that in Group 3, the use of GLP-1 RAs contributed to a significant increase in serum osteocalcin levels in patients (Table 2).

Table 2. Results of serum osteocalcin concentration determination in patients with T2DM on additional treatment with GLP-1 RAs and SGLT2is

	Group 3 (n=34)		Group 4 (n=25)	
	Before	**After**	**Before**	**After**
Median	1,0	3,8*	3,1	3,1
Q1	1,0	2,5	2,5	2,4
Q3	2,5	5,6	3,65	4,1
Minimum	1,0	1,0	1,0	1,0
Maximum	6,3	7,4	6,5	6,4
95% CI	1,0-2,2	3,1-5,3	2,6-3,5	2,5-3,9

Note: * - $p<0.001$ (comparison of data with non-normal distribution using Wilcoxon t-test).

Concurrently, among Group 4 patients, no significant increase in serum osteocalcin levels was detected after one year of additional SGLT2i use (Table 2). Thus, according to our data, SGLT2is exhibit a neutral effect on osteocalcin secretion despite its positioning as a marker of cardiovascular complications. Ultimately, it is currently unknown whether receptors for SGLT2 exist on osteoblasts or osteoclasts.

Discussion

In our opinion, an increase in blood osteocalcin levels may play a protective role against atherosclerotic damage to the cardiovascular system compared to its low concentration at the lower limit of normal.

Confirmation of osteocalcin's important contribution to myocardial cell protection is reflected in the study by Zhang X.L. et al. [9]. The cardioprotective mechanism is realized through the binding of serum osteocalcin to the GPRC6A receptor of family C, group 6, subgroup A, G-protein-coupled, which is expressed in myocardial tissues and exhibits angioprotective potential [9, 18, 19].

The protective role of osteocalcin in the development and progression of cardiovascular diseases is confirmed in several clinical studies. Based on the analysis of data from 21,021 patients presented in a systematic review and meta-analysis of 33 studies, Seidu, Kunutsor, and Khunti established that total circulating osteocalcin levels were significantly lower in patients with cardiovascular diseases compared to control group patients. The researchers demonstrated significant inverse correlational relationships between total osteocalcin values and indicators of carotid intima-media thickness, coronary atherosclerosis, aortic and coronary vessel calcification, and atherosclerotic plaque characteristics [10]. Similar results are presented in the study by Yang et al., who demonstrated a statistically significant inverse correlational relationship between serum total osteocalcin values and increased carotid intima-media thickness, and in the work by Kim et al., who established a weak inverse correlation between total osteocalcin indicators and aortic calcification [12, 20].

Serum osteocalcin is considered an important prognostic hemodynamic parameter for the course of ischemic heart disease. Specifically, lower serum osteocalcin values are significantly associated with an increased number of affected vessels [9].

Additionally, low osteocalcin values are associated with impaired left ventricular systolic dysfunction and a higher risk of cardiac death.

In a study based on the analysis of clinical and laboratory indicators of 258 patients in a cardiology department, Zhang et al. established significantly higher serum osteocalcin values in examined men with an average left ventricular ejection fraction (LVEF) >62% compared to data from men with LVEF ≤62% ($p=0.042$) and recorded an associated decrease in LVEF indicators with decreasing serum osteocalcin indicators. Based on the analysis, the researchers demonstrated a higher risk of cardiac death in the group of men with low osteocalcin levels compared to data established in the group of men with high marker values. Concurrently, in women, there were no significant differences between LVEF indicators and osteocalcin values. Thus, the researchers established that low serum osteocalcin levels are a predictor of left ventricular systolic dysfunction and cardiac death in men [9].

However, there is a series of studies indicating the absence of a significant impact of changes in osteocalcin indicators on the formation and course of cardiovascular system diseases, particularly atherosclerosis, ischemic heart disease, and their complications such as myocardial infarction or stroke [10, 21]. Thus, the issue of studying the role of osteocalcin in the occurrence and progression of cardiovascular diseases remains unresolved and requires further research.

It is known that osteocalcin is a bone hormone that, in its uncarboxylated form (GluOC), plays an important role in glucose and energy metabolism, stimulating insulin secretion and pancreatic β-cell proliferation through its putative receptor GPRC6A. It has been demonstrated that the effect of GluOC on insulin secretion is primarily mediated by glucagon-like peptide-1 (GLP-1), which is secreted by intestinal endocrine cells in response to GluOC stimulation. Additionally, oral administration of GluOC was found to reduce fasting blood glucose levels, improve glucose tolerance, and increase fasting serum insulin concentration and pancreatic β-cell area in wild-type mice. This assertion is supported by the effects of oral GluOC administration for at least 4 weeks in GLP-1 receptor knockout mice, which induced glucose intolerance in mutant mice, enhanced gluconeogenesis, and promoted both lipid accumulation in the liver and adipocyte hypertrophy and inflammation in adipose tissue, as well as activation of gluconeogenic gene expression. Thus, experimental studies demonstrate that the beneficial metabolic effects of GluOC depend on GLP-1 receptor signaling [22]. Most studies on the impact of GLP-1 RAs on bone tissue primarily address skeletal mineral density and its metabolism markers.

However, there are currently differing opinions regarding the impact of GLP-1 RAs on bone tissue. That is, glucagon-like peptide-1 receptor agonists may promote bone formation but, conversely, may also weaken bones through reduced mechanical loading associated with weight loss. However, clinical effects in humans have not been clearly demonstrated to date. Concurrently, as a result of a 2024 meta-study based on 7 randomized clinical trials with quantitative analysis, it was established that GLP-1 RA treatment significantly increased the bone resorption marker C-terminal telopeptide of type 1 collagen (CTX), while it did not cause significant changes in bone mineral density (in the femoral neck, hip, and lumbar spine) or bone formation markers such as N-terminal propeptide of type 1 procollagen (P1NP), bone-specific alkaline phosphatase, osteocalcin [23].

Additionally, the results of another meta-analysis conducted in 2024, involving 26 randomized clinical trials covering 2,268 patients, allow asserting that GLP-1 RAs can not only improve bone mineral density in the lumbar spine and femoral neck of patients with type 2 diabetes mellitus but also protect bone health by inhibiting bone resorption and promoting bone formation [24].

Thus, further double-blind randomized controlled trials are needed to draw more meaningful and important conclusions regarding the impact of GLP-1 RAs on bone tissue and their pleiotropic effects on atherosclerotic complications.

Concurrently, under current conditions, there is a substantial evidence base regarding the positive impact of SGLT2is on manifestations of heart failure and its prevention. After all, patients with type 2 diabetes mellitus often suffer from cardiovascular complications, and heart failure is one of the most common. Therefore, several cardiovascular outcome studies have focused on glucose-lowering therapy and its impact on cardiovascular outcomes. Thus, SGLT2is (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) have demonstrated positive effects on cardiovascular outcomes in long-term studies of patients with type 2 diabetes mellitus with established cardiovascular disease and/or a broad spectrum of cardiovascular risk factors [25]. Concurrently, attention should be paid to possible adverse effects associated with the mechanism of action of SGLT2is. In five randomized clinical trials involving patients with both reduced and preserved ejection fraction and chronic heart failure, the risk of adverse effects was evaluated. There were no differences between SGLT2is and placebo regarding the risk of diabetic ketoacidosis, hypoglycemia, hyperkalemia, hypokalemia, bone fractures, and amputations [26].

Thus, in contemporary scientific literature, studies on GLP-1 RAs and SGLT2is are mostly focused on the effects of these drugs on bone tissue in terms of fractures and bone mineral density, leaving aside the features of cardiovascular changes associated with the bone hormone osteocalcin, which will require further analysis in the future. The existing limitations of our work—lack of stratification by sex and age, limited number of echocardiographic examinations—prompt further study and examinations. Therefore, the strength of our research is the attempt to link low osteocalcin levels as one of the pathogenetic factors of atherosclerotic lesions with a way to prevent their progression.

Conclusions

Low serum osteocalcin values are associated with the development of diastolic dysfunction characterized by impaired relaxation, left ventricular hypertrophy, and atherosclerotic aortic wall involvement in patients without clinical signs of cardiovascular diseases, which is not observed in patients with type 2 diabetes mellitus with higher values.

Low serum osteocalcin levels at the lower limit of normal may be considered a marker for future severe cardiovascular diseases and used in practical medicine.

It was established that additional use of GLP-1 RAs with baseline glucose-lowering therapy (metformin/sulfonylurea derivatives) significantly increases blood osteocalcin levels, indicating a positive impact on the cardiovascular system.

Additional use of SGLT2is with baseline glucose-lowering therapy did not demonstrate a significant change in blood osteocalcin levels, which is evidence of a neutral impact of representatives of this drug class on the bone system and does not contradict their cardioprotective action.

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