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Bone remodeling markers in assessing of sternal reparative regeneration in patients with carbohydrate metabolism disorders after coronary bypass surgery

Aim	To study time-related changes in bone remodeling markers in patients with ischemic heart disease (IHD) associated with type 2 diabetes mellitus (DM) and disorders of carbohydrate metabolism (CM). Also, a possibility was studied of using these markers for evaluation of breast bone reparative regeneration in early and late postoperative periods following coronary bypass (CB).
Material and methods	This study included 28 patients with IHD and functional class II–III exertional angina after CB. Patients were divided into 2 groups based on the presence (group 1) and absence (group 2) of CM disorders. Contents of osteocalcin (OC), C-terminal telopeptide (CTTP) of type 1 collagen, deoxypyridinoline (DPD), and alkaline phosphatase bone isoenzyme (ALPBI) were measured by enzyme immunoassay on admission (T1) and at early (T2) and late (T3) postoperative stages. Sternal scintigraphy with a radiopharmaceutical (RP) was performed at stage 3 following sternotomy.
Results	The content of OC and CTTP was reduced in group 1 compared to the values in the group without CM disorders ($p<0.005$) at stages T1 and T2. There were no significant intergroup differences in concentrations of ALPBI and DPD throughout the study. Time-related changes in OC, CTTP, and DPD had some intergroup differences: the increase in biomarkers was observed in group 1 considerably later, at stage T3 ($p<0.005$), while in group 2, it was observed at stage T2 after sternotomy. Scintigraphy revealed significant intergroup differences in the intensity of RP accumulation in sternal tissue.
Conclusion	The intergroup differences in the content of biomarkers evidenced a disbalance among processes of formation and resorption of bone tissue and delayed remodeling processes in patients with IHD associated with type 2 DM and CM disorders. The study confirmed significance of comprehensive evaluation of time-related changes in markers for bone tissue metabolism and sternal scintigraphy for diagnosis and evaluation of sternal reparative regeneration following sternotomy in patients with IHD associated with type 2 DM and disorders of CM metabolism.

Keywords	Type 2 diabetes mellitus; sternotomy; bone remodeling biomarkers; osteocalcin; bone scintigraphy
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Introduction

Coronary artery disease (CAD) is a common cardiovascular disease associated with a high risk of vascular complications and death. Coronary artery bypass grafting (CABG) is an effective treatment for patients with multivessel coronary atherosclerosis and complicated forms of CAD. According to international studies, between 22% and 48% of all myocardial revascularization procedures are performed in patients with severe concomitant pathology, such as type 2 diabetes mellitus [1]. In Russian studies, patients with DM account for 20–23% of those subjected to CABG [2]. Bezdenezhnykh et al. [3] showed that most observations are associated with worse long-term post-surgery prognosis in patients with type 2 DM exposed to any type of revascularization, when compared to patients without disorders of carbohydrate metabolism. Hyperglycemia, insulin resistance, and hyperinsulinemia cause a long trail of pathogenetic reactions and can lead to damage, dysfunction, failure of various organs and tissues [4, 5]. Data was collected on the association of DM with increased risk of bone fragility and osteoporotic fractures [6, 7]. Moreover, carbohydrate metabolism disorders and DM are among the most clinically significant concomitant pathologies. They exacerbate healing and cause complications associated with the poor post-sternotomy sternal union. According to Olbrecht et al. [8], sternal non-union occurs in 0.2–5% of patients after median sternotomy. However, sternal diastasis caused by

wound infection is a complication associated with 10–40% mortality [9]. Complications such as aseptic failure of sternal sutures, superficial wound infection, mediastinitis, sternum osteomyelitis, nonunion and/or displacement of the sternal edges significantly affect the outcomes of treatment and increase the duration of hospital stay. Retrospective analysis of bimammary CABG procedures in patients with CAD showed a higher incidence of infections of deep post-surgery sternal wounds and duration of hospital stay in patients with DM, than in those without DM [10]. Patients with DM are at higher risk of diastasis and complications in sternal injury [8, 11]. Thus, the degree of sternal union for timely prevention and treatment of possible complications after cardiac surgeries needs to be evaluated objectively.

There is still no single objective method of monitoring the post-surgery process of sternum regeneration. Markers of bone formation and resorption are used to diagnose bone remodeling disorders.

Current studies of bone metabolism markers are aimed at investigating mechanisms of osteoporosis as a complication of type 2 DM, improving early diagnosis, evaluating the efficacy of osteoporosis therapy and determining the prognostic value for fracture risk in patients with type 2 DM. The heterogeneous and inconsistent findings of most studies of bone remodeling markers are due to the heterogeneity of the DM patient group in terms of differences in metabolic status, disease duration, drug therapy, associated pathologies and complications, and marker measurement methods. There is no information on the effects of type 2 DM on processes of sternum restoration and the post-surgery changes of bone metabolism markers following CABG in patients with CAD.

Objective

To study the trends of bone remodeling markers in patients with CAD associated with type 2 DM and disorders of carbohydrate metabolism, as well as the possibility of their use in evaluating sternum restoration in the short- and long-term post-CABG periods.

Material and methods

The retrospective study included 28 patients aged 62.5±6.0 with CAD, exertional angina pectoris functional class II–III. All patients were admitted to the Cardiovascular Surgery Unit of the Cardiology Research Institute for direct myocardial revascularization using the left internal thoracic artery. Surgeries were performed using cardiopulmonary bypass and antegrade cold cardioplegia. The traditional sternal osteosynthesis scheme using separate wire ligatures was applied, in order to stabilize the dissected sternal halves. All surgeries were conducted under the guidance of one surgeon and two assistants who performed access and closure of the chest wall using one technique to minimize the individual specificities of the surgeon's work, to prevent skewing the results of the study.

The protocol of this study was approved by the Ethics Committee of the Cardiology Research Institute. All patients signed informed consent for inclusion in the study.

Patients were divided into two groups based on the presence or absence of metabolic disorders. Group 1 included 14 patients with type 2 DM and impaired glucose tolerance (IGT). Group 2 included 14 patients without carbohydrate metabolism disorders. Type 2 DM was established following the national clinical guidelines [8]: venous plasma fasting glucose ≥7.0 mmol/L; two hours after oral glucose tolerance test (OGTT) ≥of 11.1 mmol/L; glycated hemoglobin ≥6.5%. The diagnostic criteria for IGT were fasting glucose <7.0 mmol/L (venous plasma); ≥7.8 and <11.1 mmol/L two hours after OGTT [8].

Changes in bone metabolism biomarkers were evaluated at admission, in the short-term (in two weeks) and long-term (in six months) post-surgery periods. Blood samples were collected in all patients at the specified time points. They were incubated at room temperature for 30 to 45 minutes and centrifuged at 3,000 rpm for 15 minutes at room temperature. During the specific stages of the study, a portion of first-morning urine was collected for centrifuging and storage at –40°C. Serum osteocalcin (OC) was determined using an N-MID™ Osteocalcin ELISA test system. Blood serum bone alkaline phosphatase isoenzyme (bALP) was quantified using a Metra®BAP set. Carboxy-terminal telopeptide of type I collagen (I–CTP) was determined using a Serum CrossLapsTM ELISA test system. Deoxypyridinoline (DPD) levels were determined in the urine using a Metra DPD EIA kit. Quantification was performed using an Elisa test. The results of the DPD assessment were adjusted for the creatinine concentration, determined in urine using a Chronolab enzymatic colorimetric kinetic test based on the Jaffe reaction.

All patients were hospitalized for control examination and subjected to bone gamma-ray scanning, in order to assess the sternum condition in the long-term post-surgery period. Technophore99m Tc 640–960 MBq was used as a radiopharmaceutical drug (RPD). Planar and tomographic gamma-ray scanning was performed four hours after the injection of RPD. The scans were recorded for 25 minutes using a Forte gamma camera and a GE Discovery Nm/CT570C hybrid CT scanner. The resulting gamma-ray scans were processed using the JetStream Workspace Release 3.0 and Xeleris Workspace Release 3.1 software suites. The intensity of RPD accumulation was measured by the number of pulses in the area of interest. Radionuclide effective dose did not exceed the permissible dose.

The statistical analysis of the data obtained was performed using the Statistica 10.0 software suite. Due to the small samples and non-normal distributions in the groups, all quantitative variables were described using the median (Me) and the

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interquartile range [25th percentile; 75th percentile]. The Kruskal–Wallis test was used for pairwise comparisons. The statistical significance of differences was assessed using the non-parametric Wilcoxon test. Spearman's rank correlation coefficient was calculated to assess the relationship between variables. The critical significance level (p) was equal to 0.05 in all statistical analysis procedures.

Results

At the time of inclusion, the groups were comparable by the underlying disease, types of surgical correction, duration of surgery and cardiopulmonary bypass, and other concomitant pathologies (Table 1).

Comparative analysis showed that the levels of bone formation marker OC before sternotomy (T1) and two weeks after the surgery (T2) were statistically lower in the group of patients with carbohydrate disorders than in the group of patients without this pathology (Table 2).

The evaluation of OC changes in both groups showed slight changes between stages T1 and T2 with subsequent increases in the long-term post-surgery period (p=0.0005 and p=0.016, respectively). There were no intergroup differences in the OC expression in the T3 period. Evaluation of OC changes showed that the levels of OC in Group 1 reached the same levels of OC, as measured two weeks after the surgery in Group 2, only after six months of follow-up (T3).

Table 1. Clinical and anamnestic characteristics of patients

Parameter	Group 1 (n=14)	Group 2 (n=14)	p
Diabetes mellitus type 2	9 (64.3%)	0	0.0004
IGT	5 (35.7%)	0	0.017
Obesity	10 (71.4%)	7 (50.0%)	0.266
COPD	3 (21.4%)	2 (14.3%)	0.653
BA	1 (7%)	0	0.353
Chronic gastritis/duodenitis	10 (71.4%)	10 (71.4%)	1.000
Peptic/duodenal ulcer, n (%)	3 (21.4%)	5 (35.7%)	0.428
GSD/chronic cholecystitis	7 (50%)	3 (21.4%)	0.128
KSD/chronic pyelonephritis	6 (42.8%)	5 (35.7%)	0.724
Spine osteochondrosis	10 (71.4%)	7 (50%)	0.266
CRF	1 (7%)	2 (14.3%)	0.577
Goiter	3 (21.4%)	2 (14.3%)	0.653
Age>70 years	0	2 (14.3%)	0.165
Smoking	12 (85.7%)	14 (100%)	0.165
IMA isolation	14 (100%)	14 (100%)	1.000
LVEF <50%	2 (14.3%)	2 (14.3%)	1.000
Duration of ventilation more than 48 hours	1 (7%)	0	0.353

IGT, impaired glucose tolerance; COPD, chronic obstructive pulmonary disease; BA, bronchial asthma; GSD, gallstone disease; KSD, kidney stone disease; CRF, chronic renal failure; IMA, internal mammary artery; LVEF, left ventricular ejection fraction.

Comparative analysis of the biomarker of type I collagen degradation I–CTP revealed statistically significant intergroup differences. In Group 1, the levels of I–CTP at T1 and T2 were statistically lower than in Group 2 (see Table 2). Assessment of changes of I–CTP in both groups showed that the levels of biomarker increased by T2 (p=0.005). Six months after sternotomy in Group 2, a decrease in I–CTP was observed. This was not statistically significantly different from the baseline levels. In Group 1, the I–CTP levels changed insignificantly by T3 and remained higher than the baseline (p=0.0005). No intergroup differences in the I–CTP levels were found at T3.

Correlation analysis established positive associations between the I–CTP levels and OC in both groups (Table 3).

Two weeks after sternotomy, a significant increase in the content of bone formation marker bALP was observed in both groups (p=0.003 and p=0.0005, respectively). In the long-term period, the bALP level did not differ from that at T2, but remained statistically significantly higher than the baseline level at T1 (p=0.0005 in both groups). The study did not establish statistically significant intergroup differences in bALP levels throughout the duration. In Group 2, the activity of bALP was directly correlated at T1 and T2 with the pre-sternotomy I–CTP levels (R=0.732; p=0.003 and R=0.67; p=0.009, respectively).

No statistically significant intergroup differences were found during the comparative analysis of bone resorption marker DPD. In Group 1, the evaluation of DPD changes showed no statistically significant changes between T1 and T2. An increase in DPD levels six months was detected after sternotomy when compared to the baseline levels (p=0.003). Analysis of the DPD changes in Group 2 showed a significant increase in the biomarker by T2 (p=0.016). The levels of DPD remained unchanged in the long-term post-surgery period. In Group 1, direct correlations were established between the levels of OC and DPD at T1 and T2.

The results of the sternum gamma-ray scanning are shown in Figure 1.

The increased accumulation of RPD in the manubrium and lower half of the sternum (metasternum) was observed in patients with metabolic disorders when compared to patients of Group 2 (p=0.021 and p=0.024, respectively). The intensity of RPD accumulation in the upper half of the sternum in patients of Group 1 was on average 62% higher (p=0.139). In Group 1, strong positive associations were established between the intensity of RPD accumulation in the manubrium and the I–CTP levels at T1 (Figure 2A) and T3 (Figure 2B).

There were direct correlations between the OC levels in the short-term post-surgery period and the intensity of RPD accumulation in the manubrium (Figure 2C) and the metasternum (Figure 2D).

Pre-surgery levels of bALP in Group 1 were inversely correlated with the intensity of RPD accumulation in the metasternum area (R= – 0.683; p=0.042).

Table 2. Changes of biochemical markers before sternotomy, in the short- and long-term post-surgery periods

Parameter	Group 1 (n=14)			p	Group 2 (n=14)			p	p (intergroup differences)
	T1	T2	T3		T1	T2	T3		
OC, ng/mL	8.38 [3.60; 12.91]#	4.75 [1.80; 11.83]##	19.12 [14.24; 25.22]**.***	p_{T1-T3}=0.000 p_{T2-T3}=0.003	14.47 [11.99; 20.04]	19.35 [11.04; 23.02]	24.36 [17.15; 28.03]**.***	p_{T1-T3}=0.016 p_{T2-T3}=0.016	p_{T1}=0.008 p_{T2}=0.003
bALP, MU/L	19.15 [17.41; 20.50]	31.47 [28.69; 41.01]*	28.06 [26.42; 39.36]**	p_{T1-T2}=0.003 p_{T1-T3}=0.005	21.28 [19.54; 24.15]	34.48 [27.54; 40.11]*	29.24 [26.00; 36.27]**	p_{T1-T2}=0.000 p_{T1-T3}=0.000	н/д
DPD, nmol/L	7.43 [6.37; 10.07]	10.76 [8.50; 16.06]	11.99 [9.53; 15.16]**	p_{T1-T3}=0.003	8.13 [6.07; 9.33]	11.98 [9.54; 18.16]*	9.51 [7.65; 13.54]**	p_{T1-T2}=0.016 p_{T1-T3}=0.016	н/д
I-CTP, ng/mL	0.367 [0.238; 0.415]#	0.631 [0.53; 0.931]*.##	0.683 [0.518; 0.779]**	p_{T1-T2}=0.000 p_{T1-T3}=0.000	0.622 [0.346; 0.886]	1.096 [0.693; 1.239]*	0.605 [0.424; 1.093]***	p_{T1-T2}=0.000 p_{T2-T3}=0.003	p_{T1}=0.009 p_{T2}=0.007

The data is presented as the median and the interquartile range – Me [25th percentile; 75th percentile].
T1, baseline; T2, after two weeks; T3, after six months. Significant differences (p<0.05) follow-up periods:
* – between T1 and T2; ** – between T1 and T3; *** – between T2 and T3. Intergroup statistically significant (p<0.05) differences:
# – p<0.05 in T1; ## – in T2; ins – insignificant differences. OC, osteocalcin; bALP, bone alkaline phosphatase isoenzyme;
DPD, deoxypyridinoline; I–CTP, carboxy-terminal telopeptide of type I collagen.

Table 3. Results of correlation analysis of the bone metabolism biomarkers

Parameter		I-CTP T1	I-CTP T2	I-CTP T3
OC T3	Group 1	R=0.68; p=0.008	R=0.56; p=0.037	R=0.67; p=0.009
	Group 2	R=0.78; p=0.0009	R=0.79; p=0.0007	R=0.83; p=0.0003

OC, osteocalcin; I-CTP, carboxy-terminal telopeptide of type I collagen; T1, baseline; T2, after two weeks; T3, after six months.

There were direct correlations between the OC levels in the short-term post-surgery period and the intensity of RPD accumulation in the manubrium (R=0.783; p=0.0125) and the metasternum (R=0.717; p=0.030). Pre-surgery levels of bALP in Group 1 were inversely correlated with the intensity of RPD accumulation in the metasternum area (R= –0.683; p=0.042). There were no such correlations in patients without disorders of carbohydrate metabolism.

Discussion

We found that the OC levels before sternotomy and in the early hospital period were lower in patients with DM and IGT than in the group of patients without carbohydrate metabolism disorders (p<0.005). Our findings are consistent with the meta-analysis by Hygum et al. [7] in which patients with type 1 and type 2 DM showed decreased levels of OC and I–CTP. The decreased levels of circulating biomarker OC in patients of the main group may indicate a slowdown in bone formation.

I–CTP formed by osteoclasts during bone resorption is released into the circulation as small peptide fragments at a rate proportional to the activity of bone resorption [12]. The findings on I–CTP and correlation with DM are very contradictory. Several studies report decreased levels of I–CTP [7]. However, Sanches et al. [6] did not establish statistically significant differences in the I–CTP levels in patients with type 2 DM. We observed significant intergroup differences: the I–CTP levels were statistically significantly lower in the group of patients with DM and IGT than in Group 2 before sternotomy and two weeks after CABG. The assessment of changes of the I–CTP level also showed intergroup differences. The reduced levels of I–CTP and its delayed release into the circulation in patients with DM and IGT are likely to be due to the adverse effects of increased

Figure 1. Results of gamma-ray scanning of the sternum using Technophore, ^{99m}Tc

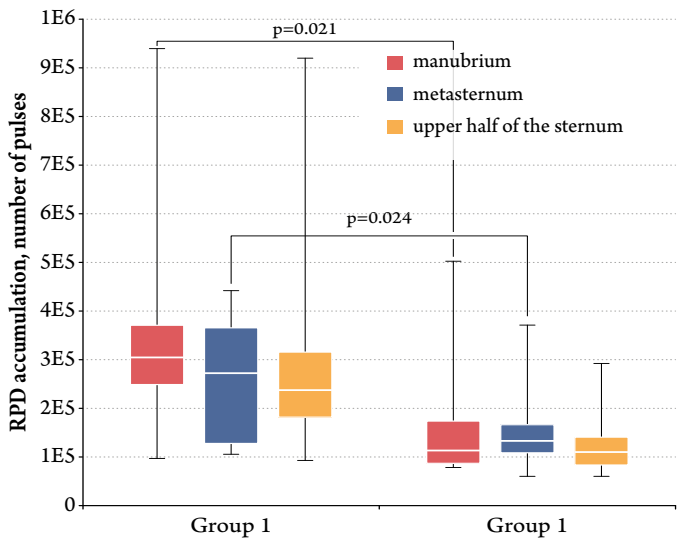

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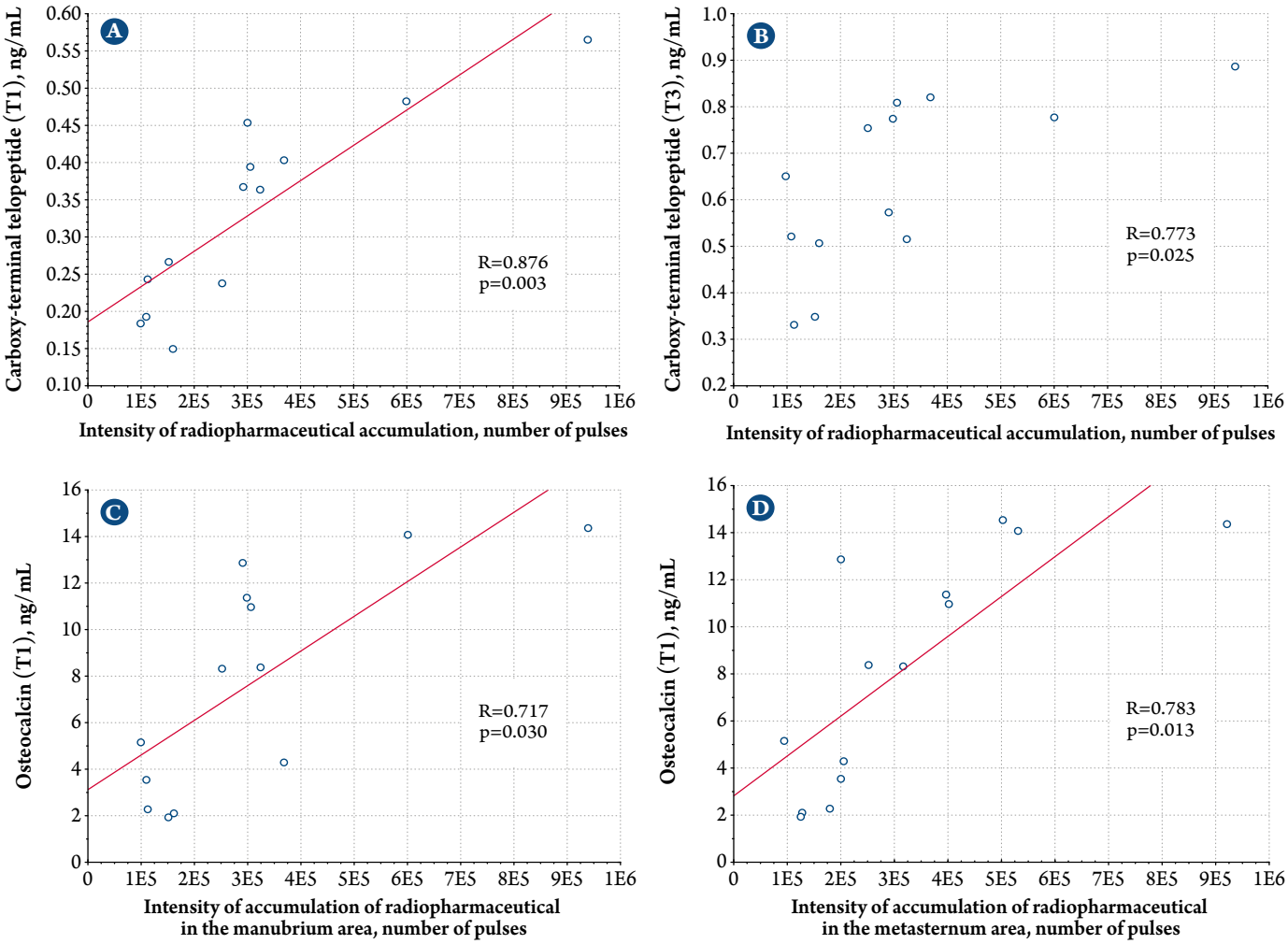
Figure 2. Results of correlation analysis



A, B – intensity of radiopharmaceutical accumulation in the manubrium area with the carboxy-terminal telopeptide levels at T1 (A) and T3 (B); C, D – the osteocalcin levels at T1 with the intensity of radiopharmaceutical accumulation in the manubrium (C) and the metasternum (D).

glucose levels on osteoblasts, reduced collagen production in insufficient insulin levels, and high levels of circulating glycation end products and hyperhomocysteinemia, increasing osteocyte apoptosis.

The analysis of bALP changes showed a significant increase in bone formation activity two weeks after sternotomy in both groups (p=0.003 and p=0.0005, respectively). Increased levels of bALP, reflecting the metabolic state of osteoblasts, indicate an intensive differentiation of the cells responsible for the formation of bone tissue. Several studies [13] show normal or even elevated levels of bALP in patients with DM. Our study did not reveal statistically significant intergroup differences in bALP levels throughout its duration. This is consistent with the findings by Greenblatt et al. [12]. This also probably due to the dissociation of the bone tissue metabolism, in which deceleration of bone resorption and formation is accompanied by intact mineralization [7]. There were direct correlations between the levels of bALP and I–CTP which may show a balance of interrelated processes of bone tissue formation and resorption only in the group of patients without carbohydrate metabolism disorders.

According to the literature, DPD levels are characteristic of the function and activity of osteoclasts. They most accurately reflect the degree of bone tissue resorption. In our study, a comparative analysis of DPD changes in the group of patients without carbohydrate disorders showed a statistically significant increase in DPD levels in the short-term post-surgery period. In Group 1, an increase in DPD was detected only six months after sternotomy (p=0.003). The findings indicate that bone resorption is slow.

The absence of statistically significant intergroup differences in the levels and changes of DPD and bALP markers is likely to be due to insufficient specificity of the marker in terms of restoration and consolidation of sternal bone tissue after such surgical interventions as sternotomy. Furthermore, DPD is known to be metabolized in the kidneys and liver, affecting the accuracy of results in concomitant

diseases of these organs, characterized by significant 24-hour variability [14].

Radionuclide imaging of bone tissues (gamma-ray scanning) reflecting blood supply and intensity of metabolic processes in bones is used to assess the degree of bone union and diagnose possible wound complications [15, 16]. The degree of RPD accumulation in bone tissue depends on local circulation. However, it also depends on the degree of osteoblast activity and thus bone formation. Gamma-ray scanning allows the condition of bone tissue, adequacy of repositioning, intensity of blood circulation, and bone restoration processes to be assessed in the area of injury. It can also be used to detect infectious complications in the area of injury.

Analysis of the results of gamma-ray scanning of the sternum carried out in the long-term post-surgery period showed statistically significant intergroup differences in the intensity of RPD accumulation by sternum tissues. Patients with carbohydrate disorders had increased RPD accumulation in the manubrium, upper and lower halves of the sternum when compared to Group 2 with varying significance. The findings may indicate incomplete sternum union in the long-term period due to slower regeneration and longer aseptic inflammation in the intervention area in patients with carbohydrate metabolism disorders.

Thus, the findings indicate an imbalance between bone formation, resorption, and slow bone remodeling in patients with CAD associated with type 2 DM and IGT. Increased intensity of RPD accumulation in various sternum areas in patients with CAD and carbohydrate metabolism disorders is due to incomplete sternum union in the long-term period caused by the slow remodeling process. Our findings confirm the importance of a comprehensive study of the changes of bone metabolism markers and gamma-ray scanning of the sternum, in order to diagnose and assess the processes of sternum restoration in patients with CAD associated with type 2 DM and carbohydrate metabolism disorders.

Conclusions

1. In the group of patients with coronary artery disease associated with type 2 diabetes mellitus and impaired glucose tolerance, a decrease in circulating markers osteocalcin and carboxy-terminal telopeptide was established. This indicates an imbalance between the processes of bone formation, bone resorption, and slower bone remodeling.
2. In patients with type 2 diabetes mellitus and impaired glucose tolerance, a statistically significant increase in deoxypyridinoline was shown six months after sternotomy when compared to patients without carbohydrate metabolism disorders who had maximum serum levels of deoxypyridinoline in the short-term post-surgery period. The findings indicate that bone resorption is slow.
3. In patients with coronary artery disease and carbohydrate metabolism disorders, a statistically significant increase in the intensity of radiopharmaceutical accumulation in various sternum areas was detected due to incomplete sternum union in the long-term period caused by the slow remodeling process.
4. In the group of patients with coronary artery disease associated with type 2 diabetes mellitus and impaired glucose tolerance, strong positive associations of the serum levels of osteocalcin and carboxy-terminal telopeptide with the intensity of radiopharmaceutical accumulation were found. This proves the association of radiopharmaceutical accumulation in bone tissue with osteoblasts activity and thus bone formation.

Limitations

Small sample size.

No conflict of interest is reported.

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