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ABSTRACT

of the dissertation for the degree of Doctor of Science

CLINICAL AND PATHOGENETIC FEATURES OF BONE TISSUE REMODELING IN DIABETES MELLITUS

Speciality: 3216.01– Endocrinology

Field of science: Medicine

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INTRODUCTION

Relevance and studying degree of the topic

The high incidence of diabetes mellitus (DM) and associated severe irreversible complications gives this disease global medical and social significance and determines the keen interest of researchers in a detailed analysis of this pathology.

Diabetes mellitus, with all its complications, places a heavy economic burden both on the patients themselves and their families, as well as on the healthcare system and the national economy. A report from the International Diabetes Federation (IDF) highlighted that as a result of the increase in the number of patients with diabetes, *"in 2019, global healthcare spending on diabetes will reach $ 760 billion, which is 4.5% more than in 2017"* (IDF Diabetes Atlas, 9th ed.).[1]

According to IDF estimates, *"over 425 million people currently suffer from diabetes, a third of whom are over 65. The number of people with diabetes is projected to rise to 629 million by 2045, although incidence has certainly begun to decline in some high-income countries. At the same time, an additional 352 million people with impaired glucose tolerance are at high risk of developing diabetes"* (IDF Diabetes Atlas, 8th ed.).[2]

The combination of the prevalence of diabetes mellitus with an increase in life expectancy leads to a diversification of associated complications. Actually, they determine the quality of life, and often the life prognosis in this category of patients, increasing the cumulative risk of premature mortality.

Among a number of deeply studied complications of diabetes, a special place in clinical practice is taken by disorders of bone tissue remodeling, which contribute to the development of diabetic osteopathy (DO).The social significance of this complication is determined by its consequences - *"low-energy fractures of the vertebrae and the appendicular skeleton bones, characterized by a*

[1]IDF Diabetes Atlas, 9 th ed. Brussels, International Diabetes Federation; 2019. 176p.
[2] IDF Diabetes Atlas, 8th ed. Brussels, International Diabetes Federation; 2017. 150p.

high level of disability and mortality" [3], and taking the problem of diabetic osteopathy beyond a narrow specialty, making it the subject of extensive scientific research.

According to WHO estimates, *"more than 8.9 million osteoporotic fractures occur annually in the world, approximately one in three women and one in five men over the age of 50 experience a low-traumatic fracture".*[4] *"The incidence of femoral neck fractures in people with type 1 diabetes is seven times, and in type 2 diabetes is 1.4 times higher than in the general population".*[5,6] *"Mortality in the first year after fracture reaches 37%. About 33% of patients remain bedridden, 42% have limited mobility, and only 31% of patients return to their original level of activity".*[7]

In 1948, Albright F. and Reinfenstein E.[8] have suggested that there is a link between diabetes and bone loss. Over the past 70 years, understanding of the relationship between osteopathy and diabetes has progressed markedly.

Type 1 and 2 diabetes mellitus have unique and overlapping mechanisms for bone loss. The hyperglycemic factor present in diabetes affects the structure of bone matrix proteins, such as collagen I, through non-enzymatic glycosylation, which can reduce bone strength and increase the risk of low-energy fractures even with a visible absence of bone loss.[9] Diabetes also activates inflammatory

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[3] McCabe, L., Zhang, J., Raehtz, S. Understanding the skeletal pathology of type 1 and 2 diabetes mellitus // Critical Reviews in Eukaryotic Gene Expression, – 2011. 21 (2), – p. 187-206.

[4] Blackie, R. Diagnosis, assessment and management of osteoporosis. Prescriber, – 2020. 31, – p.14-19.

[5] Starup-Linde J., Hygum K., Harsløf T., Langdahl B. Type 1 diabetes and bone fragility: links and risks // Diabetes Metab Syndr Obes., – 2019. 12, – p. 2539-2547.

[6] Oei, L., Rivadeneira, F., Zillikens, M.C. et al. Diabetes, diabetic complications, and fracture risk // Curr Osteoporos Rep, – 2015. 13, – p.106-115.

[7] Tang, V.L., Sudore, R., Cenzer, I.S. [et al.] Rates of Recovery to Pre-Fracture Function in Older Persons with Hip Fracture: an Observational Study // Journal of general internal medicine, – 2017. 32(2), – p.153-158.

[8] Albright, F., Reifenstein, E.C. The parathyroid glands and metabolic bone disease: selected studies. Baltimore: Williams & Wilkins; 1948.p. 227.

[9] GLOBAL REPORT ON DIABETES. World Health Organization 2016. 88p.

processes, affects electrolyte homeostasis, the concentration of calcitropic hormones, which further contributes to the development of destructive processes in bone tissue. The relative risk of femoral neck fractures in patients with type 1 diabetes increases by 6 times, and in type 2 diabetes increases by 2 times compared with the general population.

Since the achievements of modern medicine significantly increase the life expectancy of patients, the risk of diabetic complications and, accordingly, osteoporotic fractures also increases. The urgency of identifying patients with low-traumatic fractures becomes obvious.

Many of the diagnostically important parameters developed to describe the structural properties of bone can be easily assessed by non-invasive methods for detecting osteoporosis. A variety of methods, ranging from plain X-ray and Dual Energy X-ray Absorptiometry (DXA), computed tomography and magnetic resonance imaging, are based on the structural analysis of bone tissue. [10]

Despite the fact that bone mineral density (BMD) is the most important quantitative indicator to help assess bone strength, qualitative characteristics also play a significant role. [11] These include the degree of mineralization, metabolism (processes of formation and resorption) of bone tissue, the distribution of bone mass in space, known as the micro- and macroarchitectonics of bone.

Biochemical markers of bone metabolism reveal the dynamics of changes in reparative osteogenesis earlier than DXA, which significantly improves the quality of early diagnosis and assessment of the effectiveness of therapy. [12] At the same time, one should be aware that none of the parameters separately is comprehensive or integral in identifying these changes. Each method has its own advantages and disadvantages, and a comprehensive examination is necessary for a

[10] Russo, G.T., Giandalia, A., Romeo, E.L. [et al.] Fracture risk in type 2 diabetes: current perspectives and gender differences // International Journal of Endocrinology, – 2016. 2016 (1), – p. 1-11.

[11] Starup-Linde, J., Vestergaard, P. Biochemical bone turnover markers in diabetes mellitus - a systematic review // Bone, – 2016. 82 (1), – p.69-78.

[12] Ghosal, S., Ghosal, A. Diabetes and musculoskeletal disorders-a review // Journal of Diabetes, Metabolic Disorders & Control, – 2020. 7 (2), – p. 63-71.

thorough analysis of the clinical picture. This information complements the understanding of how diabetes affects bone metabolism and contributes to the development of low-energy fractures.

More information is needed on the pathogenesis of these disorders and their relationship to the increased risk of fractures seen in diabetes mellitus. It remains to be determined what factors are capable of changing the properties of the bone matrix, increasing the porosity of the cortex. Further study of the processes of reparative osteogenesis can optimize the diagnostic capabilities and prevention of bone changes in diabetes, thereby potentially reducing the risk of serious disorders in this population group and, as a consequence, determines the increased scientific interest in the problem of the state of bone tissue in diabetes mellitus.

Due to the increased risk of low-energy fractures in diabetes mellitus, the question of the very mechanisms of diabetic damage to bone tissue, combined and aggravated by the changes occurring in it, associated with the processes of natural aging of the body, attracts close attention.

In this regard, the problem of early diagnosis of bone metabolism disorders, which allows initially build the correct management strategy, thereby preventing the severe consequences of this complication of diabetes, has led to the urgency of the problem, on the solution of which the present study is focused.

Object and Subject of the Research. The main object of the dissertation work is the processes of reparative osteogenesis in type 1 and 2 diabetes mellitus. The subject of the dissertation research is the parameters that assess the qualitative and quantitative characteristics of bone tissue, forming an idea of the activity of bone remodeling processes in diabetes mellitus.

The aim and the tasks of the research. The main aim of this dissertation is to study the pathogenetic basis of changes in metabolic processes in bone tissue in type 1 and 2 diabetes mellitus, to identify predictors of diabetic osteopathy for the development of methods for early screening of shifts in bone remodeling processes aimed at preventing the progression of this pathology.

For this purpose, the following tasks are to be solved:

1. To conduct a systematic study of the processes occurring in bone tissue in diabetes mellitus, to reveal the factors that cause changes in reparative osteogenesis associated with the impact of gender and age parameters, as well as the duration and type of diabetes.

2. To identify the leading clinical and anamnestic determinants of the development of bone disorders in patients with type 1 and 2 diabetes mellitus based on the assessment of the state of a number of biochemical blood parameters, calcium-phosphorus-homeostasis and the content of calcium-regulating hormones.

3. To evaluate the structural and functional characteristics of bone tissue due to the type of diabetes mellitus based on the analysis of qualitative indicators of reparative osteogenesis.

4. To study the orientation of the shifts of osteometabolic processes associated with the type of diabetes mellitus, based on the analysis of markers of bone remodeling.

5. To determine the most informative in type 1 and 2 diabetes mellitus biomarkers of reparative osteogenesis, characterizing the state of bone metabolism.

6. To evaluate the quantitative characteristics of the axial and appendicular skeleton for type 1 and 2 diabetes based on measurements of the density of the mineral component of the bone by Dual-energy X-ray Absorptiometry.

7. Conduct a comparative analysis of the information content of quality indicators (markers of bone remodeling) for the diagnosis of diabetic osteopathy with the traditionally used method of Dual-energy X-ray Absorptiometry.

8. To build a diagnostic algorithm for stratification of patients with diabetes-related changes in bone tissue, aimed at leveling the risk of developing low-traumatic fractures.

9. Develop a structure and implement software for an intelligent decision support system using artificial neural networks, which allows predicting the values of indicators characterizing the qualitative and quantitative state of the bone based on the measurement results of a number of laboratory variables, for early diagnosis of the risks of structural and functional changes in bone tissue patients with diabetes.

Methods of Research. In the study, the following methods were

used to study the state of the qualitative and quantitative characteristics of bone tissue: determination of the state of electrolyte homeostasis; functional state of the kidneys; the content of calcium-regulating hormones; markers of reparative osteogenesis activity; measuring the mineral density of the axial and peripheral skeleton according to the bone mineral density (BMD) T- and Z-score; the data were analyzed using the generally accepted methods of variation statistics.

The clinical study included 317 persons who met the criteria for inclusion in the study, of which the first study group consisted of 98 (42%) patients with type 1 diabetes (57 (58%) women and 41(42%) men). The second main group consisted of 137 (58%) patients with type 2 diabetes, of which 85 (62%) were women and 52 (38%) were men. The control group consisted of 82 individuals, of whom: 43 (52%) women and 39 (48%) men without a history of diabetes. Additionally, depending on the functional state of the reproductive system, female patients were divided into 2 subgroups: subgroup 1 - premenopausal patients, subgroup 2 - postmenopausal patients. Postmenopause was diagnosed after a twelve month period of amenorrhea.

All patients included in the study underwent a comprehensive examination using modern clinical diagnostic methods. The compliance of the results of this study with the accepted scientific standards of validity was achieved due to objective assessment criteria using discriminant data processing methods.

Main Postulates Represented for Defense:

1. Determinants have been identified that regulate bone remodeling processes in patients with type 1 and 2 diabetes who need a specialized diagnostic approach to identify diabetic osteopathy.

2. The algorithm for screening changes in bone remodeling has been supplemented, which allows limiting the indications for the use of economically costly diagnostic methods and decreasing the interval between the detection of violations and timely actions preventing the progression of this complication for the category of patients with type 1 and 2 diabetes.

3. It was revealed that C-terminal telopeptide of type I collagen (b-CTx) is a highly sensitive marker of bone resorption, the values of which are higher mainly in patients with type 1 diabetes, which

indicates an active decrease in bone tissue regeneration and, associated with this, a slightly more pronounced decrease in the quantitative characteristics of bone than with type 2 diabetes. b-CTx values correlate with factors such as glycemic homeostasis, insulin secretion, and duration of diabetes.

4. As a result of diagnostic diversification of a model that evaluates the state of reparative osteogenesis processes, the practical possibilities of bone remodeling biomarkers have been identified as a tool for predicting bone destruction processes in diabetes mellitus.

5. A technique has been developed to build a decision support system based on an artificial neural network that increases the efficiency of the process of analyzing the state of the bone structure, helps the clinician to make an informed decision in order to identify shifts in metabolic processes in bone tissue in the presence of diabetes mellitus.

Scientific Novelty of the Research

- on the basis of a systematic approach to clinical analysis, a comparative assessment of the features of reparative osteogenesis in patients with type 1 diabetes is compared with patients of the corresponding sex with type 2 diabetes, and the dependences of bone remodeling processes on metabolic shifts associated with diabetes mellitus have been identified;

- the most informative biochemical markers of bone remodeling were determined, which give an additive prognostic assessment of the risk of low-traumatic fractures in people with diabetes;

- for the first time in Azerbaijan, on the basis of the study, a methodology was developed and an intelligent clinical decision support system based on artificial neural networks was developed, which allows predicting the values of indicators characterizing the qualitative and quantitative state of the bone according to the results of measurements of a number of laboratory variables, for screening patients with bone remodeling disorders from total number of patients with diabetes. The authorship of the method is documented by a copyright registration certificate (No. 10711) issued by the Intellectual Property Agency of the Republic of Azerbaijan.

Theoretical and practical significance of the research

The theoretical significance of the study lies in the development and implementation of an integrated approach to solving the problem of bone remodeling in diabetes mellitus, based on the study of shifts occurring in the bone tissue and the identification of informative methods for screening the ongoing processes. A mathematical model has been built based on the use of an intelligent clinical decision support system to obtain prognostic information about bone changes, which helps to identify persons at high risk of diabetic osteopathy from the general cohort of patients with diabetes mellitus.

The practical significance of the work is determined by the possibility of introducing the developed software into the treatment and prophylactic activity for the convenience of calculating the individual risk of developing bone changes in diabetes mellitus. The research results can be introduced into a unified program for examining patients with diabetes mellitus.

Approbation and implementation of research results. Theresultsoftheresearchandthemainprovisionsofthedissertationwererepo rtedon: Республиканской научно-практической конференции, посвященной 70-летнему юбилею профессора А.А.Ахундбейли (Баку, 2008); Научно-практической конференции, посвященной 115-летию со дня рождения А.М. Алиева (Баку, 2012); Научно-практической конференции, посвященной 70-летнему юбилею профессора А.Т.Агаева (Баку, 2014); Международной практической конференции, посвященной 95-летнему юбилею кафедры анатомии человека (Баку, 2014); Theoretical and Applied Sciences in the USA: Papers of the 3rd International Scientific Conference (New York, 2015); Научно-практической конференции, посвященной 120-летию со дня рождения А.М.Алиева (Баку, 2017); Научно-практической конференции, посвященной 120-летию со дня рождения А.М.Алиева (Баку, 2017); XX Международной конференции «Мультимодальные Аспекты возрастных особенностей профилактике и терапии цереброваскулярных заболеваний» (Украина, 2018); Материалах XXII Международной научной конференции «Онкология – XXI век», VIII Итало-российской научной конференции по онкологии и эндокринологии

(Черногория, 2018); Тезисах Всероссийский научно-практической конференции с международным участием «Актуальные вопросы современной эндокринологии: фокус на регионы» (Санкт Петербург, 2018); Материалах конференции посвященной 95-летию со дня рождения академика З. Алиевой «Современные достижения в здравоохранении» (Баку, 2018); материалах XV международной научно-практической конференции «Научный форум: инновационная наука», (Москва, 2018); материалах XIV конференции «Современная медицина: новые подходы и актуальные исследования», (Москва, 2018); III международной конференции Прикаспийских государств «Актуальные вопросы современной медицины», (Астрахань, 2018); Научно-практической конференции по детской хирургии, посвященной 80-летию кафедры детской хирургии АТУ, (Баку, 2019); Материалах XXIII Международной научной конференции «Онкология-XXI век» IX Итало-российская конференция по онкологии и эндокринной хирургии, (Баку, 2019); XI-я Всероссийская научно-практическая конференция «Актуальные вопросы диагностики, лечения и профилактики синдрома диабетической стопы» (Казань, 2019); 67-я годичная международная научно-практическая конференция ТГМУ им. Абуали ибни Сино «Медицинская наука XXI века – взгляд в будущее» (Душанбе, 2019); III Всероссийская конференция с межународным участием «Сахарный диабет, его осложнения и хирургические инфекции» (Москва, 2019); Международная научно-практическая конференция «Компьютерные технологии и моделирование в экономике, образовании, управлении и технике тенденции и развитие» (Махачкала, 2019); XXVI Всероссийском конгресса с международным участием и специализированной выставочной экспозицией «Амбулаторно-поликлиническая помощь в эпицентре женского здоровья от менархе до менопаузы» (Москва, 2020); Межрегиональной научно-практической конференции «Актуальные проблемы общественного здоровья и истории медицины», посвященной 100-летию со дня рождения профессора Н.А. Фроловой (Тверь, 2020); I Международной конференции «Генетика человека и генетические заболевания: проблемы и перспективы» (Баку, 2020); The first

international scientific –practical virtual conference science and technology in modern society: problems, prognoses and solutions (İzmireylül 2020); The 7th International Conference on Control and Optimization with Industrial Applications COIA 2020, (Baku, 2020); 14th International Conference on Applications of Fuzzy Systems, Soft Computing and Artificial Intelligence Tools (ICAFS 2020); XXIV Международной научной конференции «ОНКОЛОГИЯ – XXI ВЕК» X Итало-российской научной конференции по онкологии и эндокринной хирургии XXIV Международной научной конференции «ЗДОРОВЬЕ НАЦИИ – XXI ВЕК» (Пермь – Стамбул, 2020); 68-я годичной международной научно-практической конференции ТГМУ им. Абуали ибни Сино «Достижения и проблемы фундаментальной науки и клинической медицины» (Душанбе, 2020); Международной научной конференции, посвященной 100-летию АМУ, (Баку, 2020); The Second International Scientific – Practical Virtual Conference “Modern Medicine: Problems, Prognoses and Solutions" (Баку, 2020); The First International Scientific – Practical Virtual Conference "Clinical Endocrinology and Endocrine system disease: Prognosis, achievement and challenges” (Баку, 2021); VIII Конгресс с международным участием “Проблема остеопороза в травматологии и ортопедии” (Москва, 2021).

On the topic of the dissertation, 70 scientific papers were published: 12 articles in journals published in Azerbaijan and 22 articles in peer-reviewed foreign journals, 35 publications in collections of scientific and practical conferences and congresses, 1 study guide book for doctors approved by the Ministry of Health of the Republic of Azerbaijan, 1 certificate of state registration of copyright for a computer program (No. 10711) issued by the Intellectual Property Agency of the Republic of Azerbaijan.

The obtained results of the study have found application in the educational process when giving lectures, conducting seminars and practical exercises at the Department of Internal Medicine of the Azerbaijan Medical University, in the practical work of the Department of Endocrinology at the Educational-Therapeutic clinic of Azerbaijan Medical University. The main results of the dissertation research were published and distributed among endocrinologists in the form of

methodological materials, including the study guide book.

The name of the institution where the dissertation research was carried out. The study was carried out on the basis of the Department of Endocrinology at the Educational-Therapeutic clinic of Azerbaijan Medical University (AMU) in 2015 - 2017.

Structure and total volume of the dissertation work. The dissertation work is presented on 360 pages of computer text and consists of an introduction, a literature review, materials and research methods, 3 chapters of own research, conclusions, practical recommendations and list of references including 396 bibliographic sources. The dissertation is illustrated by 44 figures and diagrams, contains 62 tables. The list of references includes 396 bibliographic sources, published mainly over the past 10 years.

WORK CONTENT

CHAPTER I. LITERATURE SUMMARY

This chapter is dedicated to the overview of scientific sources and results derived from them in the fields of: epidemiological characteristics of diabetic osteopathy; bone morphology and its dependence on gender, age and ethnicity; calcium-regulating system and bone homeostasis; bone remodeling in diabetes mellitus; primary biochemical markers of the assessment of reparative osteogenesis; quantitative methods for the diagnosis of reparative osteogenesis; the main aspects of prevention and treatment of diabetic osteopathy.

The basis of the carried out analysis has revealed the relevance and insufficient coverage of the problem of changed in reparative osteogenesis in diabetes mellitus.

CHAPTER II. MATERIALS AND RESEARCH METHODS

The study was carried out on the basis of the Department of Endocrinology at the Educational-Therapeutic clinic of Azerbaijan Medical University (AMU) in 2015 - 2017.

A prospective study was carried out to study the state of the qualitative and quantitative characteristics of bone tissue with the measurement of the density of the mineral component of the axial

and peripheral skeleton, markers of reparative osteogenesis, indicators of phosphorus-calcium homeostasis, calcium-regulating hormones used to assess the effectiveness and in formativeness of complex diagnostic actions to identify early stages of development and prevent progression osteopathy in patients with type 1 and type 2 diabetes.

The selection of patients for the clinical study was carried out according to the following criteria.

Inclusion criteria:

• male and female persons with type 1 and 2 diabetes mellitus;

• age 40-70 years;

Exclusion criteria:

• patients with diabetes with persistent decompensation of the glycemic profile, patients with severe stages of chronic diabetes complications, including stage 4-5 diabetic nephropathy, as well as patients with other endocrinopathies;

• persons with previous therapy for osteoporosis or having a history of fracture, with diseases of the musculoskeletal system of functional classes III and IV;

• with diseases of the liver and kidneys of a non-diabetic nature, chronic processes in internal organs above II degree of insufficiency;

• malignant diseases, with comorbid diseases and processes clustering with a decrease in BMD.

The clinical study included 317 persons who met the criteria for inclusion in the study, of which the first study group consisted of 98 (42%) patients with type 1 diabetes, of which 57 (58%) were women and 41 (42%) were men. The second main group consisted of 137 (58%) patients with type 2 diabetes, of which 85 (62%) were women and 52 (38%) were men. The control group of 82 persons consisted of 43 (52%) women and 39 (48%) men, without anamnestic, clinical and laboratory-instrumental signs of endocrine system pathology, corresponding in age to patients with diabetes.

Additionally, in order to assess the quantitative and qualitative parameters of the axial and peripheral skeleton, risk factors and pathophysiological mechanisms for the development of disorders of

the processes of reparative osteogenesis, depending on the age-related characteristics of the functioning of the reproductive system, a female patient with type 1 diabetes (n = 57), type 2 diabetes (n = 85) and control groups (n = 43) in the course of stratification randomization were divided into 2 subgroups: subgroup I - patients in the premenopausal period, subgroup II - patients in the postmenopausal period. Postmenopause was diagnosed after a twelve month period of amenorrhea. The women in this study did not use estrogen-containing drugs. During the research period patients did not take calcium and vitamin D supplements.

Comprehensive clinical diagnostics of the patients included in the study was carried out. All patients underwent data collection (questionnaire survey), including: passport data, anthropometric parameters; family anamnesis; disease anamnesis, as well as concomitant diseases; results of clinical and laboratory-instrumental examination; for patients included in prospective sections of the work, additional survey data were entered.

So, in women included in the study, an additional gynecological history was collected, including:

- characteristics of the menstrual cycle;
- the number of births in the anamnesis;
- duration of lactation periods;
- transferred gynecological diseases;
- age of onset of menopause;
- features of the course of the pre- and postmenopausal period;

Since anthropometric data contain indirect information about bone mineral density, an anthropometric study was carried out according to the recommendations. The subjects were measured height in an upright position, without outerwear and shoes on a standard height meter.

Comprehensive examination included determination of the state of calcium-phosphorus homeostasis, potassium, magnesium, sodium ions, markers of the functional state of the kidneys, calcitropic hormones in patients with type 1 and 2 diabetes, as well as in the control group. Predictors influencing changes in bone remodeling processes

caused by gender and age parameters, as well as the duration and type of diabetes were studied. The direction of metabolic processes in bone tissue was studied depending on the type of diabetes mellitus: the assessment was carried out based on the analysis of the values of bone formation and resorption indicators. Also, diagnostics of the state of quantitative characteristics of bone tissue was carried out with an assessment of the mineral density of the axial and appendicular skeleton according to the values of the T- and Z-score measured using the method of Dual-energy X-ray Absorptiometry (DXA).

In the process of performing the work, the developed program was modeled and tested on the basis of an intelligent decision support system using the apparatus of artificial neural networks, which helps to conduct early diagnosis and predict the risks of developing bone tissue alteration in patients with type 1 and 2 DM.

The data of the research results were processed by typical methods of variation statistics, using the programs "Microsoft Excel 2010", "BioStat 6.0", "Statistica 10.0" and "MATLAB R2015b". The normal distribution of variables was checked using the Kolmogorov-Smirnov test. All continuous variables are presented as the arithmetic mean and standard error of the mean M ± m, the width of the 95% confidence interval (95% CI) was also indicated, categorical variables were expressed as a number (in percent). Due to the prevalence of parameters with a distribution other than normal, statistical analysis of the study results, comparing groups by quantitative parameters, was carried out using nonparametric analysis criteria: two independent groups were compared using the Mann-Whitney U test. To analyze the correlation between the variables (indicators), Spearman's rank correlation coefficient (r) was used. The quantitative characteristic of the dependence of the studied characteristics was given on the basis of the analysis of the indicators of the strength of the connection between the correlation coefficients and the determination of the conditionality of one characteristic from the changes in another (the regression coefficient). Differences between the compared variation series were regarded as statistically significant at the $p < 0.05$ level.

CHAPTER III. STATE OF QUALITATIVE BONE METABOLISM INDICATORS IN TYPE 1 DIABETES MELLITUS

3.1. Assessment of changes in qualitative indicators of reparative osteogenesis in patients with type 1 Diabetes Mellitus

The study assessed a number of indicators that presumably play an important role in the pathogenesis of diabetic osteopathy. In patients with type 1 diabetes, a pronounced violation of mineral metabolism was detected.

Table 1 shows the clinical and laboratory characteristics of the patients with type 1 diabetes included in the group.

Table 1

Patients with type 1 diabetes and the control group, mean (M) and 95% CI

Index	Type 1 DM group, n=98	Control group, n=82
Age, years	54,8 (53,4-56,2)	55,9 (54,2-57,7)
Sex Male / Female	41/57	39/43
BMI, kg/m^2	26,1 (25,6-26,5) $^{2)*}$	28,7 (27,9-29,5)
DM duration, year	16,6 (15,4-17,8)	–
HbA1c,%	7,4 (7,1-7,8) $^{3)*}$	4,9 (4,7-5,0)
HOMA-IR	–	2,8 (2,4-3,1)
Ca^{2+}, mmol/L	1,09 (1,07-1,11) $^{1)*}$	1,13 (1,11-1,15)
P^{+}, mq/dl	5,4 (5,2-5,6) $^{1)*}$	5,1 (4,9-5,2)
GFR, ml/min 1,73 m^2	86,7 (83,1-90,4) $^{3)*}$	95,2 (91,8-98,6)
Albumen, g/dL	4,2 (4,1-4,3) $^{1)*}$	4,5 (4,3-4,6)
PTH, pg/dL	51,16 (47,17-55,13) $^{1)*}$	45,09 (40,38-49,79)
CT, pg/mL	12,07 (9,75-14,38) $^{4)*}$	5,5 (4,19-6,84)
Vit. D, ng/mL	24,09 (21,32-26,86) $^{3)*}$	30,41 (26,95-33,86)
ALP, IU/L	118,3 (110,1-126,4)	123,5 (113,8-133,2)
P1NP, ng/mL	40,58 (37,18-43,98) $^{1)*}$	47,09 (42,82-51,35)
b-CTX, ng/mL	0,525 (0,468-0,582) $^{2)*}$	0,424 (0,383-0,466)
T-score (L1–L4)	-2,04 (-2,3; -1,7) $^{4)*}$	-0,73 (-1,1; -0,3)
Z -score (L1–L4)	-0,99 (-1,3; -0,6) $^{4)*}$	0,27 (-0,08; 0,6)
T-score (Fem. neck)	-1,68 (-1,9; -1,3) $^{4)*}$	-0,64 (-1,0; -0,2)
Z-score (Fem. neck)	-0,56 (-0,8; -0,2) $^{3)*}$	0,22 (-0,1; 0,5)

Note: statistically significant difference: $^{1)*}p<0,05$; $^{2)*}p<0,01$; $^{3)*}p<0,005$; $^{4)*}p<0,001$ in comparison with the control group.

3.1.1. Assessment of phosphorus-calcium metabolism in type 1 Diabetes Mellitus

Serum ionized calcium (Ca^{2+}) levels decrease, was detected, with normal serum total calcium levels. Moreover, in women, a change in the Ca^{2+}levels was somewhat more common than in men. In postmenopausal women, serum Ca^{2+} level in type 1 diabetes was significantly lower than in premenopausal women. Decrease in measured ionized Ca^{2+} concentration was revealed with an increase in the duration of the disease. However, no correlation was established between this marker and the age of the patients.

Vitamin D ($25(OH)D_3$) plays an important role in maintaining calcium homeostasis and the functioning of bone tissue, as evidenced by the presence of a relationship between the Ca^{2+}level and vitamin D in type 1 diabetes ($r = 0.507$, $p = 0.001$). The serum phosphorus (P^+) level in type 1 diabetes were slightly differ from those in the control group ($p< 0.05$). Serum P^+ concentration decrease in women with type 1diabetes was detected almost 2-fold more often than in men. This may be partly due to the fact that estrogens reduce the expression of sodium phosphate cotransporters by the kidneys.[13]This assumption can explain the lower serum phosphorus level in premenopausal women (in our study, there were more premenopausal women with type 1 diabetes) and the relative increase serum phosphorus concentration in postmenopausal women, associated with a decrease in estrogen production.[14]

3.1.2. Assessment of given biochemical markers: magnesium, potassium and sodium, creatinine, GFR and serum albumin in type 1 Diabetes Mellitus

Also, in patients with type 1 diabetes, decrease in serum magnesium (Mg^{2+}) level was revealed compared to control group. Hypomagnesemia was detected in 13% of patients with type 1diabetes; in women with type 1 diabetes, serum Mg^{2+} levels decreased

[13] Lederer, E. Regulation of serum phosphate // J Physiol., - 2014. v. 592, N 18, - p. 3985–3995.

[14]Zhang, D., Maalouf, M., Adams-Huet B.[et al.] Effects of sex and postmenopausal estrogen use on serum phosphorus levels: a cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) 2003-2006 // American Journal of Kidney Diseases, – 2014. 63 (2), – p.198-205.

approximately 1.5–2 times more often than in men. A low Mg^{2+} level scan decrease the activity of parathyroid hormone (PTH) (leads to target tissue resistance to the action of PTH) by decreasing the synthesis of 1alpha-hydroxylase, which in turn reduces the concentration of the active form of vitamin D (1.25 (OH) 2D3) and serum Ca^{2+}, having a negative biological effect on the metabolism of the bone mineral component, changing the structure of hydroxyapatite crystals and bone architectonics in general.[15] In our study, a positive relationship was determined between the concentration of serum Mg^{2+} and vitamin D levels in patients with type 1 diabetes ($r = 0.516$ $p = 0.002$).

Serum potassium (K^+) levels in patients with type 1 diabetes did not significantly differ from the control. However, in diabetes, serum potassium levels are dependent on blood glucose levels. (r=0,330, p=0,01). Presumably, hyperglycemia and insulin deficiency are responsible for the relative rise in the serum potassium concentration, which may explain the direct relationship observed with type 1 diabetes. A statistically significant positive relationship was found between K^+ concentration and blood creatinine level, with a rank correlation coefficient ($r = 0.324$, $p = 0.02$) and a negative relationship with GFR ($r = -0.285$, $p = 0.04$). Also, changes in the content of potassium were revealed based on the degree of compensation of type 1 diabetes. An increase in the level of glycemia in patients observed an increase in the level of K^+, with the Spearman rank correlation coefficient ($r = 0.330$, $p = 0.01$).

In patients with type 1 diabetes significantly higher serum sodium (Na) levels were found in comparison with the control group. In men, change in serum Na concentration was observed 2 times more often than in women. In postmenopausal women with type 1 diabetes, serum Na level was significantly higher than in premenopausal women. Although the underlying mechanism remains unknown, presumably, hypernatremia induces a decrease in the expression of gonadotropin-releasing hormone in hypothalamic neurons.[16]

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[15] Castiglioni, S., Cazzaniga, A., Albisetti, W. [et al.] Magnesium and osteoporosis: current state of knowledge and future research directions // Nutrients, – 2013. 5 (8), – p. 3022-3033.

[16] Liamis, G., Liberopoulos, E., Barkas F. [et al.] Diabetes mellitus and electrolyte disorders // World Journal of Clinical Cases, – 2014. 2 (10), – p. 488-496.

A negative statistically significant relationship was determined between the level of glycemia and GFR, with the Spearman rank correlation coefficient (r = -0.292, p = 0.004). A negative, statistically significant relationship between cholesterol level and GFR was also determined, with the Spearman rank correlation coefficient (r = -0.333, p = 0.01). A statistically significant negative relationship between GFR and a positive relationship between serum creatinine and K^+ level was revealed, with the Spearman rank correlation coefficient (r = -0.285, p = 0.04) and (r = 0.324, p = 0.02). In patients with type 1 diabetes, a statistically significant, positive relationship between the level of creatinine and the age of patients with type 1 diabetes was revealed, with the Spearman rank correlation coefficient (r = 0.302, p = 0.003). A strong negative association with a high level of statistical significance was determined between creatinine and GFR, with the Spearman rank correlation coefficient (r = -0.758, p = 0.000). Patients with type 1 diabetes mellitus showed a statistically significant positive relationship between the albumin level and GFR, with the Spearman rank correlation coefficient (r = 0.265, p = 0.04). Also, in patients with type 1 diabetes, a statistically significant negative relationship between albumin concentration and age and duration of type 1 diabetes was revealed, with the Spearman rank correlation coefficient (r = -0.293, p = 0.02) and (r = -0.343, p = 0.009).

3.1.3. Assessment of the state of secretion of calcium-regulating hormones in type 1 Diabetes Mellitus

Vitamin D levels in patients with type 1 diabetes were statistically significantly lower than in the control group (p <0.005).Vitamin D deficiency was detected in 30% of patients with type 1diabetes (Fig. 1).

Higher serum calcitonin (CT) levels were found in patients with type 1 diabetes in comparison with control group. In women with diabetes, the calsitonincontent was 12,3% higher than in men. Analysis showed that, depending on conditions of reproductive system, the serum calcitonin level in postmenopausal women with type 1 diabetes mellitus was statistically significantly higher than in premenopausal women (p <0.05). A positive, statistically significant relationship (r = 0.357, p = 0.01) was established between the level

of CT and creatinine in patients with type 1 diabetes and a negative, moderately close relationship between the level of CT and GFR according to Spearman's criterion, with a correlation coefficient (r = -0.505, p = 0.001).

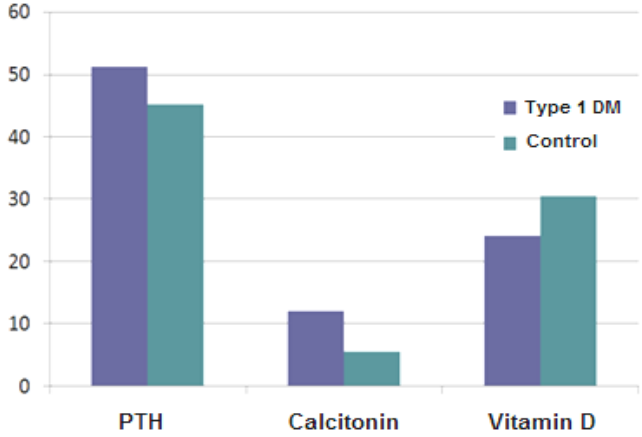

Figure 1. Changes in the exchange of PTH, CT, and vitamin D in patients with type 1 diabetes and the control group

The serum PTH levels in patients with type 1 were slightly higher than the levels of this marker in the control group, but within the reference range ($p < 0.05$). In type 1 diabetes, men had lower PTH levels than women (45.49 ± 3.71 and 53.98 ± 2.21 pg / dL, respectively). According to the results of the study, markers of bone metabolism correlated with serum PTH levels. Serum PTH levels increase was associated with changes in bone remodeling processes with an increase in resorption, which confirms the revealed significant inverse relationship of PTH concentration with the bone formation marker Procollagen type I N-terminal propeptide (P1NP) ($r = -0.328$, $p = 0.01$) and direct with bone resorption marker C-terminal telopeptide of type I collagen (b-CTX) ($r = 0.278$, $p = 0.04$).

These studies show a statistically significant increase in the PTH concentration in patients with type 1 diabetes with age and duration of type 1 diabetes. A direct correlation was established between these indicators with the Spearman rank correlation

coefficient (r = 0.341, p = 0.01) and (r = 0.363, p = 0.007). Also, a positive relationship was established, with sufficient statistical significance (r = 0.271, p = 0.04), between the PTH level and glycemia in patients with type 1 diabetes. Analysis with other indicators did not reveal statistically significant correlations.

3.1.4. Parameters of bone remodeling markers in assessing reparative osteogenesis processes in type 1 Diabetes Mellitus

The bone formation marker P1NP was significantly decrease in patients with type 1 diabetes compared with the control group levels ($p < 0.01$). Perhaps this is due to a critical decrease in insulin production, which leads to a negative regulation of the function of osteoblasts and may be associated with the pathogenesis of bone disorders, by affecting the production of collagen necessary for the formation of an organic matrix and bone mineralization.[17] The values of the bone resorption marker b-CTx in patients with type 1 diabetes were higher compared with the control, which indicates an increase in bone resorption in this group.

Some patients showed a decrease in the marker of bone formation PINP, against the background of unchanged bone resorption. Our results of the study on the assessment of the content of markers of bone metabolism in blood serum in patients with type 1 diabetes compared with the control group indicate the presence of pathological changes in bone remodeling processes in the form of a 16% decrease in the marker of bone formation of PINP in patients with type 1 diabetes compared with the control group and increasing the b-CTx bone resorption marker in 32%, in which there were 1.5 times more women than men; as well as inconsistencies in changes in bone remodeling processes, with a predominant change in the bone resorption rate, determined in 28% of cases with type 1 diabetes. In pre- and postmenopausal women with diabetes, an assessment of bone metabolism markers revealed a decrease in bone formation in 35.5% of patients with type 1 diabetes, as well as increased bone

[17]Ghodsi, M., Larijani, B., Keshtkar, A. A., Nasli-Esfahani, E. [et al.] Mechanisms involved in altered bone metabolism in diabetes: a narrative review // Journal of Diabetes and Metabolic Disorders, – 2016. 15 (1), – p. 52.

resorption in 16.6%; also, in patients with diabetes, inconsistency of changes in bone remodeling processes was revealed ($p < 0.001$), with a predominant decrease in bone formation, against the background of unchanged bone resorption, which defined in 83.4% cases. An analysis of the data did not reveal a significant change in the total alkaline phosphatase (ALP) levels and showed that its use as a bone marker is uninformative, due to the fact that patients with diabetes have a number of metabolic changes that affect this marker.

In type 1 DM a negative relationship was revealed between albumin levels and bone resorption marker b-CTx ($r = -0.330$, $p = 0.01$); Research results show that a decrease within the reference Glomerular filtration rate(GFR) values is an independent risk factor for fracture in diabetes mellitus, which may be indicated by the negative correlation between GFR and b-CTx level revealed in the study ($r = -0.204$, $p = 0.04$). In type 1 diabetes, inhibition of bone formation processes was revealed to a greater extent and resorptive processes of bone tissue were enhanced.

3.2. Assessment of the state of mineral density of the bones of axial and appendicular skeleton in patients with type 1 Diabetes Mellitus based on Dual-energy Absorptiometry data

One of the main components of bone strength and a valid predictor of osteoporotic fractures is a decrease in bone mineral density (BMD).[18] It is known that different areas of the proximal femur are not uniform in terms of the density of the mineral components of the bone tissue.

Evaluation of the results of dual-energy X-ray absorptiometry (DXA), according to various authors, indicated a significant decrease in BMD in patients with type 1 diabetes in various parts of the skeleton.[19] The average values of the T-score characterizing BMD in comparison

[18] Мамедгасанов, Р.М., Мазовецкий, А.Г., Перелыгина, А.А. К патогенезу диабетических ангиопатий нижних конечностей у больных инсулиннезависимым сахарным диабетом // Пробл. эндокринол., - 1991. N 3, - с. 31-34.

[19] Coe, L.M., Irwin, R., Lippner D. [et al.] The bone marrow microenvironment contributes to type I diabetes induced osteoblast death // Journal of Cellular Physiology, – 2011. 226 (2), – p. 477-483.

with the control group in the lumbar spine area (L1-L4)and femoral neck area (FN) shown in the table (Table 1).The results of this study indicate the highest likelihood of developing osteoporotic fractures according to the results of T-score changes in patients with type 1 diabetes in the L1-L4 and FN, while at the same time, a lower risk of developing a fracture was revealed according to the results of determining the BMD in the proximal femur area (PFA) (Fig. 2).

Figure 2. Changes in BMD by the T-score of the L1-L4 region, PFA and FN in patients with type 1 diabetes and control group

In the present study, the detectability of low BMD according to the results of T-score changes was in patients with type 1 diabetes in the L1-L4 region (64% and 26% in control group) and in the femoral neck (41% and 22% in control group), at the same time, a lower risk of developing a fracture was revealed by the results of a decrease in BMD in the proximal femur area (36% and 20% in control group). In addition, the measurement values of the T-score BMD in the lumbar spine area and in the femoral neck area in the diabetes groups of type 1 was significantly lower than observed in the control group. According to absorptiometry data, an isolated change in either the vertebrae or the femur was detected in 75% of cases with type 1 diabetes. Accordingly, in 15% of cases there were changes in the spine and in the femoral neck area. Thus, in the case of measuring the BMD of only one zone, some

patients may be at risk of misdiagnosis. The results obtained indicate changes in the BMD of both the axial and appendicular skeleton in patients with type 1 diabetes.

In type 1 diabetes, the highest risk of a decrease in BMD according to the T-score was found in the L1-L4 area in 72% women with type 1 diabetes and in 54% men of cases. The femoral neck area T-score BMD in patients with type 1 diabetes in both men and women in approximately the same percentage of cases was significantly lower than in the control group, but slightly more often in men (41%). In patients with type 1 diabetes, a decrease in BMD in 50% of cases was diagnosed as osteoporosis. In patients with type 1 diabetes, a statistically significant negative relationship was also found between the lumbar spine area T-score and b-CTX levels ($r = - 0.431$, $p = 0.000$).

Changes in the T-score in the spine were determined as less intense in men with type 1 diabetes than in women ($p < 0.005$). An analogous situation was observed in the femoral neck area, where the differences in the bone density in men and women with type 1 diabetes were also statistically significantly different ($p < 0.05$). In comparison with control men, bone density in the studied areas of men with type 1 diabetes was lowered considerably. Deviations in bone mineralization, the reactivity of which depended on the duration of the main process, was most clearly observed in the lumbar spine area in men with type 1 diabetes compared with men in the control group.

CAPTER IV. STATE OF QUALITATIVE BONE METABOLISM INDICATORS IN TYPE 2 DIABETES MELLITUS

4.1. Change assessment in qualitative indicators of reparative osteogenesis in patients with type 2 Diabetes Mellitus

Studies have reported conflicting results on BMD status in diabetes mellitus. Whereas in type 1 diabetes, a decrease in BMD is observed, in type 2 diabetes it is either increased or not changed, in conditions of an increased risk of developing low-fragility fractures compared to the general population.[20] The relationship between type

[20] Puspitasari, M., Purnamasari, D. Setyohadi, B. [et al.] Bone metabolism and fracture risk in diabetes mellitus // Journal of the Asean Federation of Endocrine Societies, – 2017. 32 (2), – p. 90-99.

2 diabetes and changes in the processes of reparative osteogenesis has complex mechanisms that are still not fully understood. Table 2 shows the clinical and laboratory characteristics of the patients with type 2 diabetes included in the group.

Table 2

Patients with type 2 diabetes and the control group, mean (M) and 95% CI

Index	Type 2 DM group, n=137	Control group, n=82
Age, years	58,4 (57,3-59,5) [1)*]	55,9 (54,2-57,7)
Sex Male / Female	52/85	39/43
BMI, kg/m^2	30,0 (29,4-30,6) [1)*]	28,7 (27,9-29,5)
DM duration, year	8,1 (7,2-8,8)	–
HbA1c,%	7,5 (7,2-7,8) [3)*]	4,9 (4,7-5,0)
HOMA-IR	8,6 (7,5-9,6) [3)*]	2,8 (2,4-3,1)
Ca^{2+}, mmol/L	1,07 (1,04-1,08) [4)*]	1,13 (1,11-1,15)
P^{+}, mq/dl	5,0 (4,8-5,2)	5,1 (4,9-5,2)
GFR, ml/min 1,73 m^2	88,5 (85,4-91,5) [1)*]	95,2 (91,8-98,6)
Albumen, g/dL	4,3 (4,1-4,4) [1)*]	4,5 (4,3-4,6)
PTH, pg/dL	51,69 (48,82-54,56) [1)*]	45,09 (40,38-49,79)
CT, pg/mL	10,23 (8,84-11,62) [4)*]	5,5 (4,19-6,84)
Vitamin D, ng/mL	25,12 (22,98-27,28) [3)*]	30,41 (26,95-33,86)
ALP, IU/L	122,2 (116,2-128,1)	123,5 (113,8-133,2)
P1NP, ng/mL	42,08 (39,81-44,35)	47,09 (42,82-51,35)
b-CTX, ng/mL	0,495 (0,456-0,533) [1)*]	0,424 (0,383-0,466)
T-score (L1–L4)	-1,08 (-1,3; -0,8) [1)*]	-0,73 (-1,1; -0,3)
Z -score (L1–L4)	-0,03 (-0,3; 0,2) [1)*]	0,27 (-0,08; 0,6)
T-score (Fem. neck)	-1,12 (-1,3; -0,8) [1)*]	-0,64 (-1,0; -0,2)
Z-score (Fem. neck)	0,02 (-0,2; 0,3)	0,22 (-0,1; 0,5)

Note: statistically significant difference: [1)*]p<0,05; [2)*]p<0,01; [3)*]p<0,005; [4)*]p<0,001 in comparison with the control group.

4.1.1. Data assessment of phosphorus-calcium metabolism in type 2 Diabetes Mellitus

Serum ionized calcium (Ca^{2+}) levels decrease, was detected, with normal serum total calcium levels. Moreover, in women, a change in the Ca^{2+} levels was somewhat more common than in men. In postmenopausal women, serum Ca^{2+} level in type 2 diabetes was significantly lower than in premenopausal women. Decrease in measured ionized Ca^{2+} concentration was revealed with an increase in the duration of the disease. However, no correlation was established between this marker and the age of the patients. In type 2 diabetes defined relationship between the Ca^{2+} level and vitamin D ($r = 0.277$, $p = 0.01$). The serum phosphorus level in type 2 diabetes were not differ from those in the control group ($p > 0.05$). Serum P^{+} levels did not differ between women and men with type 2 diabetes. Serum P^{+} level in type 2 diabetes is directly related to serum PTH and b-CTx levels.

4.1.2 Assessment of given biochemical markers: magnesium, potassium and sodium, creatinine, GFR and serum albumin in type 2 Diabetes Mellitus

In patients with type 2 diabetes, decrease in serum Mg^{2+} level was revealed compared to control group. Hypomagnesemia was detected in 11% of patients with type 2 diabetes; in women with type 2 diabetes, serum Mg^{2+} levels decreased approximately 1.5–2 times more often than in men. Insulin regulates intracellular Mg^{2+} concentrations, where it activates the exchange of Na, Mg^{2+} on the plasma membrane, and this may explain the occurrence of low cellular Mg^{2+} concentrations as a result of the development of insulin resistance.[21] In type 2 diabetes mellitus, both hyperglycemia and hyperinsulinemia can increase urinary Mg^{2+} excretion, which explains the identification of hypomagnesemia, which contributes to the development of metabolic acidosis.[22] In our research defined

[21]Moe, S.M. Disorders involving calcium, phosphorus and magnesium // Primary Care Clinics in Office Practice, – 2008. 35 (2), – p. 215-237.

[22] Martins, J.M., Aranha, P. Bone turnover and bone mineral density in old persons with type 2 diabetes // Journal of Clinical and Translational Endocrinology, – 2018. 24 (14), – p. 12-18.

relationship between the Mg^{2+} level and vitamin D in patients with type 2 diabetes (r = 0.321, p = 0.01), and relationship between the Mg^{2+} level and Ca^{2+} (r = 0.318, p = 0.04).Actually a deficiency of serum magnesium concentration and intercellular fluid is accompanied by hypocalcemia. Serum potassium in patients with type 2 diabetes did not differ significantly from the control. In type 2 diabetes, the dependence of changes in K^+ concentration on the level of C-peptide was revealed. A statistically significant inverse relationship was found between a decrease in K^+ level with an increase in C-peptide, HOMA-IR and BMI index, with a rank correlation coefficient (r = -0.332, p = 0.03), (r = -0.346, p = 0.005) and (r = -0.218, p = 0.04). Also, a direct relationship was determined between the level of potassium and the concentration of creatinine in the blood, and an inverse relationship between the level of potassium and GFR ,with the rank correlation coefficient (r = 0.283, p = 0.01) and (r = -0.220, p = 0.04).Changes in the content of K^+ were revealed to depend on the degree of compensation of type 2 diabetes. Thus, with an increase in the level of glycemia and HbA1c, patients observed a decrease in the level of K^+, with the Spearman rank correlation coefficient (r = -0.309, p = 0.02) and (r = -0.483, p = 0.002). Evidently, Insulin have some mechanism for regulating the potassium range that is not related to its ability to maintain glucose in the normal range.[23]

Patients with type 2 diabetes were found to have significantly higher serum Na levels compared to the control group. In men, the change in the concentration of serum Na levels was observed 2 times more often than in women. In postmenopausal women with type 2 diabetes Na level was significantly higher than in premenopausal women.

Patients with a longer duration of type 2 diabetes have registered relatively higher creatinine levels and lower GFR. Thus, an increase in the duration of diabetes mellitus was accompanied by a decrease of GFR in patients, with the Spearman rank correlation

[23] Nguyen, T.Q., Maalouf, N.M., Sakhaee, K. [et al.] Comparison of insulin action on glucose versus potassium uptake in humans // Clinical Journal of the American Society of Nephrology, – 2011. 6 (7), – p. 1533-1539.

coefficient (r = -0.360, p = 0.001). In patients with type 2 diabetes, a statistically significant, weakly bonded positive relationship between the creatinine level and the age of patients with type 2 diabetes was concluded, with the rank correlation coefficient (r = 0.338, p = 0.001). A positive statistically significant relationship was determined between glycemia and creatinine levels, with the Spearman rank correlation coefficient (r = 0.222, p = 0.009). Also, a negative statistically significant relationship was determined between the level of glycemia and GFR, with a rank correlation coefficient (r = -0.171, p = 0.04). The relationship between C-peptide and creatinine levels was established as statistically significantly negative, with the Spearman rank correlation coefficient (r = -0.338, p = 0.006). Also, the relationship between the level of urea and GFR was established as statistically significantly negative, with the Spearman rank correlation coefficient (r = -0.245, p = 0.02) and between GFR and b-CTx, with the Spearman rank correlation coefficient (r = -0.203, p = 0.01). In patients with type 2 diabetes, a statistically significant negative relationship was revelaed between the concentration of albumin and the level of glycemia, HbA1c and urea, with a rank correlation coefficient equal to (r = -0.244 p = 0.03), (r = -0.380, p = 0.001) and (r = -0.304, p = 0.04). Also, in patients with type 2 diabetes, a statistically significant positive relationship was found between the albumin level and GFR, with the Spearman rank correlation coefficient (r = 0.283, p = 0.01).

4.1.3. Assessment of the state of secretion of calcium-regulating hormones in type 2 Diabetes Mellitus

Vitamin D levels in patients with type 2 diabetes were statistically significantly lower than those in the control group (p <0.005). With an increase of the disease duration, the concentration of vitamin D decreases. Also, research results confirmed the presence of a relationship between the vitamin D level and C-peptide in the serum of patients with type 2 diabetes. Decrease in the ionized calcium levels in patients with type 2 diabetes may be associated with insulin resistance, which is indirectly indicated by this correlation (r = 0.299, p = 0.04). Obviously, this is due to the fact that insulin secretion in response to an

increased concentration of glucose in plasma is a Ca^{2+} dependent process, and since a decrease in the concentration of vitamin D also affects the concentration of calcium, this process, as a result, can affect the mechanisms of release insulin (Fig. 3).[24]

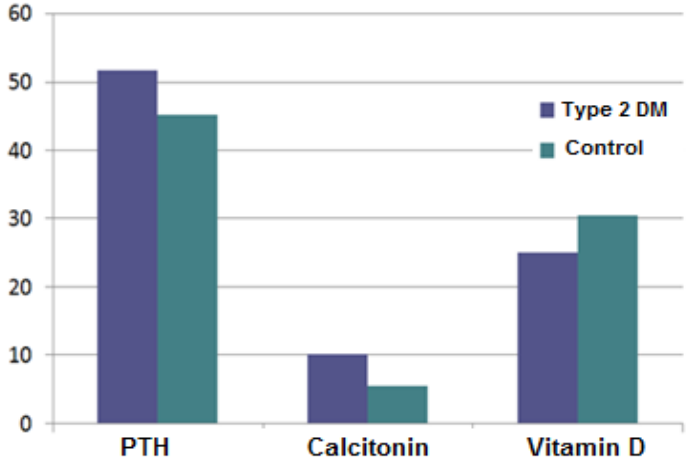

Figure 3. Changes in the exchange of PTH, CT, and vitamin D in patients with type 2 diabetes, and the control group

Vitamin D has a stimulating effect on the processes of bone formation and resorption. Data analysis revealed a significant positive correlation between the level of the bone formation marker P1NP and vitamin D ($r = 0.300$, $p = 0.002$).

There were less high serum calcitonin levels in patients with type 2 diabetes in comparison with those in patients with type 1 diabetes. Analysis showed that, depending on conditions of reproductive system, the serum calcitonin level in postmenopausal women with type 2 diabetes mellitus was statistically significantly higher than in premenopausal women ($p < 0.05$). Apparently, estrogen levels decrease in conditions of insulin resistance against a background of hyperinsulinemia, in which the concentration of serum calcium increases, which in turn

[24]Nada, A.M., Shaheen, D.A. Cholecalciferol improves glycemic control in type 2 diabetic patients: a 6-month prospective interventional study // Therapeutics and Clinical Risk Management, – 2017. 2017 (13), – p. 813-820.

stimulates the production of calcitonin, resulting in increased urinary calcium excretion.[25]

Serum PTH levels in patients with type 2 diabetes were statistically insignificant, within the reference values above the levels of the control group ($p < 0.05$), which may be associated with hyperinsulinemia. In men with type 2 diabetes, the level PTH was higher than in women (54.28 ± 2.57 and 50.18 ± 1.71 pg / dl).Research indicate the presence of a relationship between the PTH levels in patients with type 2 diabetes with Ca^{2+} and vitamin D ($r = -0.357$, $p = 0.003$) and ($r = -0.364$, $p = 0.001$). In patients with type 2 diabetes, the serum PTH level was also associated with the HOMA-IR index, as indicated by a weakly expressed relationship ($r = -0.273$, $p = 0.01$), which is possibly related to the effect of PTH on insulin release by the pancreas and its ability to affect the metabolism of insulin and glucose. Presumably, development of insulin resistance is associated with the effect of PTH on a decrease in the expression of the GLUT4 protein and the insulin receptor IRS-1. [26] Revealed significant inverse relationship of PTH concentration with the marker of bone formation P1NP ($r = -0.327$, $p = 0.002$) and direct with b-CTX ($r = 0.434$, $p = 0.001$).

An increase in the duration of the disease marks a statistically significant increase in the concentration of CT, according to Spearman's correlation coefficient($r = 0.430$, $p = 0.001$). A clear correlation is marked between the degree of diabetes compensation and the level of calcitonin, with a correlation coefficient ($r = 0.237$, $p = 0.04$). Also, in patients with T2DM, a positive, statistically significant relationship was established between the level of CT and creatinine ($r = 0.320$, $p = 0.006$) and a negative, moderately close connection between the level of CT and GFR, according to

[25] Afsar, B., Karaca, H. The relationship between insulin, insulin resistance, parathyroid hormone, cortisol, testosterone, and thyroid function tests in the presence of nephrolithiasis: a comprehensive analysis // Central European Journal Urology, – 2014. 67 (1), – p. 58-64.

[26]Szymczak-Pajor, I., Drzewoski, J., Sliwinska, A. The molecular mechanisms by which vitamin d prevents insulin resistance and associated disorders // International Journal of Molecular Sciences, – 2020. 21 (18), – p. 6644.

Spearman's correlation coefficient (r = -0.390, p = 0.001). A direct moderate connection between the serum concentration of PTH and CT was revealed, with a rank correlation coefficient (r = 0.536 p = 0.001). Patients with type 2 diabetes with a disease duration of more than ten years showed a moderate relationship between the CT level and the HOMA-IR index values, with the rank correlation coefficient (r = 0.615, p = 0.03).

4.1.4. Parameters of bone remodeling markers in assessing reparative osteogenesis processes in type 2 Diabetes Mellitus

In patients with type 2 diabetes, the levels of bone formation marker P1NP were comparable to the control group levels. The results of our study showed that the HbA1c level in patients with diabetes has a negative correlation with the marker of bone formation P1NP (r = -0.254, p = 0.01).

Bone resorption marker b-CTx level in patients with type 2 diabetes were higher compared to controls, which indicates an increase in bone resorption. The results obtained indicate an increase in the bone resorption marker b-CTx in 25% of patients with type 2 diabetes, 1.5 times higher in women than in men; as well as inconsistency of changes in the processes of bone remodeling, with a predominant change in the bone resorption rate, determined in 13% of cases with type 2 diabetes. Patients with type 2 diabetes had lower levels of bone resorption marker b-CTx and a relatively higher level of bone formation marker P1NP, which reflects less severity of changes in bone metabolism compared to patients with type 1 diabetes, regardless of age and duration of the disease.

In pre- and postmenopausal women with type 2 diabetes mellitus, the assessment of bone metabolism markers revealed a decrease in bone formation by 18.3%, as well as an increase in bone resorption by 5.8%; Also, in patients with diabetes mellitus, inconsistency of changes in the processes of bone tissue remodeling with a predominant decrease in bone formation in conditions of unchanged bone resorption, determined in 94.2% of cases, was revealed.

In type 2 diabetes, a negative relationship was found between the albumin level and the bone resorption marker b-CTx (r = -0.387, p =

0.001). Perhaps partly the inverse relationship between bone remodeling markers and kidney function is associated with the ability of the kidneys to eliminate them, thereby purifying the blood, and, therefore, an increase in the level of b-CTx is expected as GFR decreases. Thus, research results show that a decrease within the reference GFR levels is an independent risk factor for fracture in diabetes mellitus, which may be indicated by the negative correlation between GFR and serum b-CTx level ($r = -0.203$, $p = 0.01$) revealed in the study. An increased BMI was found in individuals with a low value of the serum bone resorption marker b-CTx. In type 2 diabetes, significant correlations were observed between the bone resorption marker b-CTx, body mass index (BMI) measure, and insulin concentration ($r = -0.163$, $p = 0.04$). Analysis of the data did not reveal a significant change in the ALP levels in patients with type 2 diabetes.

Research results revealed a less significant change in bone remodeling markers in patients with type 2 diabetes compared with type 1 diabetes. In type 2 diabetes, an increase in the activity of the bone resorption marker was determined less pronounced than in type 1 diabetes, while the formation marker did not differ from the levels of the control group. This indicates the multidirectional pathophysiological processes in diabetic osteopathy, depending on the type of diabetes mellitus.

4.2. Assessment of the state of mineral density of the bones of axial and appendicular skeleton in patients with type 2 Diabetes Mellitus based on Dual-energy Absorptiometry data

The average values of the T-score characterizing BMD in comparison with the control group in the spine and cervical femur are shown in the table (Table 2). Data on the state of reparative osteogenesis, in particular, on the BMD values measured by the DXA method in type 2 diabetes remain ambiguous.[27] The results of this study indicate a higher likelihood of developing osteoporotic fractures based on the results of changes in the T-score measured in

[27] Merlotti, D., Gennari, L., Dotta, F. [et al.] Mechanisms of impaired bone strengthin type 1 and 2 diabetes // Nutrition, metabolism, and cardiovascular diseases: NMCD, – 2010. 20 (9), – p. 683-690.

L1-L4 and femoral neck areas in patients with diabetes, at the same time, there was a lower risk of fracture development based on BMD measurements in the proximal femur (Figure 4).

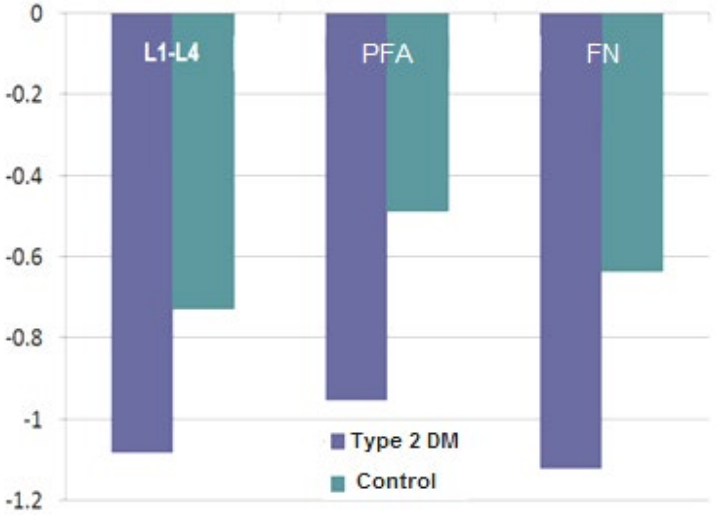

Figure 4. Changes in BMD by the T-score of the L1-L4 region, PFA and FN in patients with type 2 diabetes and control group

In the present research, the detectability of low BMD based on the results of changes in the T-score was in patients with type 2 diabetes in the L1-L4 area (44%; in the control group - 26%) and in the femoral neck (36%; in the control group). - 22%), at the same time, a lower risk of developing a fracture was revealed based on the results of a decrease in BMD in the proximal femur (31%; in the control group - 20%).These results were similar to those described at Chen Hl. et al. research.[28]Data from Sta R. et al. also indicate an increase in the frequency of detecting changes in BMD in type 2 diabetes in comparison with the general population.[29]

[28] Chen, G., Deng, C., Li, Y.P. TGF-β and BMP signaling in osteoblast differentiation and bone formation // Journal of Medical Systems, – 2019. 43 (4), – p. 1-8.

[29] Sta Romana, M., Li-Yu, J.T. Investigation of the relationship between type 2 diabetes and osteoporosis using Bayesian inference // Journal of Clinical Densitometry, – 2007. 10 (4), – p.386-390.

The contradictions according to the data in patients with type 2 diabetes given by different authors could probably be associated with the influence of complex pathogenetic mechanisms, including age, diabetes duration, severity treatment methods of type 2 diabetes. Although the connection between osteoporosis and type 2 diabetes remains not completely clarified, patients with it are exposed to a 2 times greater high of fractures.[30]

An isolated change either in the spine or in the femur according to absorptiometry was detected in 44% of patients with type 2 diabetes. Accordingly, in 18% of cases there were changes in both the spine and the femur. Thus, in the case of measuring BMD of only one area, some patients may be at risk of misdiagnosis. The results obtained indicate changes in the BMD of both the axial and appendicular skeleton in patients with type 2 diabetes. . Accordingly, a gradual decrease in the mineral density of the bone tissue of the spine occurs with an increase in the disease duration. Similar results were obtained when conducting a correlation analysis between the duration of type 2 diabetes and a decrease in the BMD T-score in the region of the proximal femur and femoral neck. Patients with type 2 diabetes mellitus have revealed a negative correlation, with a high statistical significance ($r = - 0.447$, $p = 0.001$) and ($r = - 0.434$, $p = 0.001$). Deviations in bone mineralization, the reactivity of which depended on the duration of the main process, was most clearly observed in the lumbar spine in men with type 2 diabetes compared with men in the control group.

In patients with type 2 diabetes, osteoporosis was detected only in 13% of cases and much more often, was diagnosed osteopenia. At the same time, in men with type 2 diabetes, a positiv correlation was found between the change in T scores for L1-L4 area and body mass index (BMI).In patients with type 2 diabetes, a statistically significant negative relationship was also revealed between the T scores for L1-L4 and b-CTX ($r = - 0.231$, $p = 0.02$).

[30] Montagnani, A. Osteoporosis and risk of fracture in patients with diabetes: an update / A. Montagnani, S. Gonnelli, M. Alessandri [et al.] // Aging Clinical and Experimental Research, – 2011. 23 (2), – p. 84-90.

In type 2 diabetes, a positive correlation was found between the level of C-peptide and the T-score for L1-L4 area ($r = 0.346$, $p = 0.02$) and the femoral neck ($r = 0.481$, $p = 0.002$). The existence of a positive relationship between BMI and bone mineral density is also confirmed by the data of other authors.[31]

The study at hand has shown a slightly different nature of changes in type 2 diabetes than in the control group. Thus, in the L1-L4 region and the proximal femur region, the BMD T-score in men did not differ statistically significantly from these indicators in women. However, in men with type 2 diabetes, the T-criterion changes in the femoral neck region were revealed to be less intense than in women ($p < 0.05$). In women, the BMD T-score in the femoral neck region was lowered in 46% of cases, in men - 21%. The results of the mean value of the T-criterion determined that in men with type 2 diabetes, compared with controls men, bone density in the studied regions was reduced significantly. This determinant was recorded to be most pronounced in the lumbar spine region in men with type 2 diabetes in comparison with men in the control group..

In type 2 diabetes, the number of the vertebral (L1-L4)osteoporosis cases in women significantly exceeded the changes in men (10% and 2%, respectively), as well as in the proximal and in the femoral neck (12% and 0%; 8% and 2% of cases). In men, osteopenia in the vertebral was detected in 37% of cases, in women - 51%; in the proximal femur region, osteopenia in type 2 diabetes was detected in 33% of men and 55% of women. In the femoral neck area, osteopenia in men with T2DM was detected in 20% of the cases, while in women - 70%.

In type 1 diabetes, biochemical markers of bone remodeling, as well as absoptiometry, are reliable, informative indicators of the state of bone metabolism. However, bone markers may be more significant in some cases for assessing the state of bone tissue, when

[31] Miazgowski, T. Serum adiponectin, bone mineral density and bone turnover markers in postmenopausal women with newly diagnosed Type 2 diabetes: a 12-month followup / T. Miazgowski, M. Noworyta-Ziętara, K. Safranow [et al.] // Diabetic Medicine, – 2012. 29 (1), – p. 62-69.

BMD measurement is poorly informative, in particular, in the initial stages of type 2 diabetes.

CAPTER V. DEVELOPMENT AND IMPLEMENTATION OF AN INTELLECTUAL DECISION SUPPORT SYSTEM FOR DIAGNOSTICS OF CLINICAL AND PATHOGENETIC FEATURES OF BONE REMODELING IN DIABETES MELLITUS BASED ON ARTIFICIAL HEALTH

The availability of a wide extent of laboratory and instrumental analysis methods necessitates processing a large range of data, which creates many difficulties for doctors at the stage of diagnosis and prognosis. In this regard, clinical trials observe an increased usage of intelligent decision support systems (DSS), tasked with helping clinicians understand the disease and plan its treatment.

The development of the direction of intelligent DSS in medical diagnostics is associated with the fact that the processes occurring in bioorganisms are very complex, characterized by a high degree of uncertainty, and, as a result, are difficult to formalize. Systems created based on classical mathematical methods (including the probability theory) in such cases are ineffective as a consequence of their large dimension and, at the same time, the low adequacy of the models embedded in them.

The results of the application of diagnostic systems using artificial intelligence methods revealed their wide capabilities and high efficiency in establishing links between the data of clinical, instrumental studies and the symptomatology of the disease in a complex, which makes it possible to consider such systems as a practical tool for a doctor in analyzing and understanding complex clinical data on a wide range. medical problems.

The foregoing allows us to conclude that, due to the increase in the efficiency of DSS used in clinical diagnostics, the latter are becoming more and more popular tools for developing individual approaches and adjustments for diagnosing and determining prognosis for a number of diseases, and, as a result, developing optimal treatment tactics due to more accurate and rapid analysis of

complex systemic, interrelated processes in the body, taking into account the fact that an active experiment on a living organism is excluded, and late diagnosis is fraught with the development of irreversible processes.

All this and the competence for self-learning determined the choice of neural networks as the basis for creating a decision support system in the diagnosis of clinical and pathogenetic features of bone remodelling in diabetes mellitus.

Based on the analysis of indicators affecting and related to bone metabolism, a specialized program based on artificial neural network (ANN) was developed and applied based on the results of a clinical study, which provides the clinician with the opportunity to make a right and timely decision on bone remodeling shifts to identify patients with destructive changes in bone tissue from among patients with diabetes.

The following describes the construction methodology, structure, main parameters of a diagnostic system that uses information on receipt from electronic medical records, generating a model for the development of the risk of osteoporosis in patients with diabetes in order to increase the level of validity of diagnostic decisions made by clinicians and reduce the incidence of diagnostic errors.

5.1. Methodology development for the construction and structure of a neural network model for risk development of osteoporotic changes in bone tissue in patients with Diabetes Mellitus

Based on the results of the above study, the task was set to create a model for a decision support system (DSS) in the field of diagnosing changes in bone remodeling in diabetes mellitus: to predict the values of bone metabolism parameters (total alkaline phosphatase, N-terminal propeptide of type I procollagen, C-terminal telopeptide product of type I collagen degradation, BMD T-score of the lumbar spine area, BMD Z-score of the lumbar spine area) in a particular patient, based on initial data (duration of diabetes, glycosylated hemoglobin values, glomerular filtration rate, ionized calcium, parathyrin , vitamin D, etc.).

The functioning of the proposed DSS is to cluster the indicators

necessary for screening patients with osteometabolic changes from the total number of patients with diabetes mellitus based on biomedical data. The mathematical model of this process is reduced to a Bayesian regularization algorithm with an introduced set of initial data, which helps to minimize errors in prediction for identifying patients at risk of developing diabetic osteopathy. The learning algorithm is used to tune a dynamically constructed neural network, which leads to minimization of errors by continuous training, until the optimal level of adequacy is achieved. The performance of the approach is verified by testing against benchmarking data constituting a test set used only to assess performance when training is complete. The performance of a neural network is measured according to the principle of determining the sensitivity to various training algorithms.

Modeling and implementation of a self-learning prediction system based on the apparatus of neural networks for intelligent DSS that diagnoses the clinical and pathogenetic features of bone remodeling in diabetes mellitus involves the development of a methodology consisting of: setting a problem, preparing input data, creating and training a network, completing learning and, if necessary, redesign based on the assessment of adequacy by an expert (clinician) and the actual diagnosis.

Building a self-learning forecasting system based on neural networks for intelligent DSS includes the following 5 stages:

Stage 1. Statement of the problem. This stage includes the formation of the goal of the functioning of the system, the format for presenting the predicted data and is the prerogative of clinicians.

Stage 2. Formation and structuring of input data. At this stage:

- analysis and selection of input parameters according to the criterion of maximum coverage of the diagnosed process;
- preliminary data processing, namely, their normalization.

The correctness of the selection of data, their structuredness noticeably affect the adequacy of the model, and, consequently, the accuracy of the diagnostic results.

Stage 3. Modeling and training of a neural network. At this stage, the clinician forms a training sample, determines the starting parameters

and initializes the neural network. The modeling process is reduced to the following stages: 3.1 Specifying the type of neural network; 3.2 Setting the training data supply scheme; 3.3 Enabling or disabling the normalization of input data in the range [-1,1] in order to unify the presentation of information within the neural network model and therefore relieves the need to control the ranges of numerical values of clinical data; 3.4 Determination of the optimal number of neurons, which largely depends on the problem being solved, is determined as a result of running test problems according to the principle from simple to complex; 3.5 Determination of the optimal number of neurons to which one input signal is supplied, which ultimately affects the quality of training. The neural network is trained automatically. The results are evaluated by a clinician. At the same time, it is important to avoid "overtraining" the model, since such a network remembers the test set well, but is unable to give an adequate answer to new data. Learning errors can result from the following factors:

- too few examples in the training sample.
- bias in the sample itself
- an insufficient number of training parameters in the sample itself, as a result of which the network cannot identify patterns.
- incorrect selection of the structure and parameters of the neural network.

Stage 4. Teaching, optimization and testing of the neural network. This stage is used to ensure the adequacy of the neural network model.

Stage 5. Creation of the artificial neural network interface. After the implementation of the four stages discussed above, the neural network is ready for the last stage - to work out the methods of interaction of the system with the user: the numerical form of data input and receiving an answer.

The above-described neural network modeling technique was used to construct a DSS to predict such indicators as markers of bone tissue remodeling, bone mineral density, for early diagnosis and assessment of the risk of developing diabetic osteopathy, i.e. indicators used to control diagnostic processes.

5.2 Practical implementation and evaluation of the results of using a neural network model for risk development of osteoporotic changes in bone tissue in patients with Diabetes Mellitus

The implementation of the neural network model was carried out using the MATLAB R2015b software package (subsystem Neural Network Toolbox).[32] For the convenience of users of the system, a visual interface was created (Fig. 5).

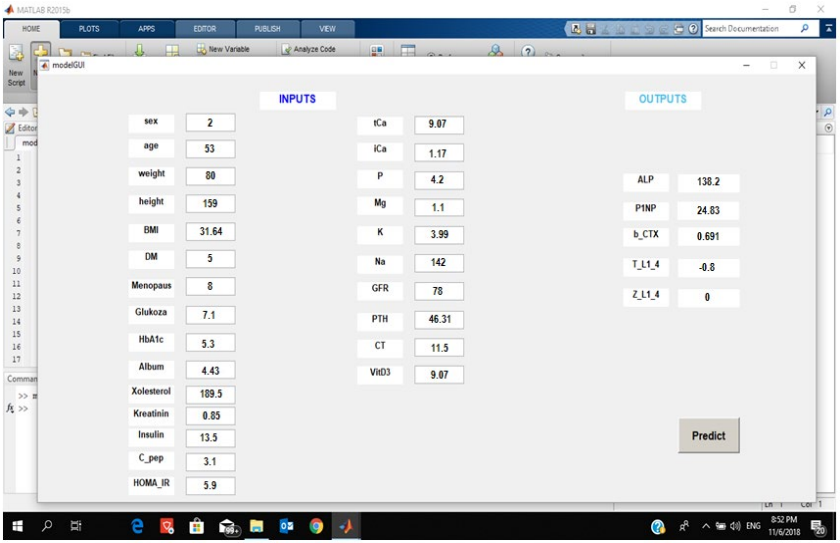

Figure 5. DECISION MAKING SUPPORT SYSTEM for clinical diagnosis and prognosis (program interface)

This visual interface allows the user to directly use the system. The interface was programmed using the GUIDE tool from MATLAB 8.6 (R2015b).

Thanks to this visual interface, the user can:

1. Enter all information about the problem.
2. Give a subjective assessment of each input variable.
3. Analyze the relationship between different input factors and how different combinations of input factors can change the system output.

[32]MathWorks. MATLAB, - 2017. URL: www.mathworks.com

4. Get the probability of any error (diagnostics) in question.

The input and output of the neural network during training were formed as follows: using research materials, as well as data from a clinical examination, a problem statement was formulated to create a model for DSS in diagnostics by predicting the values of indicators: ALP, P1NP, b-CTx, T-SD (L1-L4), Z-SD (L1-L4) in a particular patient, taking into account 25 measurements: gender, age, weight, height, BMI, type of diabetes mellitus, duration of menopause, glucose, HbA1c, albumin, cholesterol, creatinine, insulin, C-peptide, HOMA-IR, tCa, Ca^{2+}, P^{+}, Mg^{2+}, K^{+}, Na^{+}, Glomerular Filtration Rate, PTH, CT, vitamin D.

To analyze the relationship between the input variables of the neural network with markers of bone metabolism and BMD, the design was optimized based on the design of the study (used in the deterministic method).

The developed method for predicting the values of indicators characterizing the qualitative and quantitative state of the bone based on an analysis of a number of laboratory data is aimed at early detection of the risk of developing diabetic osteopathy. The analysis included modeling the relationships between the clinical and laboratory markers of diabetes mellitus, a number of hormones, indicators of the functional state of the kidneys, ionic blood balance and markers of bone remodeling, as well as the patient's X-ray absorptiometry. These variables, as well as factors such as age, gender, height, body mass index, duration of menopause in women, type and duration of diabetes mellitus, etc., were processed to determine their significance and included as input variables in the model. As output variables, BMD measured by X-ray absorptiometry and markers of bone remodeling were used.

For primary model training, laboratory and instrumental studies from 317 patients were used. With these settings, the input vectors and output vectors are spontaneously divided into three sets in a certain way: 70% is used for training, 15% is used to test the data that the network generalizes when training stops before retraining, the last 15% is used as a completely independent test of network

generalization. The first assessment of the system was carried out by comparing the automatic diagnostic algorithm with known examples of cases of bone remodeling disorders in diabetes mellitus. As a result of this assessment, some adjustments were made to the rules to improve the efficiency of the system. The topology of the model consisted of an input layer, a hidden layer, and an output layer. A model with final parameters was trained using data from 80% of patients from a randomly selected database. Data from the remaining 20% of patients were used to verify the results. The average value of the absolute measurement error in these patients was 2.09%. As a result, some adjustments were made to the model settings to increase its adequacy. Further training was achieved during its practical operation. The learning process continued until errors were reduced for all examples and stopped at the moment when the error in the control sample began to increase.

The developed decision support system (DSS) was tested in clinical practice as a tool to help clinicians diagnose changes in metabolic processes in bone tissue in 28 patients with type 1 and 2 diabetes, between 40 and 70 years of age. As a result, 7 of them were diagnosed with changes indicating diabetic osteopathy.

The practical effectiveness of the constructed mathematical model and the intellectual DSS developed on its basis is proved, which made it possible to predict the state of BMD and the values of bone remodeling markers for diabetes based on an analysis of a number of laboratory parameters. DSS based on biomedical data has clustered the indicators necessary for screening patients with osteometabolic changes from the total number of patients with diabetes.

The application of the developed intellectual DSS in the educational process is proposed due to the capabilities to demonstrate the relationship between various factors and how this affects the diagnosis.

This study allowed us to construct a diagnostic algorithm that allows stratification of patients with bone metabolism disorders in diabetes mellitus. The results of the analysis revealed indicators that are informative in diabetes mellitus, which indirectly indicate the

state of bone remodeling, which allows one to determine the relatively early manifestations of diabetic osteopathy in the absence of direct information about the state of bone mineral density and markers of bone remodeling. An intelligent clinical decision support system has been built aimed at early diagnosis of bone remodeling disorders in patients with diabetes.

Artificial neural networks demonstrate the ability to model complex relationships between variables to identify groups at risk of developing osteoporosis or fractures from the general population of diabetic patients. A comparative analysis of this approach with the traditional ones showed that the values obtained using the neural network model of diagnosis reproduce the picture of a clinical study with a high degree of adequacy, which makes it possible to build a diagnostic algorithm for stratification of patients with disorders of bone metabolism in the setting of diabetes. This study demonstrates the usefulness of the developed method based on the construction of intelligent DSS for studying the relationship between the input variables associated with diabetes mellitus and bone mineral density, as well as markers of bone remodeling.

An individual approach to diagnosis using hybrid technologies for processing large amounts of data, increasing the efficiency of prediction within the framework of personalized medicine can give an individual prognosis for a particular patient using ANN.

Analysis suggests that artificial neural networks can also be applied at the decision-making level in the field of forecasting. We found that ANN-based solutions applied at the decision-making level suggest the prospect of its use in situations involving complex, unstructured or limited information. Timely implementation of the developed methodology for the comprehensive diagnosis of metabolic disorders of bone stomp in diabetes will predict the progression of this complication and reduce the risk of low-traumatic fractures.

CONCLUSIONS

1. In diabetes mellitus type 1 and 2, bone remodeling is significantly associated with compensation, determined by the level of glycogemoglobin, duration of diabetes mellitus, and features of impaired insulin secretion ($p < 0.05$). These predictors can have a negative effect on reparative osteogenesis [3,4,9,10,13,14,15, 21,22,32,34,35].
2. Referenced values of total calcium, contrasting with low concentrations of ionized calcium in blood serum. A distinctive characteristic of some patients with diabetes with secondary hyperparathyroidism is the established violation of mineral homeostasis with a decrease in serum magnesium values. An increase in the concentration of PTH in diabetes mellitus is associated with structural and functional bone changes with a predominance of resorptive processes, which confirms a direct correlation between the level of PTH and b-CTx [12,17,25,41, 46,49,54].
3. The results of the screening showed a decrease in the marker of bone formation PINP in patients with T1DM by 16%, with T2DM - by 12% compared with the control group. At the same time, in 32% of patients with T1DM and 25% with T2DM, an increase in the concentration of b-CTx marker of bone resorption is noted, in women 1.5 times more than men; in 28% of cases with CDT1 and in 13% of CDT2, inconsistency of bone remodeling processes was revealed, with a predominant change in the concentration of bone resorption marker [1,2,5,6,8,42,48,57].
4. In type 2 diabetes, a less pronounced increase in the activity of the biochemical marker of osteoresorption b-CTx than in type 1 diabetes, while the level of P1NP is comparable to the control values. In diabetes mellitus type 1, on the contrary, inhibition of bone formation processes was revealed in comparison with SDT2 and control, and activation of osteoresorption processes. This allows us to state the multidirectionality of the pathogenetic mechanisms of the progression of osteopathy in the initial stages of type 1 and type 2 diabetes [7,11,19,23,30,33,65].

5. There was no significant change in the values of total alkaline phosphatase in serum, which indicated its low information content as a bone marker, due to the fact that a number of metabolic changes affecting this indicator were detected in patients with diabetes [16,18,26,28,37].
6. When studying osteometabolism in patients with type 1 diabetes, a decrease in BMD was determined more often ($p < 0.05$), compared with type 2 diabetes, and in 50% of cases it was diagnosed as osteoporosis. In patients with type 2 diabetes, a decrease in BMD was detected less frequently, only 13% of cases were diagnosed with osteoporosis and much more often, osteopenia was noted. Deviations in bone mineralization due to the duration of the main process were detected in both groups (type 1 diabetes: $r = -0.239$, $p = 0.03$; type 2 diabetes: $r = -0.275$, $p = 0.008$). This determinant was clearly traced in the lumbar spine in men with type 1 and type 2 diabetes [29,38,43,52,58, 59,60,70].
7. In type 1 diabetes, the biochemical markers of bone remodeling, as well as x-ray absorptiometry, are reliable, informative indicators reflecting the state of bone metabolism. Bone remodeling biomarkers can be of great importance in some cases, for assessing the state of bone tissue, when the measurement of BMD is not sufficiently informative, in particular, in the initial stages of type 2 diabetes [27,53,61,62,66,70].
8. Markers for bone remodeling adequately predict early changes in bone homeostasis and are cost effective. The most informative marker of osteoremodeling in patients with diabetes is b-CTx. The combined use of x-ray absorptiometry and markers of bone remodeling can improve the objectivity of assessing the state of bone tissue in this category of patients [24,31,44,56,66,69].
9. In order to personalize the diagnosis of diabetic osteopathy, a specialized biotechnological computer forecasting program has been developed and applied, based on one of the varieties of intelligent decision support systems using artificial neural networks, which allows us to analyze the results of a number of

laboratory indicators to predict the parameters characterizing the qualitative and quantitative state bones, to identify patients with possible alteration of bone metabolism among patients with diabetes [20,39,40,45,47,50,51,55,63,64,67,68].

PRACTICAL RECOMMENDATIONS

1. The frequent occurrence and specificity of the manifestation of diabetic osteopathy have determined the need to include an assessment of the state of bone tissue in a unified examination program for patients with diabetes.
2. It is rational to carry out stratification of osteometabolic disorders in patients with diabetes mellitus using an integrated approach, which, along with densitometric research, includes the introduction into clinical practice of specific and sensitive biomarkers that reflect the processes of bone formation and resorption, which significantly improves the assessment of bone turnover.
3. Persons with type 1 diabetes mellitus are most in need of performing X-ray absorptiometry to solve the problem of preventing and initiating osteopathy therapy. Absorptiometry is a poorly informative method for diagnosing the initial manifestations of diabetic osteopathy in patients with type 2 diabetes mellitus, due to the fact that it does not record property changes in all circumstances bones.
4. The levels of ionized calcium, phosphate, parathyroid hormone and vitamin D should be regularly measured in individuals with GFR approaching 60 ml / min / 1.73 m^2 or more than 120 ml / min / 1.73 m^2 (category G1, G2 or G3).
5. Determination of biomarkers of reparative osteogenesis - ALP and PINP is not expressive for the diagnosis of diabetic osteopathy. The most informative laboratory marker that identifies osteometabolism disorders in patients with diabetes is the level of b-CTx.
6. Determination of biomarkers of reparative osteogenesis - ALP and PINP is not expressive for the diagnosis of diabetic osteopathy. The most informative laboratory marker that identifies osteometabolism disorders in patients with diabetes is the level of b-CTx.

The following list of scientific articles published on the topic of the dissertation

1. Сафарова С.С. Постменопаузальный метаболизм костной ткани у женщин при сахарном диабете 2 типа // – Bakı: Azərbaycan Təbabətinin Müasir Nailiyyətləri, – 2008. № 3, – s. 86-90.
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8. Сафарова С.С. Остеопороз при сахарном диабете 2 типа у женщин в постменопаузе // – Bakı: Azərbaycan Metabolizm Jurnalı, – 2015. № 4, – s. 19-22.
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LIST OF CONDITIONAL ABBREVIATIONS

$25(OH)D_3$	- calcidiol, vitaminD
ALP	- alkaline phosphatase
ANN	- Artificial neural networks
BMD	- Bone Mineral Density
b-CTx	- C-terminal telopeptide of type I collagen (marker of bone resorption)
CT	- calsitonin
Ca^{2+}	- ionised calcium
DDS	- Decision Support System
DM	- diabetes mellitus
DO	- diabetic osteopathy
DXA	- Dual-energy X-ray absorptiometry
FN	-femoral neck
GFR	- Glomerular filtration rate
HbA1c	- glycosylated hemoglobin
K^+	- potassium
L1-L4	- spine area
Mg^{2+}	- magnesium
Na	- sodium
OP	- osteoporosis
P^+	- inorganic phosphate
P1NP	- Procollagen type I N-terminal propeptide (marker of bone formation)
PFA	- proximal femur area
PTH	- parathyroid hormone
T-score	-T-score BMD
tCa	- total calcium
Z-score	- Z- score BMD

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