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# Artificial neural networks in predicting impaired bone metabolism in diabetes mellitus

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**ABSTRACT**

Growing incidence of diabetes mellitus (DM), given significant socioeconomic consequences that low-trauma fractures entail, determines a need to improve diagnostic standards and minimize the risk of medical errors, which will reduce costs and contribute to better treatment outcomes in this category of patients.

**Aim.** To assess diagnostic capabilities of the method based on the use of an artificial neural network (ANN) for predicting changes in reparative osteogenesis in diabetes mellitus.

**Materials and methods.** A single-center, one-stage, cross-sectional study included 235 patients with type 1 and type 2 diabetes mellitus and 82 persons of the control group (the total of 317 patients). Further, the obtained data were processed using the MATLAB software to develop an ANN with a training (80%) and test (20%) set. The ANN model was trained by optimizing the relationship between a set of input data (a number of clinical and laboratory parameters: gender, age, body mass index, duration of diabetes mellitus, etc.) and a set of corresponding output data (variables reflecting the state of bone metabolism: bone mineral density, markers of bone remodeling).

**Results.** The ANN-based algorithm predicted estimated values of bone metabolism parameters in the examined individuals by generating output data using deep learning. Machine learning was repeated until the error was minimized for all variables. The accuracy of the validation test to predict changes in bone metabolism based on patient data was 92.86%.

**Conclusion.** The developed ANN-based method made it possible to design an auxiliary tool for stratification of patients with changes in bone metabolism in diabetes mellitus, which will help reduce healthcare costs, speed up the diagnosis due to fast data processing, and customize treatment for this category of patients.

**Keywords:** diabetes mellitus, osteopathy, neural networks

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**Conformity with the principles of ethics.** All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Azerbaijan Medical University (Protocol No. 02/14 of 12.10.2016).

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# Искусственные нейронные сети в прогнозировании нарушений метаболизма костной ткани при сахарном диабете

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**РЕЗЮМЕ**

По мере роста заболеваемости сахарным диабетом, и учитывая существенные социально-экономические последствия, которые влекут за собой низко травматические переломы, возникает необходимость в коррекции стандартов диагностики и сведении к минимуму риска медицинских ошибок, что позволит снизить затраты и добиться лучших результатов в лечении данной категории больных.

**Цель:** оценка диагностических возможностей метода, основанного на применении искусственной нейронной сети (ИНС) в качестве инструмента прогнозирования изменений процессов репаративного остеогенеза при сахарном диабете.

**Материалы и методы.** Выборка была сформирована в ходе исследования 235 пациентов с сахарным диабетом 1-го и 2-го типа и 82 лиц контрольной группы (всего 317 человек). Далее набор полученных данных был обработан программным обеспечением MATLAB для построения ИНС с обучающим (80%) и тестовым (20%) набором. Модель ИНС обучалась путем оптимизации взаимосвязи между набором входных данных (показатели: пол, возраст, индекс массы тела, длительность диабета и т.д.) с набором соответствующих выходных данных (переменных, отражающих состояние костного метаболизма: минеральную плотность кости, маркеры костного ремоделирования).

**Результаты.** Базируемый на ИНС алгоритм с высокой точностью способен спрогнозировать значения показателей метаболизма костной ткани обследованных пациентов, сгенерировав выходные данные с помощью глубокого обучения. Процесс машинного обучения повторялся до тех пор, пока не минимизировалась ошибка для всех переменных. Точность валидационного теста для прогнозирования изменения костного метаболизма на основе данных пациентов составила 92,86%.

**Заключение.** Применение аппарата искусственных нейронных сетей позволило сконструировать вспомогательный инструмент для стратификации пациентов с сахарным диабетом, имеющих нарушения репаративного остеогенеза, что может помочь сократить затраты на обследование, ускорить диагностику за счет быстрого процесса обработки данных и скорректировать процесс лечения данной категории пациентов.

**Ключевые слова:** сахарный диабет, остеопатия, нейронные сети

**Конфликт интересов.** Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

**Источники финансирования.** Автор заявляет об отсутствии финансирования исследования при проведении исследования.

**Соответствие принципам этики**. Все пациенты подписали информационное согласие на участие в клиническом исследовании. Исследование одобрено локальным этическим комитетом Азербайджанского медицинского университета (протокол № 02/14 от 12.10.2016).

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## INTRODUCTION

Growing incidence of diabetes mellitus (DM), given significant socioeconomic consequences that low-trauma fractures entail, determines a need to improve diagnostic standards and minimize the risk of medical errors, which will reduce costs and contribute to better treatment outcomes in this category of patients. Metadata indicate higher incidence of bone fractures in patients with type 1 and type 2 DM compared with the general population [1–3]. Methods commonly used to diagnose bone diseases in DM include analysis of hormonal and electrolyte homeostasis, bone remodeling markers, and dual-energy X-ray absorptiometry (DXA). All these methods have certain limitations. In addition, diagnosis is complicated by the peculiarities of the pathogenesis of DM and is aggravated by impaired fracture healing [4].

Traditionally, the use of diagnostic methods can be minimized by data mining techniques to identify and analyze hidden information within data to better predict results and accelerate and personalize the diagnosis of bone changes in DM. These techniques include artificial intelligence, statistics, machine learning, and visualization [5].

Decision support systems (DSS) based on artificial neural networks (ANN) are effectively used in clinical diagnostics, which is why these tools are becoming more and more popular for developing individualized diagnostic approaches and predicting a number of diseases, and, as a result, developing an optimal treatment strategy due to a more accurate and rapid analysis of interrelated processes in the body [1, 5]. Nevertheless, ANN has never been used in predicting the risk of bone fractures in DM based on routine clinical and laboratory tests.

The **aim** of the study was to assess the diagnostic capabilities of the method based on the use of ANN as a tool for predicting changes in reparative osteogenesis in DM.

## MATERIALS AND METHODS

A single-center, one-stage, cross-sectional study included 235 patients with type 1 and type 2 DM and 82 persons of the control group (the total of 317 patients).The study was conducted in 2015–2017 at the Department of Endocrinology of the Educational and Therapeutic Clinic at Azerbaijan Medical University. All parameters were evaluated once.

The exclusion criteria were: bone fractures in the past medical history, treatment for osteoporosis in the medical history, endocrine diseases, non-diabetic liver and kidney diseases, and final stages of diabetic nephropathy (stage IV–V).

For all patients, we indicated sex, age, duration of DM, body mass index (BMI) and measured bone mineral density (BMD), which was defined by T- and Z-scores in the lumbar spine (T–SD L1–4; Z–SD L1–4) and femoral neck (T–SD FN; Z–SD FN) by DXA. The levels of glycated hemoglobin (HbA1c), serum bone remodeling markers (alkaline phosphatase (ALP), procollagen type I N-terminal propeptide (PINP), and beta-C-terminal telopeptide (b-CTx)), parathyroid hormone (PTH), calcitonin (CT), vitamin D3 (25 (OH) D), and insulin were determined. We measured HOMA-IR index, glomerular filtration rate (GFR), and albumin. The ionic balance in the blood was also determined: total calcium (tCa) and ionized calcium ($Ca^{2+}$), phosphorus ($P^{+}$), magnesium ($Mg^{2+}$), potassium ( $K^{+}$), and sodium ($Na^{+}$).

*Statistical analysis.* Following the previous clinical and laboratory research, we developed an ANN-based method to predict and assess the state of bone tissue in DM. The data were collected from individuals with type 1 and type 2 DM and processed by variational mathematical methods of statistical analysis using BioStatPro 6.2.2.0 software. Next, the data set was processed by MATLAB software (Attaway, 2022). The train – test split was 80% / 20%, respectively, with subsequent validation and normalization. The ANN model was trained by optimizing the relationship between a set of input data (a number of clinical and laboratory parameters: sex, age, BMI, duration of DM, etc.) and a set of corresponding output data (variables reflecting the state of bone metabolism: BMD, markers of bone remodeling). The accuracy of the validation test for predicting changes in bone metabolism in relation to the training data was 92.86%.

*Data set development.* The study was single-center, transverse and included the results of the examination of 98 patients with type 1 DM and 137 patients with type 2 DM. The control group included 82 individuals. The characteristics of all 317 patients are shown in Table.

Table

**Clinical characteristics of patients, *M* (95% CI)**

| Parameter | Type 1 DM, *n* = 98 | Type 2 DM, n = 137 | Controls, n = 82 |
|---|---|---|---|
| Age, years | 55.8 (54.4–57.3) | 58.4 (57.3–59.5) | 55.9 (54.2–57.7) |
| Sex male / female | 41/57 | 52/85 | 39/43 |
| BMI, kg / m$^2$ | 26.1 (25.6–26.5) | 30.0 (29.4–30.6) | 28.7 (27.9–29.5) |
| DM duration, years | 16.6 (15.4–17.8) | 8.1 (7.2–8.8) | – |
| HbA1c, % | 7.4 (7.1–7.8) | 7.5 (7.2–7.8) | 4.9 (4.7–5.0) |
| C-peptide, ng / ml | – | 4.3 (1.64–7.4) | 3.7 (3.1–4.7) |

Table (continued)

| Parameter | Type 1 DM, *n* = 98 | Type 2 DM, n = 137 | Controls, n = 82 |
|---|---|---|---|
| HOMA-IR | – | 8.6 (7.5–9.6) | 2.8 (2.4–3.1) |
| tCa, mg / dl | 9.3 (9.1–9.5) | 9.4 (9.3–9.5) | 9.5 (9.4–9.7) |
| $Ca^{2+}$, mmol / l | 1.09 (1.07–1.11) | 1.07 (1.04–1.08) | 1.13 (1.11–1.15) |
| $P^{+}$, mg / dl | 5.4 (5.2–5.6) | 5.0 (4.8–5.2) | 5.1 (4.9–5.2) |
| $Mg^{2+}$, mg / dl | 1.52 (0.69–2.45) | 1.54 (1.45–1.63) | 1.75 (1.61–1.89) |
| $K^{+}$, mg / dl | 4.4 (3.1–5.9) | 4.3(4.1–4.4) | 4.3 (4.1–4.5) |
| $Na^{+}$, mmol / l | 142.2 (140.6–143.8) | 140.9 (139.6–142.3) | 138.5 (137.2–39.6) |
| Creatinine, mg / dl | 0.85 (0.81–0.89) | 0.79 (0.76–0.82) | 0.75 (0.72–0.78) |
| GFR, ml / min / 1.73 $m^2$ | 86.7 (83.1–90.4) | 88.5 (85.4–91.5) | 95.2 (91.8–98.6) |
| Albumin, g / dl | 4.2 (4.1–4.3) | 4.3 (4.1–4.4) | 4.5 (4.3–4.6) |
| PTH, ng / dl | 51.16 (47.17–55.13) | 51.69 (48.82–54.56) | 45.09 (40.38–49.79) |
| Vitamin $D_3$,ng / ml | 24.09 (21.32–26.86) | 25.12 (22.98–27.28) | 30.41 (26.95–33.86) |
| CT, pg / ml | 12.07 (9.75–14.38) | 10.23 (8.84–11.62) | 5.5 (4.19–6.84) |
| ALP, UI / l | 118.3 (110.1–126.4) | 122.2 (116.2–128.1) | 123.5 (113.8–133.2) |
| P1NP, ng / ml | 40.58 (37.18–43.98) | 42.08 (39.81–44.35) | 47.09 (42.82–51.35) |
| b-CTX, ng / ml | 0.525 (0.468–0.582) | 0.495 (0.456–0.533) | 0.424 (0.383–0.466) |
| T-score (T–SD L1–L4) | –1.4 (–2.2–(–0.9)) | –1.08 (–1.3; –0.8) | –0.73 (–1.1; –0.3) |
| T-score (T–SD FN) | –1.15 (–1.9–(–0.7)) | –1.12 (–1.3; –0.8) | –0.64 (–1.0; –0.2) |

In this study, we modeled ANN which included the following input data: sex, age, weight, height, BMI, duration of DM, duration of menopause, blood glucose, HbA1c, albumin, creatinine, insulin, C-peptide, HOMA-IR index, tCa, $Ca^{2+}$, $P^{+}$, $Mg^{2+}$, $K^{+}$, $Na^{+}$, GFR, PTH, CT, vitamin $D_3$. Output data included the following Parameters: ALP, P1NP, b-CTX, T–SD L1–4, Z–SD L1–4. The input value was converted to the output value according to the activated functions shown in Fig. 1.

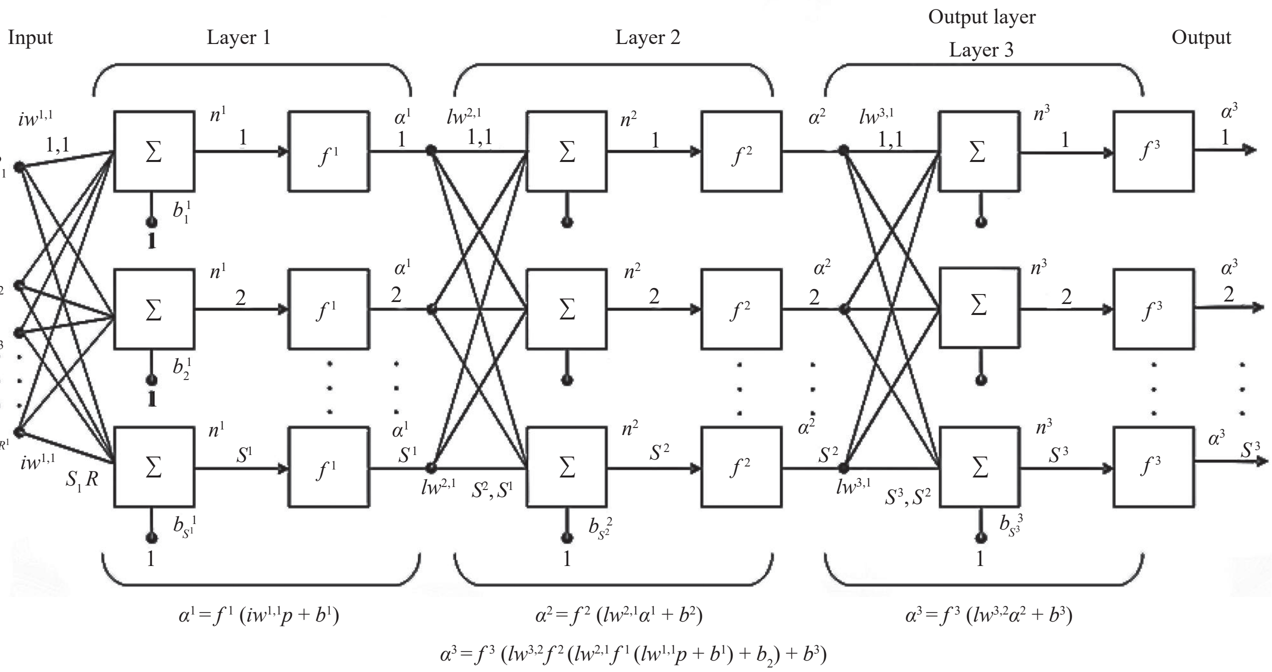


Fig. 1. Multilayer neural network

The proposed method for constructing a ANN-based self-learning predictive system for intelligent DSS that diagnoses clinical and pathogenic features of reparative osteogenesis in DM encompasses the following steps: setting a problem, preparing input data, dividing data into training and test sets, building and training a neural network including a multilayer perceptron (MLP) model, forming a training sample supply scheme that determines a set of input elements and corresponding output neurons, additional training, and, if necessary, redesigning based on an assessment of the diagnosis accuracy. The elements of the input signals were normalized (in the range from –1 to 1); the input synapse was supplied not with the parameter value, but with its equivalent, recalculated by the formula:

$$NX_i(t) = \frac{X_i(t) - X_i^{\min}}{X_i^{\max} - X_i^{\min}},$$

where $X_i(t)$ is the original signal, $NX_i(t)$ is the received normalized signal, $X_i^{\min}$ and $X_i^{\max}$ are the minimum and maximum values for the input parameter intervals in the field supplied to synapse *i*.

The Bayesian Regularization algorithm (trainer) was used to train the ANN. The backpropagation learning algorithm was based on gradient descent search algorithms that allow the correlation weight to be modified to optimize the model. The test set was used for validation grading at the end of each training stage and testing at the end of training to get an idea of how well the model coped with the problem. The initial training of the model was carried out using the data of laboratory and instrumental studies of 317 patients listed above (Table). After the implementation of the above stages, the ANN was ready for the last stage, which was predicting biomarkers of reparative osteogenesis and BMD, which are informative for early diagnosis of impaired bone remodeling in DM, i.e. parameters used to control diagnostic processes.

*Practical implementation of a neural network model for assessing the risk of osteoporotic changes in bone tissue in diabetes mellitus.* The ANN was constructed using MATLAB software (Attaway, 2022) [6], and a visual interface was developed using the GUIDE tool to make it convenient for clinicians (Fig. 2).

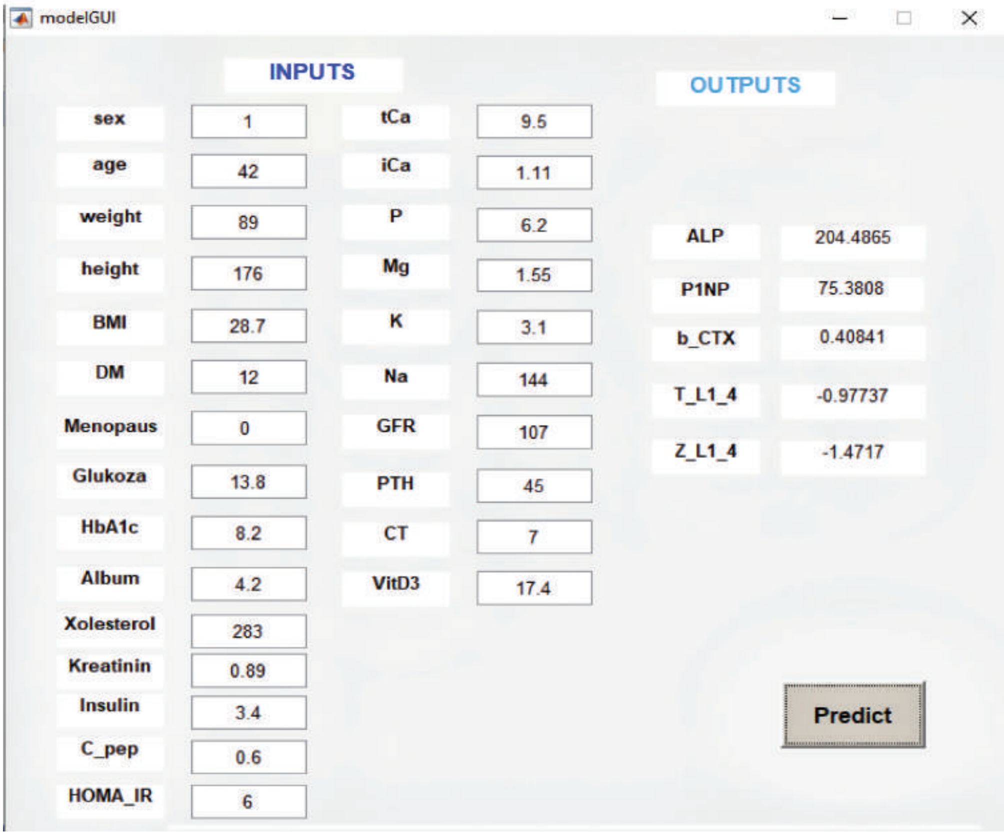


Fig. 2. Example of a calculation carried out by the ANN

## RESULTS

In type 1 DM, both biochemical bone remodeling markers and DXA are informative indicators reflecting the state of bone metabolism. Biomarkers of bone remodeling can be of great importance in assessing the state of bone tissue, when the measurement of BMD is not informative enough, in particular, at the initial stages of type 2 DM (the data are given in Table). Due to the current situation, we applied the ANN to patient data to determine the accuracy of predictions. The data from the examination of 317 patients were analyzed, of which 80% and 20% were used as training and test sets, respectively. An ANN-based DSS model was created to predict the state of bone metabolism in a particular patient with DM based on the input data: duration of DM, HbA1c values, vitamin $D_3$, etc. While developing DSS, some adjustments were made to the model settings to improve its adequacy. Further training was conducted during its practical operation. The learning process continued until the errors in all variables were minimized, and it was stopped at the moment when the error in the control sample began to increase. The accuracy of the validation test for predicting changes in bone metabolism in relation to the training data was 92.86%. The ANN-based algorithm predicted with high accuracy the values of the bone metabolism parameters in the examined individuals, generating output data via implementation of the hidden level (Fig. 3).

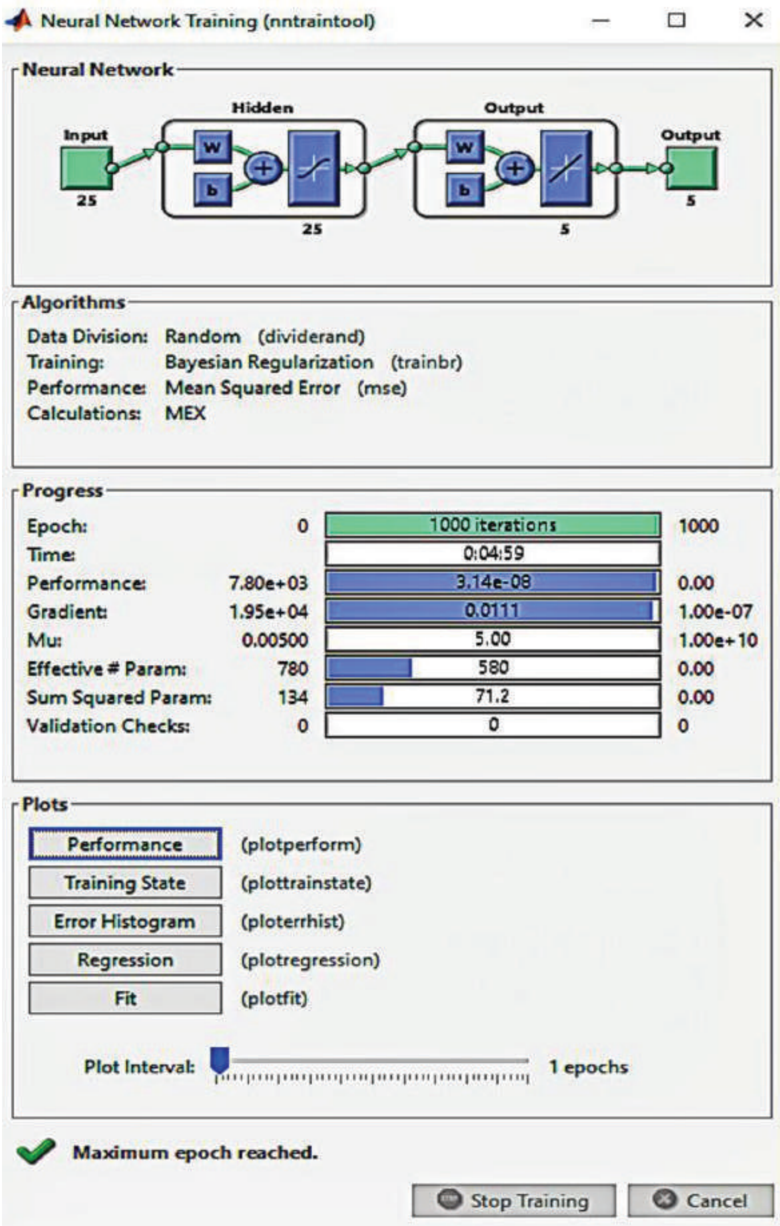


Fig. 3. ANN operation scheme

The results of the study showed the effectiveness of the developed method based on the construction of an intelligent DSS in identifying the relationships between bone metabolism parameters and a number of factors associated with DM.

## DISCUSSION

Metabolic disorders caused by DM can negatively affect BMD, increasing the likelihood of low-trauma fractures which can lead to disability or death [1, 2]. Predicting a risk of fractures in DM patients is more challenging because the DXA method and the FRAX fracture risk calculator underestimate the risk of fractures in DM patients due to higher BMD [4]. Under these conditions, biomarkers of reparative osteogenesis can show the quality of bone tissue. However, high cost of these methods and low availability of appropriate equipment in the regions of Russia can complicate early diagnosis. A possible solution to this problem is introducing advanced computing technologies that can be integrated into the diagnosis and prediction of changes in reparative osteogenesis. At the same time, it should be kept in mind that in each individual case, the doctor deals with a pathological process with individual characteristics, both known and unknown [1]. The use of artificial intelligence methods reveals their wide possibilities and high efficiency in establishing links between data of clinical and instrumental studies and symptoms of the disease, which makes it possible to consider such systems as a practical tool for the doctor in the analysis and processing of complex clinical data.

The effectiveness of applying the ANN mathematical apparatus in clinical practice is justified by a wide range of its predicting capabilities based on processing of large, interconnected, multi-parametric arrays of medical data, which eliminates the need for expensive diagnosis and prevents improper treatment [1, 7]. Data classification and clustering algorithms, modeled in this study using ANN, showed efficiency and good capability to predict the presence or absence of low-trauma fracture risk in DM.

## CONCLUSION

The developed method based on the mathematical apparatus of ANN made it possible to design an auxiliary tool for stratification of DM patients with changes in bone metabolism, which will help reduce healthcare expenses, speed up diagnosis through fast data processing, and adjust the treatment process for such patients.

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