

# Osteoporosis risk prediction in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

**The aim of the study** is to optimize the method of osteoporosis (OP) risk prediction in patients with type 2 diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD) by using specific and sensitive diagnostic criteria.

**Materials and methods.** The design of the risk prediction method of the OP development in patients with type 2 DM and NAFLD was conducted by using the most significant diagnostic indicators. The calculation method of the OP risk probability in patients with type 2 DM and NAFLD was developed by using statistical methods of multivariate factor analysis and logistic regression. The method was evaluated in the Clinic of the State Institution "V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine" in 51 patients, whose average age was  $63.2 \pm 0.99$  years with the average duration of type 2 DM  $7.84 \pm 0.68$  years.

**Results.** In order to establish the diagnostic accuracy of the proposed method of the OP development risk prediction in patients with type 2 DM and NAFLD, the data on all examined patients were analyzed and the following diagnostic characteristics were obtained: the sensitivity of the developed method is 88.23 %, the probability of a negative result with a negative prognosis, or the specificity of the developed method, is 70.58 %; the accuracy (the proportion of true-positive results and true-negative results) is 82.35 %, the odds ratio is 18.37.

**Conclusions.** The proposed OP risk prediction method in patients with type 2 DM and NAFLD allows obtaining reliable predictions with sufficient accuracy for practical use. The application of this method will serve beyond assessing the risk of OP development, but also to provide timely treatment with drugs aimed to prevent the OP progression and to avoid complications, thereby reducing disability and influencing the quality of life.

## Key words:

osteoporosis, type 2 diabetes mellitus, non-alcoholic fatty liver disease, diagnosis.

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## Прогнозування ризику розвитку остеопорозу в пацієнтів із цукровим діабетом 2 типу та неалкогольною жировою хворобою печінки

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**Мета роботи** – оптимізація способу прогнозування ризику розвитку остеопорозу (ОПЗ) у пацієнтів із цукровим діабетом (ЦД) 2 типу та неалкогольною жировою хворобою печінки (НАЖХП) шляхом використання специфічних і чутливих діагностичних критеріїв.

**Матеріали та методи.** Спосіб прогнозування ризику розвитку ОПЗ у пацієнтів із ЦД 2 типу та НАЖХП розробили, застосовуючи найбільш значущі діагностичні показники. Спосіб розрахунку ймовірності ризику розвитку ОПЗ у пацієнтів із ЦД 2 типу та НАЖХП розроблений із використанням статистичних методів багатовимірної факторного аналізу та логістичної регресії. Спосіб апробовано у клініці ДУ «Інститут проблем ендокринної патології імені В. Я. Данилевського Національної академії медичних наук України» на 51 пацієнті, середній вік яких становив  $63,2 \pm 0,99$  року з тривалістю ЦД 2 типу в середньому  $7,84 \pm 0,68$  року.

**Результати.** Для встановлення діагностичної точності запропонованого способу прогнозування ризику розвитку ОПЗ в осіб із НАЖХП і ЦД 2 типу проаналізували дані всіх пацієнтів та отримали такі діагностичні характеристики: чутливість розробленого способу становить 88,23 %, ймовірність негативного результату при негативному прогнозі, тобто специфічність розробленого способу – 70,58 %, точність (частка істинно позитивних та істинно негативних результатів) – 82,35 %, відношення шансів – 18,37.

**Висновки.** Розроблений спосіб прогнозування ризику розвитку ОПЗ у пацієнтів із ЦД 2 типу та НАЖХП дає можливість отримувати вірогідні прогнози з точністю, що достатня для практичного застосування. Використання цього способу дає змогу не тільки оцінити ризик розвитку ОПЗ, але і своєчасно проводити лікування пацієнтів препаратами для запобігання прогресуванню ОПЗ і його ускладнень, сприяючи зниженню інвалідизації та впливаючи на якість життя.

## Ключові слова:

остеопороз, цукровий діабет 2 типу, неалкогольна жирова хвороба печінки, діагностика.

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## Прогнозирование риска развития остеопороза у пациентов с сахарным диабетом 2 типа и неалкогольной жировой болезнью печени

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**Цель работы** – оптимизация способа прогнозирования риска развития остеопороза (ОПЗ) у пациентов с сахарным диабетом (СД) 2 типа и неалкогольной жировой болезнью печени (НАЖБП) за счет использования специфических и чувствительных диагностических критериев.

### Ключевые слова:

остеопороз,  
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диабет 2 типа,  
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жировая  
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**Материалы и методы.** Способ прогнозирования риска развития ОПЗ у пациентов с СД 2 типа и НАЖБП разработан с применением наиболее значимых диагностических показателей. Способ расчета вероятности риска развития ОПЗ у пациентов с СД 2 типа и НАЖБП разработан с использованием статистических методов многомерного факторного анализа и логистической регрессии. Способ апробирован в клинике ГУ «Институт проблем эндокринной патологии имени В. Я. Данилевского Национальной академии медицинских наук Украины» на 51 пациенте, средний возраст которых составил  $63,2 \pm 0,99$  года с длительностью СД 2 типа в среднем  $7,84 \pm 0,68$  года.

**Результаты.** Для установления диагностической точности предлагаемого способа прогнозирования риска развития ОПЗ у лиц с наличием НАЖБП и СД 2 типа проанализированы данные всех исследуемых пациентов и получены такие диагностические характеристики: чувствительность разработанного способа составляет 88,23 %, вероятность отрицательного результата при негативном прогнозе, то есть специфичность разработанного способа – 70,58 %, точность (доля истинно положительных и истинно отрицательных результатов) – 82,35 %, отношение шансов – 18,37.

**Выводы.** Разработанный способ прогнозирования риска развития ОПЗ у пациентов с СД 2 типа и НАЖБП позволяет получать достоверные прогнозы с точностью, достаточной для практического применения. Применение способа позволит не только оценить риск развития ОПЗ, но и своевременно проводить лечение пациентов препаратами для предотвращения прогрессирования ОПЗ и его осложнений, что будет способствовать снижению инвалидизации и влиять на качество жизни.

Diabetes mellitus (DM) and its complications are related to the essential medical, social and economic problems that medicine faces today [1]. It is known that DM increases total mortality by 2–3 times, the risk of coronary heart disease and myocardial infarction by 2 times, and arterial hypertension by 3 times [2,3]. Despite the lack of clear statistics in different countries, there are assumptions that almost 2/3 of patients with type 2 DM have NAFLD [4]. All diabetic complications influence patient's quality of life and, unfortunately, are associated with premature disability and lethality [4–8].

Osteoporosis (OP) is the most common systemic disease of the skeleton, characterized by reduced bone mass, structural changes in the bone tissue and even minimal trauma can lead to fractures [9]. According to the World Health Organization (WHO), OP is among the four diseases that occupy leading positions in terms of disability and mortality along with cardiovascular diseases, diabetes and cancer pathology [10–14].

Type 2 DM and OP are two metabolic diseases, the prevalence of which has increased significantly in recent times [14]. This can be explained by several factors and, first of all, by the global aging of population. The combination of violations causes a spectrum of problems and various states, when several pathologies observed in one individual mutually aggravate each other, thereby multiplying the pathological effect [15,16].

OP may remain asymptomatic for a long time up to a fracture occurrence, so an important aspect of this pathology study is the identification of new risk factors for its development.

The coexistence of type 2 DM and NAFLD in patients can be a consequence of vitamin D deficiency in the body or result in its deficiency causing a disruption of calcium absorption and the bone tissue calcification. The situation influences structure of the bone tissue and can cause OP [17–20].

In this case, shared etiology suggests that combined course of type 2 DM and NAFLD with concomitant OP is not accidental and this fact may enhance the pathological process development and lead to adaptive mechanisms failure and adverse course of comorbid pathology [21,22].

Diagnosis of OP in patients with type 2 DM and NAFLD has a great clinical significance, as this condition is reversible in case of appropriate treatment, as well as timely prevention measures that can reduce the complications resulting in disability [22,23].

Some aspects of the early OP diagnosis have not yet been resolved, effective methods of its development prediction in order to use timely therapeutic measures have not been developed, and this fact can be crucial for increase in life expectancy and quality of life improvement among type 2 DM patients with NAFLD [24].

There is a prediction method of femoral neck fractures that includes determination of a number of risk factors – the structural features of this region [25]. With the help of this method, according to a scanned image, the femoral neck length and width are determined, which also assess the hip fracture risk. However, such ratios are not based on the study of major risk factors, in particular, bone mineral density.

There is also a way to predict fractures of the proximal femur in women over 50 years [26], according to which Dual energy X-ray absorptiometry is performed and scanned images of the femur bone mineral density help to determine the femoral neck length and width, a hip index and hip fracture risk factors. The disadvantages of this method that allows determining the risk are its focus on a particular range of individuals who can be examined in this way, the complexity of multi-stage and duration of this kind of examination. The presence of subjective factors influences further decisions. The method does not provide the possibility to compare obtained indicators detected in dynamics, which does not allow assessing the direction of changes [26].

Another known today method to diagnose the OP severity, in particular it is applicable for patients with fractures of long tubular bones [27], includes determination of serum thermolabile alkaline phosphatase and acid phosphatase activity, and 24-hour urinary total hydroxyproline and creatinine concentrations with their ratio calculation. However, this method requires a measurement of several parameters and their ratio; it should be carried out within 2–3 days for reliable estimates, a patient must follow a diet during this period, and 24-hour urine samples should be collected daily to determine the concentration of total hydroxyproline. In addition, hydroxyproline reflects the collagen metabolism from other connective tissue sources, and not only from the bone, which reduces the sensitivity of the method. Moreover, this method is only appropriate for examination of patients with consequences of pre-existing fractures of long tubular bones and it does not involve an identification of individuals with the risk of OP development, therefore it

is not well-suited to determine the necessity of preventive measures, OP correction and prevention of osteoporotic fractures [27].

Thus, at present, some aspects of early OP diagnosis are not yet fully solved and effective methods for its development prediction for the timely application of therapeutic measures have not been developed, so this fact can be crucial for increase in life expectancy and quality of life improvement in patients with type 2 DM and NAFLD.

## Aim

The purpose of the work is to optimize the method of OP risk prediction in patients with type 2 DM and NAFLD by using specific and sensitive diagnostic criteria.

## Materials and methods

In total, 51 patients with type 2 DM and NAFLD with or without OP were selected.

The method was tested in the Clinic of the State Institution "V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine". The average age of patients was  $63.2 \pm 0.99$  years, and the average duration of type 2 DM was  $7.84 \pm 0.68$  years.

The exclusion criteria used in the study were as follows: patients with a history of type 1 DM, pathological and secondary obesity, severe somatic and mental disorders, alcohol abuse, use of hepatotoxic drugs, viral hepatitis, chronic diseases of the gastrointestinal tract, dyspepsia. The study also did not include patients with acquired and congenital heart defects, inflammatory diseases in the acute stage, functional disorders of the thyroid gland, chronic kidney disease with creatinine level  $>200 \mu\text{mol/l}$ , chronic obstructive pulmonary disease stage III–IV, concomitant cancer, a history of lymphoproliferative disease.

Written informed consent was obtained from all the patients before the study procedures. During the clinical study, the safety measures for the patient's health, protection of patient's rights, human dignity, moral and ethical standards were provided in accordance with the principles of the Helsinki Declaration (1964), the Council of Europe Convention on Human Rights and Biomedicine, and the relevant Ukrainian laws; the study protocol was approved by the Bioethics Committee of the State Institution "V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine".

It should be mentioned that type 2 DM was diagnosed according to the World Health Organization 2013 criteria and NAFLD was established in accordance with the provisions of the Ministry of Health of Ukraine Order No. 826 dated November 6, 2014 "On approval and implementation of medical and technological documents on standardization of care in chronic non-infectious hepatitis", namely "Unified Clinical Protocol for primary, secondary (specialized) medical care. Non-alcoholic steatohepatitis". Thus, the diagnosis of NAFLD was established based on the history, clinical, biochemical studies, and ultrasound, as well as on the FibroTest results. Fatty liver dystrophy was established by the following ultrasound criteria: 1) increased liver echogenicity; 2) disturbance of the ultrasound wave propagation

and signal attenuation; 3) impaired visualization of the portal and hepatic vein branches; 4) liver enlargement.

The biochemical and immunological study was performed in the certified clinical and diagnostic laboratory (certificate number 01-0166/2018 dated 21.12.2018) to measure within the scope of the State Metrological Supervision at the clinic of the SI "V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine".

The general clinical examination of a patient included the collection of complaints and anamnesis, physical examination with the measurement of anthropometric indices (height, body weight, and hip circumference (HC)), body mass index (BMI) and waist circumference (WC)/HC ratio calculation.

The serum activity of alanine aminotransferase (AIAt) was determined according to Reitman and Frankel method on a device Fluorat-02-AVLF-T. The atherogenic coefficient (AC) of plasma was calculated by the generally accepted formula.

Determination of 25-hydroxycholecalciferol was carried out by an immunoassay (norm – 30.0–50.0 ng/ml;  $<10.0 \text{ ng/ml}$  – the risk of deficiency;  $<30.0 \text{ ng/ml}$  – the risk of inadequate consumption;  $>150.0 \text{ ng/ml}$  – intoxication) Vitamin D total (Roche Diagnostics, GmbH, Germany); serum calcium was measured using colorimetric method CA2 (Roche Diagnostics, GmbH, Germany).

This prediction model can be used in endocrinology during the examination of patients with type 2 DM and NAFLD for the OP detection. The main task of this model is to predict the OP risk development using the most significant diagnostic criteria, namely clinical, laboratory and functional methods, to determine the value of BMI ( $X_1$ ), AC ( $X_2$ ), and the level of circulating total vitamin  $D_3$  ( $X_3$ ), the activity of AIAt ( $X_4$ ) and to calculate the prognostic index P according to the formula:

$$P = \frac{e^y}{1 + e^y}$$

$$\text{where: } y = 7.4796 - 0.1528 \times X_1 - 0.5037 \times X_2 + 0.1059 \times X_3 - 0.8505 \times X_4 \quad (1)$$

The value of the prognostic index  $P > 0.5$  indicates the presence of the OP risk development in patients with type 2 DM and NAFLD, and  $P < 0.5$  – the absence of such a risk.

The method of probability calculation of the OP risk development in patients with type 2 DM and NAFLD was developed using statistical methods of multivariate factor analysis and logistic regression. To implement the present method the following diagnostic parameters were measured:

- anthropometric – BMI,  $\text{kg/m}^2$ ;
- lipidic – AC;
- OP marker – the level of circulating total vitamin  $D_3$ ,  $\text{ng/ml}$ ;
- liver tests – AIAt,  $\mu\text{mol/hour.ml}$ .

Based on the obtained values of diagnostic indicators for the developed formulas, the values (y) were calculated using the formula (1),

where:  $X_1$  – BMI,  $X_2$  – AC,  $X_3$  – the level of circulating total vitamin  $D_3$ ,  $X_4$  – AIAt; and the probability of

**Table 1.** The results of the OP risk prediction method testing in patients with type 2 DM and NAFLD

Study group, the number of persons	Correct prediction obtained with the method (number of persons)	Erroneous prediction obtained with the method (number of persons)
Persons with type 2 DM, NAFLD and OP, n = 34	30	4
Persons with type 2 DM, NAFLD and without OP, n = 17	12	5

**Table 2.** Characteristic of diagnostic significance of the logistic model

Sensitivity, %	Specificity, %	Accuracy, %	Odds ratio
88.23	70.58	82.35	18.37

**Table 3.** Diagnostic characteristics of the models for the OP risk determination

Characteristics of the mathematical models	Sensitivity, %	Specificity, %	Accuracy, %	Odds ratio
Logistic regression	88.23	70.58	82.35	18.37
Discriminant analysis	85.29	64.71	78.43	10.64

the OP risk development in patients with type 2 DM and NAFLD:

where:  $e = 2.718$  – base logarithm.

The value of the prognostic index  $P > 0.5$  indicated the presence of the OP risk development in patients with type 2 DM and NAFLD, and  $P < 0.5$  – the absence of such a risk.

The statistical analysis of the study results was performed using Statistica 13.0 (StatSoft Inc., USA). For statistical data processing nonparametric methods were used. The differences between statistical indicators were significant at a level of  $P$  value  $< 0.05$ . To calculate the factor of the OP risk development changes and to perform discriminatory analysis, multiple and logistic regression were applied. Special attention was given to the informativeness of the developed model (sensitivity; specificity; accuracy). In order to construct the predictive model of the OP risk development, the logistic regression method was used.

## Results

The results of the OP risk prediction method were tested in patients with type 2 DM and NAFLD and are presented in *Table 1*.

The examples of the proposed method are presented below for a better understanding.

### *Clinical example No. 1.*

A 51-year-old patient B., a comprehensive examination was conducted.

Examination findings: BMI – 23.0 (kg/m<sup>2</sup>); AC – 1.94; the 25(OH)) vitamin-D3 level – 13.8 (ng/ml); AIAt – 0.7 (μmol/hour.ml).

In calculating the prognostic index according to the calculation formula, we obtained:

$$y = 7.4796 - 0.1528 \times 23.0 - 0.5037 \times 1.94 + 0.1059 \times 13.8 - 0.8505 \times 0.7 = 3.854.$$

Substitution of the formula for  $y$  from 3.854 enabled to calculate the probability of the OP risk, thus we obtained:

$$p = \frac{e^y}{1 + e^y} = \frac{e^{3.854}}{1 + e^{3.854}} = 0.979$$

The risk probability value of  $P = 0.999$  was greater than 0.5, so the result indicated a high risk of developing OP. The probability of the OP development was 97.9 %.

In that case, standard therapy did not demonstrate an expected outcome. Further follow-up showed signs of OP in the patient within 12 months confirming our prediction.

### *Clinical example No. 2.*

A 62-year-old patient K. was admitted to the clinic for a comprehensive examination.

Examination findings: BMI – 40.3 (kg/m<sup>2</sup>); AC – 6.05; the 25(OH)) vitamin-D3 level – 11.78 (ng/ml); AIAt – 0.72 (μmol/hour.ml).

We substitute the findings into the formula to calculate the result value:

$$y = 7.4796 - 0.1528 \times 40.3 - 0.5037 \times 6.05 + 0.1059 \times 11.78 - 0.8505 \times 0.72 = -1.0904$$

Substitution of the formula for  $y$  from 1.0904 for the calculation of the OP risk probability:

$$p = \frac{e^y}{1 + e^y} = \frac{e^{-1.0904}}{1 + e^{-1.0904}} = 0.2115$$

The OP risk probability value  $P = 0.2515$  was less than 0.5, so the result indicated the low risk of the OP development. The probability of the OP risk was 21.15 %.

Further follow-up showed no OP symptoms in the patient within 12 months confirming the prediction.

In the present work, sensitivity, specificity, accuracy of the proposed logistic regression method and the odds ratio (*Table 2*) were established analyzing the findings obtained in all patients involved in the study.

Based on the test results, the probability of OP developing within one year according to the previously predicted OP risk – 88.23 %; the probability of the negative result with a negative prediction was 70.58 %, the accuracy (the proportion of true-positive and true-negative test results) was equal to 82.35 %.

It was identified that the distribution of patients into the groups of the OP risk development (classification) according to the proposed model was 18.37 times more exactly than a random distribution of patients also indicating the feasibility of this method used for the OP risk prediction during the population study.

The above presented results were compared to the similar indicators of the models using discriminant analysis (*Table 3*).

## Discussion

In order to establish the diagnostic accuracy of the proposed prediction method for OP risk in patients with type 2 DM and NAFLD, the data of patients' examination were analyzed and the following diagnostic characteristics were obtained:

- the sensitivity of the developed method – 88.23 %;
- the probability of a negative result with a negative prognosis – 70.58 %;

– the accuracy (the proportion of true-positive and true-negative results) – 82.35 %;

– the odds ratio – 18.37 (the odds ratio indicates the risk profile of OP according to the presented method and it is 18.37 times more accurate than a random prediction).

Using the method of the OP risk prediction, similar data were obtained in a previously conducted study (I. Zakharov, 2016), which demonstrated the sensitivity of the method of 76.3 %, and the specificity of 87.5 % against 88.23 % and 70.58 %, respectively [28].

Thus, the models developed in the course of the study with the use of logistic regression and discriminant analysis are characterized by sufficient sensitivity, specificity, and accuracy. However, the logistic model demonstrated the best characteristics, so it is recommended to calculate prediction for the OP risk with a binary dependent variable (for two groups) and to use the mathematical model with logistic regression.

The developed mathematical models are aimed at identifying the OP risk development in patients with type 2 DM and NAFLD, and can be used to diagnose OP based on indirect signs. Special attention should be given to the prognostic index as it can help in the OP risk-stratification and provide timely treatment strategies for preventing OP progression as well as to avoid complications in patients with type 2 DM.

## Conclusions

1. Models that are sufficiently sensitive, specific, and accurate were developed using logistic regression and discriminant analysis.

2. According to the best characteristics of the logistic model, it is recommended to calculate the prediction of OP development with a binary dependent variable (for two groups) using the mathematical model via logistic regression.

3. Application of this method will allow not only to assess the risk of developing OP but also to provide timely therapy for preventing OP progression and possible complications.

**Prospects for further research.** Implementation of the proposed methods in diagnosis of OP in patients with type 2 DM and NAFLD using specific and sensitive diagnostic criteria that would play a valuable role in practical health care in the foreseeable future.

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