Creation of a Mathematical Model of Personalized Prediction of Osteodeficiency in Chronic Pancreatitis

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Abstract

Osteoporosis is the most common type of bone disease. Osteoporosis increases the risk of breaking a bone. About one half of all women over the age of 50 will have a fracture of the hip, wrist, or vertebra (bones of the spine) during their lifetime. Spine fractures are the most common. Worldwide, 8.9 million osteoporotic fractures occur annually, which are associated with increased morbidity and mortality. Screening programs for the prevention of osteoporotic fractures are cost-effective in reducing the incidence of new fractures, thus emphasizing the importance of identifying risk factors that contribute to the development of bone disease. The goal is to develop a model for predicting the development and degree of decrease in bone mineral content in patients with chronic pancreatitis (CP) based on certain factors that influence this process. For the personalized prediction of osteodeficiency in patients with chronic pancreatitis, a formula was developed that takes into account the parameters of the course of the disease and can be used by general practitioners: the age of the patients, the duration of the disease, the results of the ultrasound examination, the results of the coprogram in points and the level of hemoglobin. This formula is aimed at an individual approach to the prediction of the possible forecasting of the development and degree of reduction of bone mineral density (BMD) depending on various parameters of the course of CP. They can be a useful tool for practitioners who provide primary care to patients.

Keywords

Chronic pancreatitis, bone mineral density, multivariate regression analysis.

1. Introduction

Worldwide, 8.9 million osteoporotic fractures occur annually, which are associated with increased morbidity and mortality [1-3]. Screening programs for the prevention of osteoporotic fractures are cost-effective in reducing the incidence of new fractures, thus emphasizing the importance of identifying risk factors that contribute to the development of bone disease [4, 5]. There is a link between chronic pancreatitis (CP) and the risk of developing osteoporosis. CP can affect bone health through several mechanisms. Malabsorption, which develops in the inflammatory process in the pancreas, leads to a decrease in the production of enzymes necessary for the proper absorption of nutrients, such as calcium and vitamin D. This can cause the development of a deficiency of these important components for bone health. Chronic inflammation can affect the levels of hormones, such as estrogens and glucocorticoids, which have important effects on bone health. An unbalanced hormonal system can contribute to the development of osteoporosis. People with CP may lose body weight due to problems with nutrient absorption, which may contribute to a decrease in bone mineral density (BMD) [6-12].

2. Aim of Study

The aim is to develop a model for predicting the development and degree of decrease in bone mineral content in patients with chronic pancreatitis based on certain factors that influence this process.

3. Materials and Methods

117 people with CP were included in the study. All studies were conducted in compliance with the main provisions of the Council of Europe Convention on Human Rights and Biomedicine, performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) of the World Medical Association on the ethical principles of conducting scientific medical research with human participation (with subsequent additions), the Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009. All patients gave informed consent to participate in the study. The research was approved by the decision of the Commission on Bioethics of Ternopil National Medical University named after I. Gorbachev, Ministry of Health of Ukraine. Key clinical indicators affecting the course of the disease were determined for these patients. T, % was determined using two-photon X-ray densitometry. T-criterion values from + 2.5 to -1 standard deviations from peak bone mass are considered normal values of BMD. The BMD result is a factor that determines the risk of future fractures. Osteopenia – indicators of the T-criterion between -1 and -2.5 standard deviations inclusive. These indicators correspond to a moderate risk of fractures. Osteoporosis – indicators of the T-criterion -2.5. deviations and below. Severe osteoporosis – indicators of the T-criterion -2.5. deviations and below with a history of one or more fractures. These indicators correspond to a high risk of fractures. When choosing a therapy, it is necessary to take into account the patient's clinical and laboratory indicators, in addition to the gastrointestinal tract. DXA is the most acceptable method for monitoring therapy. To determine the presence and depth of exocrine insufficiency of the digestive system and concomitant enterocolitis, the coprogram was evaluated on a 5-point scale, where the following signs were taken into account as 1 point: the presence of undigested remains of meat food in feces (creatorrhoea) in the form of muscle fibers in large quantities; the presence of undigested fats (steatorrhea) in the form of neutral fats; the presence of digested fiber and starch in stools (amylorrhea); a significant amount of mucus and leukocytes as evidence of the inflammatory process in the intestines; the presence of fungi, protozoa and helminths and their products. The structural state of the software was evaluated according to the Cambridge classification, assessing the degree of severity of the process. A normal pancreas is characterized by normal dimensions, and clear contours, the size of the Versung duct is 2 mm, and the parenchyma is homogeneous. Hemoglobin was determined by the photometric method. In order to determine the clinical and pathogenetic predictors of the formation of osteodeficiency in CP, correlation and paired regression analysis of the investigated clinical and pathogenetic parameters was carried out. A multivariate regression analysis was conducted using the investigated indicators that were selected in the paired regression analysis. The result of the multivariate regression analysis was a prognostic model. In order to evaluate the effectiveness of the created regression model for predicting osteodeficiency in CP, a check was made for compliance with the normal law of distribution of the derived residuals of the results of the created regression model. A histogram, a normal-probability graph of the residuals, and the Shapiro–Wilk W-test were used, as well as an ANOVA analysis. The coefficient of determination of the regression model for predicting osteodeficiency was also investigated.

The following formula was used to determine the diagnostic sensitivity of the test:

Diagnostic sensitivity

$$DS = PR/X \times 100.0\%, \tag{1}$$

where DS is the diagnostic sensitivity, PR is the number of true positive results, X is the total number of patients with the disease.

Diagnostic specificity was calculated as follows:
Diagnostic specificity

$$DS = NR/HP \times 100.0\%,,$$ (2)

where DS - diagnostic specificity, NR - the number of truly negative results, HP - the number of healthy patients.

For data processing and statistical analysis, the software-mathematical complex for a personal computer "Microsoft Excel 2016" was used, as well as specialized programs for statistical analysis and data processing, in particular, "STATISTICA® 8.0", (Stat Soft Inc., USA), IBM ® SPSS® Statistics Version 23.0, GraphPad Prism® 8.0.

4. Results and discussion

In biological systems, each phenomenon is usually influenced by many factors, and each case is quite individual, it can be stated that the revealed level of statistical significance and expressiveness of correlations allows us to recognize these factors as predictors of the formation and degree of reduction of BMD in CP patients to the state of osteopenia and osteoporosis It was established that the age of the patient with CP, the duration of the disease, the functional capacity of the pancreas, as well as the structural-morphological-functional state of the pancreas according to the criteria of ultrasound, expressed in points, are predictors of the formation of a decrease in BMD for patients with CP.

The correlation of the densitogram indicator with the main characteristics of the disease (age of patients ($R=-0.678$) ($p<0.05$), duration of the disease ($R=-0.475$) ($p<0.05$), fecal α-elastase value ($R=0.615$) ($p<0.05$), and ultrasound characteristics of the pancreas ($R=-0.453$) ($p<0.05$)) was evaluated. The analysis of the obtained results of the correlation analysis made it possible to establish that in the pairs of the studied indicator of the densitogram with the duration of the disease and the value of ultrasound of the pancreas, expressed in points, the strength of the connection was moderate ($p<0.05$). Pairs of the densitogram indicator with the age of patients and the level of α-elastase had a reliable significant relationship ($p<0.05$).

A significant direct correlation between the level of faecal α-elastase and the level of T, % was also obtained ($R=0.615$) ($p<0.05$), however, determining the level of faecal α-elastase in the conditions of modern family medicine in Ukraine is often a difficult, expensive and unavailable method. Determining coprogram indicators in points is a simple and affordable study, more cost-effective and accessible, especially at the primary level of medical care. Therefore, a correlation and regression analysis was conducted between the level of faecal α-elastase and the total level of co-program indicators in points. An inverse strong correlation was obtained between the level of faecal α-elastase and the level of coprogram indicators in points, which indicates a statistically significant relationship between these indicators ($R=-0.798$) ($p<0.05$).

A statistically significant direct correlation was also found between the level of the relative index of BMD (T, %), which was determined by the method of two-photon densitometry of the lumbar spine of the studied patients, and the level of hemoglobin, which is an integrative indicator of trophic status in patients with CP, as well as a marker hypoxia, which is the pathogenetic basis of BMD reduction (Fig. 1).
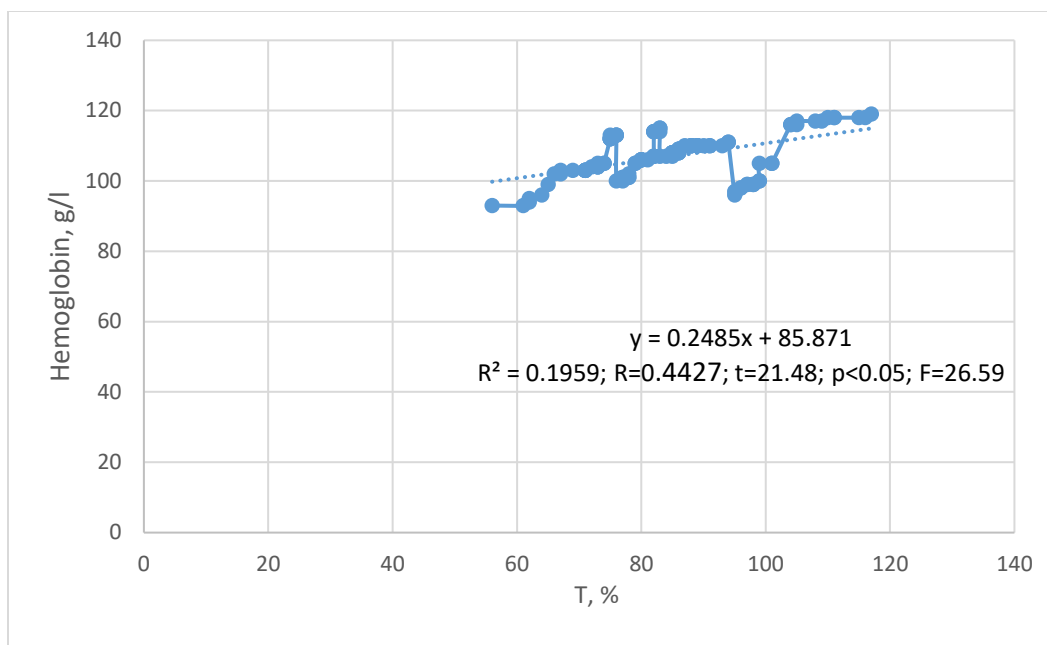
Figure 1. The relationship between the level of T, % and the content of hemoglobin

Combining the influence of all investigated factors on the formation and depth of osteodeficiency in CP, as well as considering it appropriate to include such additional factors as the duration of the CP disease, the age of CP patients, the structural characteristics of CP, according to ultrasound, expressed in points, as well as total level of coprogram in points, univariate and then multivariate regression analysis was performed (Table 1).

Table 1

Prognostic value of the influence of some anamnestic and clinical and laboratory parameters on the level of T according to the results of univariate and multivariate regression analysis

Indicator	Univariate analysis			Multivariate analysis		
	beta	SE	P-value	beta	SE	P-value
Age	0.71	0.07	p<0.0001	1.13	0.34	p<0.0001
Duration of CP	0.90	0.15	p<0.01	-5.78	0.67	p<0.05
Coprogram in points	8.39	1.20	p<0.01	10.57	1.16	p<0.05
Ultrasound examination in points	2.54	1.12	p<0.01	-0.39		p<0.05
Erythrocytes	9.14	0.61	p>0.05			
Hemoglobin	0.25	85.87	p<0.05	0.19	0.45	p<0.05
ESR	12.47	0.69	p>0.05			

Note. 1. Beta – coefficient of linear regression;

2. SE – standard error;

3. P-value is an indicator of the statistical significance of the data.

The result was the following formula for forecasting T, %:

$$Y = 29.02 + 1.13\,X_1 - 5.78X_2 + 10.57\,X_3 + 0.19\,X_4 - 0.39\,X_5,\qquad(3)$$
$$(R = 0.712;\ R^2 = 0.510;\ F = 87.43;\ t = 1.751;\ p < 0.05),$$

where

X_1 is the age of CP patients;

X_2 – disease duration (CP);

X_3 – coprogram, points;

X_4 – hemoglobin, g/l;

X_5 – quantitative value of US criteria, expressed in points.

According to the weight of the quantitative influence on T, % of patients with CP, the selected predictors are distributed as follows:

age of patients with CP > duration of history of CP > quantitative value of ultrasound criteria > quantitative determination of coprogram criteria > hemoglobin.

Thus, mathematical models for predicting the formation of osteodeficiency in patients with CP were obtained, which determine the predictability of the applied factors, which are available and generally accepted characteristics of CP in each specific patient. The derived formula can be used to identify risk groups for the occurrence of osteodeficiency (osteopenia and osteoporosis) among patients with CP for the timely implementation of preventive and therapeutic measures to correct this pathological condition. The method of mathematical forecasting developed by us was tested in 100 patients with CP. Its sensitivity in the sample was more than 95.0%, specificity - 84.0%.

5. Conclusion

For the personalized prediction of osteodeficiency in patients with chronic pancreatitis, a formula was developed that takes into account the parameters of the course of the disease and can be used by general practitioners: the age of the patients, the duration of the disease, the results of the ultrasound examination, the results of the coprogram in points and the level of hemoglobin. This formula is aimed at an individual approach to the prediction of the possible forecasting of the development and degree of reduction of BMD depending on various parameters of the course of CP. They can be a useful tool for practitioners who provide primary care to patients.

This program is simple and can be easily used in the practice of doctors of various specialties, especially in outpatient practice, to determine a cohort of patients with CP who are at risk of osteodeficiency, for further examination or empirical prescription therapy.

6. References

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