FORECASTING OF CALCITRIOL INSUFFICIENCY IN PATIENTS WITH OSTEOARTHRITIS AND COMORBIDITY OF EXOCRINE PANCREATIC INSUFFICIENCY DISEASES

Liliya S. Babinets, Iryna M. Halabitska

I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

irynkagal@gmail.com

Abstract

The prescription of vitamin D should be justified. Very often in the routine practice of a general practitioner to determine the level of active metabolites of this vitamin is difficult due to the remoteness of specialized laboratories. Therefore, it remains important to determine the prognostic level of active metabolites of vitamin D using mathematical prediction, which allows identifying the risk group of patients with the development of this hypovitaminosis. This is especially true in patients with chronic comorbid pathology of the gastrointestinal tract and musculoskeletal system.

Objective: to develop a formula for predicting the level of 25(OH) vitamin D in patients with exocrine pancreatic insufficiency.

Methods. It was used multivariate regression analysis to predict possible deficiency of 25(OH) vitamin D (calcitriol) in patients with primary osteoarthritis in comorbidity with exocrine pancreatic insufficiency using the identified clinical predictor parameters significant for hypovitaminosis D categories of patients which had the strongest predictor effect on the dependent variable (calcitriol level).

Results. The result of the analysis was a multiple regression formula for predicting the level of 25 (OH) vitamin D, which can be used in the practice of physicians of various specialties, especially primary care physicians. The sensitivity and specificity of the developed model are calculated.

Discussion. With the help of the formula, the family doctor forms a cohort of patients who must be referred for biochemical determination of calcitriol (25(OH) vitamin D) to a specialized laboratory.

Keywords: *calcitriol hypovitaminosis, exocrine pancreatic insufficiency, osteoarthritis*

Introduction

Vitamin D is a group of biologically active substances (including cholecalciferol and ergocalciferol). Cholecalciferol is synthesized under the action of ultraviolet rays in the skin and enters the human body with food. Ergocalciferol can only come with food [3, 4, 12]. To activate, cholecalciferol must first be converted in the liver to 25-hydroxycholecalciferol and then in the kidneys to 1,25-dihydroxy-cholecalciferol (calcitriol). When assessing the adequacy of providing a particular person with vitamin D, the most indicative and significant laboratory indicator is the concentration of 25-hydroxy-cholecalciferol (active fraction of vitamin D) in the serum [1, 2, 9, 11].

Vitamin D is involved in proper calcium metabolism, regulates immune responses, and even hair growth. This is due to the predisposition to depression, muscle weakness in athletes, and even polycystic ovary syndrome in women [5, 9, 12]. Insufficient vitamin reduces the content of inorganic phosphorus in the blood (hypophosphatemia), impaired absorption in the intestine, and bone absorption of calcium, phosphate. Lack of ergocalciferol causes softening of bone tissue, rickets in children, and osteomalacia in adults [6, 7, 12].

However, this vitamin does not always help adults to overcome certain problems, as was believed until recently. For example, a meta-study of people over the age of 50 did not show the effectiveness of routine intake of vitamin D and calcium to prevent bone fractures[3]. A meta-study of people with depression who took vitamin D did not prove the effectiveness of these supplements [9, 10, 12].

However, the effectiveness of vitamin D in the prevention of upper respiratory tract diseases has been definitively proven, which is especially relevant during the pandemic caused by Covid-19. The positive effect of this vitamin on the course of asthma exacerbations has also been revealed[6].

There is evidence that vitamin D has a good effect on the condition of the arteries and can also be useful in polycystic ovaries [8, 9, 11].

It is important to understand that taking vitamin D unnecessarily is unacceptable, as excessive doses can be harmful to health. Overdose causes hypervitaminosis, which is characterized by anorexia (loss of appetite), constipation, low blood pressure, accelerated ESR, dehydration, dystrophic changes, increased calcium in the blood, and its deposition in soft tissues [3, 9, 12]. Therefore, the prescription of this vitamin should be justified. Very often in the routine practice of a general practitioner to determine the level of active metabolites of this vitamin is difficult due to the remoteness of specialized laboratories and their high cost. Therefore, it remains important to determine the prognostic level of active metabolites of vitamin D using mathematical prediction, which allows identifying the risk group of patients with the development of this hypovitaminosis [8, 12]. This is especially true in patients with chronic comorbid pathology of the gastrointestinal tract and musculoskeletal system [4, 9, 12].

Objective: to develop a formula for predicting the level of 25(OH) vitamin D in patients with exocrine pancreatic insufficiency using available and generally accepted parameters that can be determined in primary care.

Methods

It was examined 112 patients with primary osteoarthritis in comorbidity with diseases accompanied by exocrine pancreatic insufficiency (chronic pancreatitis, chronic non-stone cholecystitis, functional diseases of the gastrointestinal tract and gallbladder). Exclusion criteria were cancer, acute and exacerbation of chronic pathologies of vital organs, severe diabetes mellitus, type 1 diabetes mellitus, active gastric and duodenal ulcers, viral hepatitis and liver cirrhosis, Crohn's disease, ulcerative colitis, cystic fibrosis. Patients were identified the main clinical indicators

influencing the course of primary osteoarthritis and comorbid pathology, accompanied by exocrine insufficiency of the pancreas. Initially, a univariate regression analysis was performed to determine the factors that could potentially affect the level of 25(OH) vitamin D by selecting the most significant factors. Later, a multivariate regression analysis was performed, which resulted in a multiple regression formula that identified a cohort of patients who could potentially have low level of 25(OH) vitamin D.

Regression analysis was used to calculate the mathematical formulas of forecasting: first, a pairwise regression analysis was performed to identify predictors of the dependent change with the construction of a dependence graph to determine its nature. Next, a multivariate regression analysis was performed using the factors that had the strongest predictor effect on the dependent variable. The diagnostic sensitivity of the test was calculated by the formula:

$$MS = PR/X \times 100{,}0\ \%, \qquad (1)$$

where DS - diagnostic sensitivity, PR - truly positive results, X - the number of patients with the disease.

Diagnostic specificity was calculated as follows:

$$DS = NR/HP \times 100{,}0\ \%, \qquad (2)$$

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

Results

A statistically significant reduction of the 25-OH vitamin D to level $(34{,}17 \pm 1{,}21)$ nmol/L in the cohort of the studied patients was found in comparison with the control group ($p < 0.05$), that indicates the formation of hypovitaminosis in patients with primary osteoarthritis and exocrine insufficiency of the pancreas.

Conducting a univariate regression analysis, a number of indicators were identified that had a statistically significant correlation with the level of 25(OH) vitamin D. A univariate regression analysis revealed a significant correlation ($R = 0.912$) between the level of 25(OH) vitamin D and the level of fecal

α-elatase-1 ($p < 0.05$). However, the definition of this indicator is often difficult at the primary care level, so a correlation analysis was performed between fecal α-elastase-1 and the total score of the coprogram, as well as the total score of pathological ultrasound (US) criteria for changes in the pancreas, which showed high strength of correlations ($R = 0.879$) and ($R = 0.852$), respectively ($p < 0.05$). Therefore, in order to reduce the cost and make the forecasting formula more accessible, it was decided to include in its structure more economically accessible parameters that are comparable in importance for the assessment of exocrine insufficiency of the pancreas (according to our study).

A multivariate regression analysis was performed, which resulted in a multiple regression formula:

$$Y = 26.5382 - 0.00224X_1 - 0.117X_2 + 0.03418X_3 + 0.03177X_4 + 0.03905X_5 - 0.4505X_6 + 3.4461X_7 \quad (3)$$

($R = 0{,}996$; $R^2 = 0{,}992$; $F = 10{,}32$; $t = 2{,}27$; $p < 0{,}05$),

where x_1 - age, years;

x_2 - duration of comorbid pathology of primary osteoarthritis and diseases with exocrine insufficiency of the pancreas, years;

x_3 - hemoglobin, g/l;

x_4 - quantitative determination of the total score of the coprogram;

x_5 - the quantitative value of the total score value of ultrasound criteria;

x_6 - cholesterol level, mmol/l;

x_7 - calcium level, mmol/l.

According to the severity of the quantitative effect on the content of calcitriol in the serum of patients with OA, the identified factors are distributed as follows:

calcium level>cholesterol level>duration of comorbid pathology>total score of ultrasound criteria>hemoglobin>total score of coprogram>age.

This mathematical model for predicting the formation of 25(OH) vitamin D hypovitaminosis in patients with primary osteoarthritis on the

background of exocrine pancreatic insufficiency uses well-defined predictors of hypovitaminosis, which are available for determination and generally accepted in general clinical practice. The developed method of mathematical prediction was tested in 100 patients with primary osteoarthritis with comorbid conditions with existing exocrine insufficiency of the pancreas. Its sensitivity in the sample was more than 95.0%, specificity - 84.0%.

Discussion

The proposed formula can be used to determine the prognostic content of 25(OH) vitamin D (calcitriol) in the serum of patients with primary osteoarthritis on the background of exocrine insufficiency of the pancreas due to comorbid conditions using economically available and clinically accepted characteristics of the study. With the help of the formula, the family doctor forms a cohort of patients who must be referred for biochemical determination of calcitriol (25(OH) vitamin D) to a specialized laboratory. The proposed and substantiated method is economically and clinically feasible in the practice of primary care physicians to determine the cohort of patients with a prognostically possible decrease in the content of calcitriol (25(OH) vitamin D).

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