PharmacologyOnLine

Archives • 2021 • vol.3 • 585-594

# PREDICTION FACTORS FOR THE RISK OF HYPOTHYROIDISM DEVELOPMENT IN TYPE 2 DIABETIC PATIENTS

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**Abstract**

Type 2 diabetes mellitus (T2DM) patient outcomes, treatment options, and corresponding healthcare expenses are affected by the presence of different comorbidities. The aim of this work was to develop an algorithm for predicting the risk of hypothyroidism development in patients with T2DM according to a mathematical model obtained by regression analysis, for the timely implementation of appropriate preventive measures among T2DM patients. We analyzed 538 medical records of T2DM patients. It was found the following risk factors influencing the occurrence of hypothyroidism in patients with T2DM: hemoglobin, total cholesterol, non-HDL-cholesterol, glycated hemoglobin, and thyroid stimulating hormone levels. Prognostic model of the risk of hypothyroidism development in T2DM patients was built using multiple regression analysis. In order to stratify the risk of hypothyroidism development in T2DM patients, the following criteria were proposed: no risk at RC HT ≤ 5.0; low risk at 5.1≤ RC HT≤14,9; high risk at RC HT ≥15.0; where RC HT — risk coefficient for the hypothyroidism development in T2DM patients. Therefore, the developed algorithm and mathematical model for predicting the development of hypothyroidism in T2DM patients are highly informative and allow to determine in advance the contingent of patients with a high probability of hypothyroidism risk based on routine laboratory data.

**Keywords**: *type 2 diabetes mellitus, hypothyroidism, risk, mathematical model*

Introduction

Diabetes mellitus (DM) is one of the key challenges to human population, as this disorder now has reached pandemic levels (1-4). Data of the International Diabetes Federation reveal that 463 million people throughout the world were diagnosed with DM in 2019 alone, and 91% of them had Type 2 diabetes mellitus (T2DM) (5). DM patient outcomes, treatment options, management methods, and corresponding healthcare expenses are affected by the presence of different comorbidities or chronic diseases, which exist in addition to DM (6-8). Most frequently, T2DM was associated with such disorders as dyslipidemia, obesity and insulin resistance (IR) (9, 10).

Hypothyroidism can also be connected to dyslipidemia, obesity, and IR (11, 12). The association of IR with overt hypothyroidism is well described, as numerous epidemiological studies indicate the higher prevalence of overt hypothyroidism among T2DM population compared to the general population. Concurrently, little to no information is available about insulin action during subclinical hypothyroidism (SCH), which is defined as an elevated thyroid stimulating hormone (TSH) serum level with the normal levels of free thyroxine (fT4) and free triiodothyronine (fT3). Maratou et al. described increased Homeostatic Model Assessment for Insulin Resistance (HOMA IR) index and decreased Matsuda index in both groups of overweight patients (average body mass index (BMI) of approximately 26 kg/m2) – with overt hypothyroidism and with SCH, compared to euthyreoids (13). Vyakaranam S. et al. found that the mean insulin levels and HOMA IR were significantly elevated among patients with SCH if compared with euthyroids (12). Furthermore, the correlative analysis showed that TSH levels positively and moderately correlated with insulin and HOMA IR; FT3 levels negatively and strongly correlated with insulin, while moderately with HOMA IR; FT4 levels negatively and weakly correlated with insulin and HOMA IR (11). Other studies have reported hyperinsulinemia in SCH (13, 14). However, Owecki M. et al. did not find a significant difference in insulin level and HOMA IR in 22 patients with overt hypothyroidism compared to 17 healthy individuals (15). They suggested that hypothyroidism had no impact on insulin sensitivity.

SCH hallmarks include changes in both carbohydrate and lipid metabolism, such as decreased gastrointestinal glucose absorption, protracted peripheral glucose accumulation, decreased hepatic glucose output, increased gluconeogenesis, reduced hepatic disposal of glucose, as well as hyperlipidemia. Together with these changes, SCH influences insulin secretion and damages both micro- and macrovascular functions, thus elevating cardiovascular risks in DM patients (16, 17). Han C. et al. indicate that SCH is closely associated with arterial hypertension, high blood cholesterol levels, and abnormal homocysteine, resulting in a higher risk of metabolic syndrome, atherosclerosis, cardiovascular events, and mortality (18). Other researchers also suggest that combination of hypothyroidism and DM is characterized by more frequent diabetic complications, worse glycemic control, and more pronounced negative changes in lipid metabolism, as well as an additional negative effect on the cardiovascular system is observed (19, 20).

Therefore, it is important to predict factors for the risk of hypothyroidism development in the patients with T2DM. Meanwhile, there have been no previous studies of relative risk of hypothyroidism development among T2DM patients in Ukraine. Therefore, the aim of our study was to develop an algorithm for predicting the risk of hypothyroidism development in patients with T2DM according to a mathematical model obtained by

regression analysis, for the timely implementation of appropriate preventive measures among T2DM patients.

Materials and methods

For the purpose of retrospective analysis of medical records, the study included 538 patients with T2DM who were hospitalized to the endocrinology department of the municipal non-profit enterprise "Ternopil University Hospital" of Ternopil Regional Council in 2019. Patients were divided into 2 groups: group 1 (501 patients with T2DM without comorbid hypothyroidism), and group 2 (37 patients with T2DM and comorbid hypothyroidism).

The diagnosis of T2DM was confirmed according to the recommendations of the American Diabetes Association. The diagnostic criterion was glycosylated hemoglobin (HbA1c) equal to or above 6.5% (21).

Hypothyroidism was diagnosed according to the criteria of the European Thyroid Association: elevated levels of thyroid-stimulating hormone (TSH) in combination with a decrease in free thyroxine (T4) (22). If T4 values were within normal limits, SCH was diagnosed.

Patients with a history of hyperthyroidism or other thyroid diseases (other than hypothyroidism), patients which were prescribed thyroid hormone-related drugs, patients with pregnancy or lactation, as well as with cancer, were excluded from the study.

Using a multiple regression analysis, a prognostic multifactor model of the risk of hypothyroidism development in T2DM patients was proposed. Statistical processing of the results was performed using STATISTICA ver. 10.0. The relationship between indicators (quantitative, qualitative) was estimated using the Spearman correlation coefficient (r). Prognostic model of the risk of hypothyroidism development in T2DM patients was built using multiple regression analysis. To assess the quality of the regression model, the Nigelkerk's test of association-strength (R-squared) was calculated. To confirm the overall quality of the developed prognostic mathematical model, the residual deviations were checked for compliance to the normal distribution, as well as their evaluation on the scattering diagram was done. The result of the evaluation of the acceptability of the model for predicting the risk of hypothyroidism in T2DM patients was performed using one-way ANOVA.

Results

To predict the risk of hypothyroidism in type 2 diabetic patients, a mathematical model was developed based on the method of multifactor regression analysis, which allows, while using regression coefficients and values of risk factors, which have possible impact on the development of hypothyroidism, to identify the relationship between them and predict probability of hypothyroidism occurrence in T2DM patients. Using linear regression analysis among the proposed factors of influence/risk factors (age, sex, BMI, complete blood count and blood biochemical profile data, thyroid hormone levels), we identified the following risk factors influencing the occurrence of hypothyroidism in T2DM patients: hemoglobin (Hb), total cholesterol (TC), non-HDL-cholesterol, glycated hemoglobin (HbA1c), thyroid stimulating hormone (TSH) levels (23). According to the literature review, they were conditionally indexed (from 0 to 2) depending on the significance of their impact on the risk of hypothyroidism development in T2DM patients (Table 1).

The next stage of our study was to determine the relative significance of multicollinear factors in predicting the occurrence of hypothyroidism in T2DM patients using regression coefficient β. According to the results of statistical analysis, we revealed five risk factors at the significance level of $p<0.05$, which were used to construct a

mathematical model of the risk of hypothyroidism development in T2DM patients (Table 2). Analyzing the coefficients of the multiple regression mathematical model, it was found that the most important predictors were the blood levels of TC and non-HDL-cholesterol.

The quality of the regression model was checked by residual analysis (Figure 1). They were checked for the normality of their distribution over the entire range of variable values. The histogram of the residues is symmetric, so the hypothesis of the distribution of residues that corresponds to the normal distribution is not rejected.

To check for the presence or absence of dependence of residues on the predicted values, a scattering diagram is constructed (Figure 2). The residues relative to the predicted values are scattered chaotically, there is no definite system of accuracy of the positions of the points over the entire range of values of the variables. Thus, the analysis of residues showed that our mathematical model is adequate for predicting the risk of hypothyroidism in T2DM patients.

To assess the quality of the regression model, we calculated the Nigelkerk coefficient (R-squared), which shows what part of the factors is taken into account in our model. The value varies from 0 to 1 and shows the degree to which one random variable is related to another one. The greater its value, the better the linear regression model approximates the correlation result. In our study, Nigelkerk coefficient R2 = 0.63. Thus, 63% of factors were taken into account in the model for predicting the HT risk in T2DM patients.

Based on the obtained data of the multiple regression analysis to predict the probability of hypothyroidism in T2DM patients (Table 2), we constructed a multiple regression equation to determine the risk for the development of hypothyroidism:

RC HT = 0.081×TSH + 0.444×HbA1c + 3.104×non-HDL-cholesterol + 4.132×TC − 0.177×Hb − 14.446;

where RC HT — risk coefficient for the hypothyroidism development in T2DM patients; 0.081×TSH and others – risk factors with regression coefficients; 14.446 – constant value.

In order to stratify the risk of hypothyroidism development in T2DM patients, the following criteria were proposed: no risk at RC HT ≤ 5.0; low risk at 5.1≤ RC HT≤14,9; high risk at RC HT ≥15.0.

To confirm the quality of the developed prognostic model, the predicted value of the dependent variable of risk coefficient for the hypothyroidism development in T2DM patients (RC HT) was calculated using ANOVA analysis (Table 3). The results of analysis of variance indicated a high quality model for predicting the risk of hypothyroidism in T2DM patients, as the significance level of $p<0.001$ confirmed the higher efficiency of this model relative to a simple prognosis based on average values of the studied indicators.

The quality of the proposed model was verified in real-life situation when predicting the risk of hypothyroidism development in T2DM patients who were hospitalized to the Department of Endocrinology, as well as to the Endocrinology Dispensary of the Ternopil University Hospital.

Discussion

Thyroid dysfunction, obesity, and type II diabetes mellitus (T2DM) are among the most common endocrine disorders and they are often concomitantly present in the same patient (24, 25). The frequency of thyroid dysfunction among T2DM patients is higher than that of the general population. There are data available that the prevalence of hypothyroidism in T2DM patients ranges from 6% to 20% across different ethnic groups (18, 26). On the contrary, Smithson reported lower prevalence rates for thyroid dysfunction in

T2DM patients (27). These inconsistencies could be explained by differences in age, sex, and iodine intake in the populations surveyed (28). Undiagnosed thyroid dysfunction may affect the metabolic control and enhance cardiovascular, and other chronic complication risks in diabetic patients (29), therefore, it is very important to determine risk factors for hypothyroidism development among T2DM patients.

It was found that female gender, older age, obesity, positive thyroid peroxidase antibody, and hospitalization were associated with an increased risk of hypothyroidism development in T2DM patients (28, 29). Similar data were published by Song F. et al., which investigated the prevalence of hypothyroidism among 1662 hospitalized T2DM patients and the related factors (30). They also assessed the prevalence of macrovascular and microvascular complications among T2DM patients with hypothyroidism and euthyroidism. The prevalence of hypothyroidism increased with age, and was higher in females (10.8 %) than in males (3.4 %). Older age, female gender, and positive thyroid peroxidase antibody were associated with higher odds of hypothyroidism among type 2 diabetes mellitus patients. Moreover, the T2DM patients with hypothyroidism had higher prevalence of cerebrovascular diseases than those with euthyroidism after adjustment for age and gender.

J. J. Díez and P. Iglesias also studied the relative risk for hypothyroidism in 1112 patients with T2DM (31). The gender-, age- and weight-adjusted relative risk (odds ratio) of newly identified hypothyroidism in patients with T2DM in comparison with control subjects was 2.81 (1.77–4.48). This odds ratio was significant in patients over 65 years old [4.02 (1.95–8.31)], as well as in males [4.84 (1.58–14.80)] and females [2.60 (1.54–4.38)], in obese patients [2.56 (1.36–4.82)] and non-obese patients [3.11 (1.56–6.20)], and in individuals with [4.26 (1.73–10.46)] and without [2.93 (1.50–5.75)] thyroid autoantibodies.

A. H. Khassawneh et al. determined the prevalence and predictors of thyroid disorders in T2DM patients (32). A total of 1341 participants were included in the study. The mean age ± SD was 60.14 ± 12.21, and 47.9% were females. Among T2DM patients, 14.1% were documented to have thyroid disorders; and 12.6% new cases of thyroid disorder were diagnosed. Thus, the overall prevalence of thyroid disorders was found to be 26.7% in T2DM patients, which was significantly higher than in control (13.7%). SCH was the most commonly found thyroid disorder (31). Using logistic regression, after adjustments for age, gender, obesity, smoking, anemia, presence of goiter, disease duration, researchers found that the prevalence of thyroid disorders was significantly increased as the age increased independent of T2DM, and age (≥50 years) was a significant predictor for thyroid dysfunction among T2DM. However, they did not find any significant associations between thyroid dysfunction and complications or duration of diabetes. Interestingly, Al-Geffari et al. found that the duration of diabetes of more than 10 years is a risk factor for developing hypothyroidism in diabetic patients (26).

S. U. Ogbonna and I. U. Ezeani determined the risk factors of thyroid dysfunction in patients with T2DM (33). Three hundred and fifty-four T2DM patients and one hundred and eighteen non-diabetic individuals (control group) were recruited for the study. Using a combination of TSH, fT3, and fT4 values analysis, 12.4% of the T2DM patients were observed to have thyroid dysfunction (hypothyroidism - 11.6% and hyperthyroidism - 0.8%). Researchers found that about 56.5% of the T2DM patients were females; the T2DM patients had significantly higher BMI than controls; mean HbA1c was significantly higher in T2DM patients than among the

controls. Female gender, obesity, DM nephropathy, HbA1c of ≥7%, and DM duration of > 5years, were significantly associated with thyroid dysfunction in T2DM patients in this study. Moreover, S. A. P. Chubb et al. did not found independent associations between SCH and serum cholesterol level, HbA1c or hypoglycaemic therapy in T2DM patients (34).

Present study revealed the following risk factors influencing the occurrence of hypothyroidism in patients with T2DM: Hb, TC, non-HDL-cholesterol, HbA1c, TSH levels. Based on the obtained data of multiple regression analysis of predicting the probability of hypothyroidism in T2DM patients, we constructed a multiple regression equation to determine the risk factors for hypothyroidism and proposed criteria for stratification of hypothyroidism risk (absent, low and high).

Decreased Hb levels as a risk factor for hypothyroidism can probably be explained by the fact that hypothyroidism and anemia can occur simultaneously as thyroid hormones are responsible for the proliferation of erythrocyte precursors both directly and via stimulating erythropoietin production, while iron-deficient anemia negatively influences thyroid hormone status (32). The level of HbA1c above 7% as a predictor of thyroid dysfunction in T2DM patients was identified by other researchers as well (20, 33).

Analyzing the coefficients of the multiple regression of the proposed mathematical model, it was found that the most important predictors of hypothyroidism risk were elevated levels of TC and non-HDL-cholesterol. The link between T2DM and dyslipidaemia is characterised by increased production of free fatty acids (FFAs) by insulin-resistant fat cells. High FFAs levels promote TG production, which in turn stimulates the secretion of apolipoprotein B (ApoB) and very low-density lipoprotein cholesterol (VLDL-C). In addition to high ApoB and VLDL-C, hyperinsulinemia is associated with low HDL-C levels (35-37).

Thyroid hormones influence cholesterol metabolism by controlling the activity of cholesterol ester transfer protein, the hepatic lipase, and the lipoprotein lipase; they also control the bile acid flow and the low density lipoprotein (LDL) receptor activity in the liver. Patients with hypothyroidism had a negative lipid profile with elevated levels of total cholesterol (TC) and increased oxidation of LDL cholesterol (LDL-C), which promoted atherogenesis (38). S. U. Ogbonna and I. U. Ezeani noted obesity as a predictor of thyroid disorder development in T2DM patients (33).

## Conclusions

We recommend regular monitoring of T2DM patients for thyroid function, especially of those in the risk group, which may enhance wellness, as well as the quality of life in T2DM patients. The developed algorithm and mathematical model for predicting the development of hypothyroidism in T2DM patients are highly informative and allow to determine in advance the contingent of patients with a high probability of hypothyroidism risk based on routine laboratory data, such as hemoglobin, total cholesterol, non-HDL-cholesterol, glycosylated hemoglobin, and TSH levels.

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Table 1. Risk factors for hypothyroidism development in T2DM patients

| Risk factor / Indexation | Hb, g/L | TC, mmol/L | Non-HDL-cholesterol mmol/L | HbA1c, % | TSH, mIU/mL |
|---|---|---|---|---|---|
| 0 (< 0.49) | males> 130; females > 120 | < 5 | < 3.37 | < 5 | < 2.5 |
| 1 (0.5-1.49) | males - 110–130; females - 100–120 | 5 – 6 | 3.37 – 4.0 | 5 – 7 | 2.5 – 4.2 |
| 2 (>1.5) | males <110; females < 100 | > 6 | > 4.0 | > 7 | > 4.2 |

Table 2. Multiple regression model coefficients to determine the risk of hypothyroidism in patients with T2DM

| value | regression coefficient (β) | standard error (SE) | p-value |
|---|---|---|---|
| Hb | -0.1774 | 0.56289 | 0.004 |
| TC | 4.1316 | 1.125213 | 0.0001 |
| non-HDL-cholesterol | 3.1038 | 1.204586 | 0.014 |
| HbA1c | 0.4435 | 0.148552 | 0.005 |
| TSH | 0.0807 | 0.025177 | 0.003 |
| Constant | -14.4461 | 4.740488 | 0.045 |

Table. 3. The result of assessing the acceptability of the model for predicting the hypothyroidism risk in T2DM patients using ANOVA

| | Sums of squares of deviations (SS) | Degrees of freedom (df) | Mean square value | Fisher criterion (F) | p-value |
|---|---|---|---|---|---|
| Between groups ($SS_B$) | 108.0120 | 5 | 21.60239 | 10.44796 | 0.000006 |
| Within groups ($SS_W$) | 64.0961 | 31 | 2.06762 | | |
| Total ($SS_T$) | 172.1081 | | | | |

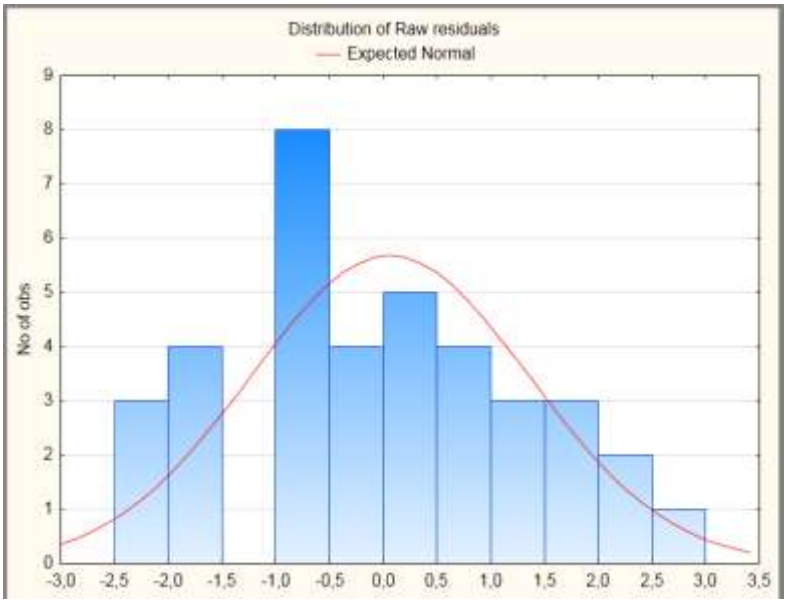


Figure. 1. Frequency histogram of residual deviations of risk factors for hypothyroidism in T2DM patients

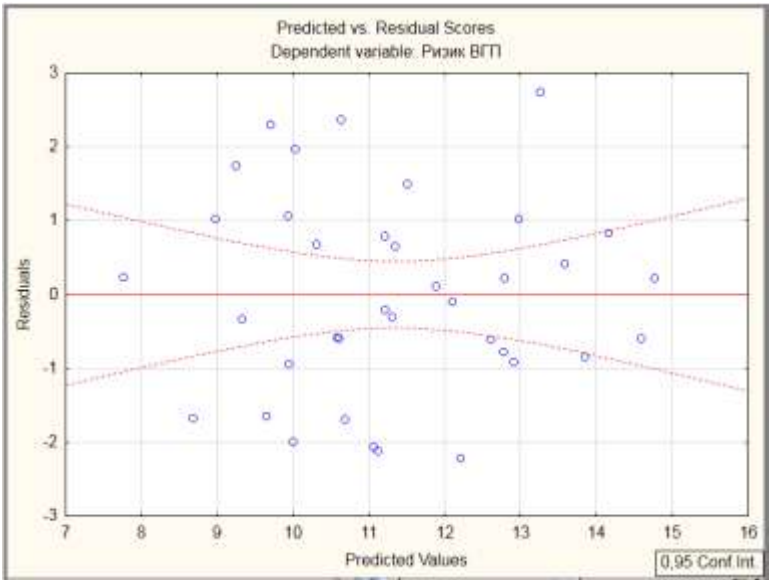


Figure. 2. Scattering diagram of the residues of risk factors for hypothyroidism development in T2DM patients.