ORIGINAL ARTICLE

Evaluation of serum Neopterin levels in patients with type 2 diabetes mellitus and hypothyroidism

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ABSTRACT

Aim: This study aims to investigate the variation in serum Neopterin levels between adult individuals (T2DM with hypothyroidism and without hypothyroidism).
Materials and Methods: Ninety participants were divided into three group: 30 patients with T2DM and hypothyroidism, 30 patients with T2DM and without hypothyroidism and 30 Control patients. They were obtained from national diabetes center, Mustansiriyah University.
Results: The current findings have found that patients in Group I (T2DM with hypothyroidism) showed significantly raised neopterin levels (614.87 ± 166.27 pg/ml) as compared to Group II (T2DM without hypothyroidism) which is (335.27 ± 173.34 pg/ml) and healthy control group (267.29 ± 254.4 pg/ml). The level of neopterin in T2DM with hypothyroidism patients, and T2DM without hypothyroidism patients have a significant ($P<0.05$) positive correlation coefficient with BMI, HbA1c, TC, TG, AIP and TSH. Furthermore, a high significant ($P<0.01$) positive correlation with FBS, HOMA-IR and LDL-C was also found.
Conclusions: The elevated levels of neopterin in type 2 diabetic patients with hypothyroidism and without hypothyroidism play as a regulator of energy consumption, leading to the hypothesis that thyroid gland disease may influence its level. In addition, the potential for use as a diagnostic marker for diabetics with thyroid disease due to the occurrence of complications of diabetes, including cardiovascular diseases.

KEY WORDS: hypothyroidism, insulin resistance, lipid profile, Neopterin, T2DM

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INTRODUCTION

Diabetes mellitus (DM) ranks as one of the most widespread metabolic disorders worldwide, characterized by persistent hyperglycemia and disturbances in the metabolism of different nutritional molecules [1]. Insulin metabolism is impaired in diabetes mellitus, which results in a wide range of clinical symptoms. A metabolically hypoactive state is a hallmark of hypothyroidism, a condition in which thyroid hormones are insufficient for a variety of reasons [2]. Thyroid hormones and insulin, which are linked to diabetes mellitus, work together to control the body's metabolism in a complex dance [3]. Females with diabetes are more likely to have thyroid issues [4]. Diabetic patients with longstanding hyperlipidemia, obesity, and anemia are at greater chance of having underlying hypothyroidism [5]. Similar to hypothyroidism affects the emergence of diabetes problems, there is typically a substantial clinical association between these two common endocrine disorders [6]. Neopterin (NP) is a biomarker of immune system activation that is produced by activated macrophages and monocytes, which causes its concentration to rise in various inflammatory conditions [7]. When T-lymphocytes identify the pathogen and damaged tissue, they release interferon-gamma (INF-γ), which activates guanosine triphosphate cyclohydrolase I (GCH I). This produces 7,8-dihydroneopterin, which under oxidative stress breaks down into neopterin, a small molecule also called a pteridine molecule [8]. Since NP is a byproduct of 7,8-dihydroneopterin's oxidation, its concentration indicates the degree of oxidative stress that occurs during inflammation. In addition to the extracellular marker of activated immune cells, it also induces antioxidant and anti-inflammatory conditions, that act as mediators and modulators of inflammation [9]. It offers a possible instrument for assessing the emergence of various inflammatory conditions [10]. It has been found that the serum concentration of NP is strongly associated with the parameters of glucose metabolism and is closely related to glucose intolerance. In addition, NP is described as a sign of diabetes progression and its associated consequences [11].

AIM

This study aims to investigate the variation in serum Neopterin levels between adult individuals (T2DM with hypothyroidism and without hypothyroidism).

MATERIAL AND METHODS

Between December and the end of March 2024, 90 participants from the National Diabetes Centre at Mustansiriya University took part in the study. They were further divided into three groups: Group G1 included 30 patients with type 2 diabetes mellitus (T2DM) and hypothyroidism. Group G2 comprised of 30 patients with only T2DM, and Group 3 (G3) comprised additional 30 healthy control subjects. Informed verbal consent was obtained from all participants after explaining the study objectives and ethical considerations. All participants underwent a detailed clinical evaluation to exclude other comorbid conditions. Demographic data; age, sex, weight, height, and BMI were documented. Fasting blood sugar (FBS) was measured using an enzymatic colorimetric method with aid of automated biochemical analyzer (Cobas c 111 analyzer, Roche Diagnostics). Total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, HbA1c have been measured using immunoturbidimetric method. Serum insulin levels were measured using chemiluminescent immunoassay. Insulin resistance was calculated by using the formula Homeostatic Model Assessment of Insulin Resistance; that is, [Fasting Insulin (μU/mL) × Fasting Glucose (mg/dL)/405]. The Atherogenic Index of Plasma (AIP) was calculated as the logarithm of (TG/HDL-C). Thyroid function tests total triiodothyronine (T3), total thyroxine (T4), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were measured in miniVIDAS immunoassay system (BioMérieux, France) which works on ELFA principles. Neopterin levels were measured by ELISA through available commercial kit (Cosiabio, Cat. No. E09144h).

Excluding criteria: It did not include patients with hyperthyroidism, type 1 diabetes mellitus, pregnancy, current insulin therapy, or any other systemic disease.

Including criteria: The study included adults aged 35 to 60 years with T2DM for more than 5 years.

ETHICAL APPROVAL

The study procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki (protocol number 148# in 2025).

STATISTICAL ANALYSIS

All data were reported as mean ± SD. LSD (Least Significant Difference) for ANOVA was used for the statistical analysis, with $p<0.05$ serving as the minimum level of significance. Version 22 of the SPSS software (SPSS, Chicago, IL, USA) is utilized.

RESULTS

Table 1 presents the anthropometric measurements of the three groups in this study: group I, T2DM with hypothyroidism; group II, T2DM without hypothyroidism; and the control group. The mean ages of the participants for all groups were not significantly different ($p=0.124$), suggesting a comparable distribution of ages. Although group I had a slightly higher mean weight than group II and the control group (83.13±9.64 *vs.* 79.53±8.52 *vs.* 73.17±6.43 kg), it was bordering on being statistically significant ($p=0.05$). No significant difference in height was observed among the groups ($p=0.103$). The body mass index was maximum in group I (33.21±3.44 kg/m^2) than in group II (28.41±2.22 kg/m^2) and control group (24.33±3.25 kg/m^2), with a borderline significant difference ($p=0.05$). It may indicate that patients having both T2DM and hypothyroidism would have an increased tendency toward higher BMI values as an additive metabolic burden from hypothyroidism.

Table 2 exhibits the clinical markers for the three study groups: group I (T2DM with hypothyroidism), group II (T2DM without hypothyroidism), and healthy controls. Most markers varied significantly between the groups ($p<0.05$). FBS, HbA1c, insulin levels, and HOMA-IR were all raised in both diabetic groups versus controls; however, values were highest in group I indicating more severe insulin resistance and glycaemic derangement among T2DM patients if associated with hypothyroidism. Lipid profile parameters of total cholesterol, triglycerides, LDL-C and AIP were also significantly raised in group I as compared to group II and control implying a more atherogenic lipid profile in patients when hypothyroidism coexists. The highest level of HDL-C was seen in the control. Regarding thyroid hormones, Group I was found to have significantly lower levels of T3 and T4 along with raised TSH levels as compared to Groups II and controls.

The current findings have reported that patients in group I (T2DM with hypothyroidism) showed significantly raised neopterin levels (614.87±166.27 pg/ml) as compared to group II (T2DM without hypothyroidism) which is (335.27±173.34 pg/ml) and healthy control group (267.29±254.4 pg/ml), as illustrated in table 3.

Correlation analysis shows that neopterin levels positively correlate with metabolic parameters in both group I (T2DM with hypothyroidism) and group II (T2DM without hypothyroidism). In group I, it is correlated strongly with LDL-C ($r=0.687$, $p<0.01$), HOMA-IR ($r=0.655$, $p<0.01$), and FBS ($r=0.502$, $p<0.01$). This may indicate a link between

Table 1. Anthropometric measurements among groups of study

Variables	Mean±SD			p-value
	Group I (n=30)	Group II (n=30)	Control (n=30)	
Age (years)	48.53 ± 3.57	47.1 ± 3.34	44.4 ± 3.12	0.124
Weight(kg)	83.13 ± 9.64	79.53 ± 8.52	73.17 ± 6.43	0.05
High (cm)	169.67 ± 5.48	168.8 ± 8.62	169 ± 0.08	0.103
BMI (kg/m^2)	33.21 ± 3.44	28.41 ± 2.22	24.33 ± 3.25	0.05

Source: Own material

Table 2. Clinical markers among the three study groups

Markers	Mean±SD		
	Group I (n=30)	Group II (n=30)	Control (n=30)
FBS (mg/dl)	142.9 ± 25.1 ^{A}	145.67 ± 58.7 ^{A}	86.9 ± 8.48 ^{B}
HbA1c %	9.89 ± 1.02 ^{A}	8.27 ± 1.85 ^{A}	5.31 ± 0.21 ^{B}
Insulin level (U/l)	18.59 ± 4.38 ^{A}	16.87 ± 7.08 ^{A}	11.71 ± 5.51 ^{B}
HOMA-IR	7.22 ± 1.32 ^{A}	6.25 ± 1.52 ^{A}	2.00 ± 0.84 ^{A}
TC (mg/dl)	299.97 ± 40.7 ^{A}	262.83 ± 18.3 ^{B}	159 ± 29.2 ^{C}
TG (mg/dl)	263.13 ± 42.9 ^{A}	203.73 ± 103.7 ^{B}	112.33 ± 21.21 ^{C}
HDL-C (mg/dl)	47.93 ± 6.48	45.13 ± 3.15	50.93 ± 1.41
LDL-C (mg/dl)	119.41 ± 9.68 ^{A}	98.25 ± 7.93 ^{A}	91.43 ± 7.21 ^{C}
AIP (log TG/HDL-C)	4.52± 0.79 ^{A}	3.00± 0.85 ^{B}	2.02± 0.19 ^{C}
T3 (nmol/l)	0.64 ± 0.19 ^{A}	1.84 ± 0.55 ^{B}	1.11 ± 0.28 ^{B}
T4 (nmol/l)	49.77 ± 6.72 ^{A}	79.03 ± 13.82 ^{B}	78.2 ± 4.95 ^{B}
TSH (IU/L)	18.83 ± 5.77 ^{A}	4.25 ± 1.07 ^{B}	53.35 ± 0.99 ^{C}

^{A}, ^{B}, ^{C}: different letters refer to statistically significant difference at $p<0.05$
Source: Own material

Table 3. Differences in neopterin levels among study groups

	Mean±SD			p-value
	Group I (n=30)	Group II (n=30)	Control (n=30)	
Neopterin (pg/ml)	614.87± 166.27	335.27 ± 173.34	267.29 ± 254.4	0.001

Source: Own material

neopterin and insulin resistance or dyslipidemia when hypothyroidism coexists. It is also correlated moderately with BMI, TG, AIP, and TSH. In Group II it is also correlated significantly with LDL-C (r=0.621), FBS (r=0.586), and HOMA-IR; (r=0.547). However, correlation with HDL-C was negative and not significant (Table 4).

The analysis of the ROC curve of neopterin shows that area under the curve (AUC) equals 0.98 and hence gives diagnostic accuracy of the most excellent level (Fig.1., Table 5). The cut-off value for neopterin was set at 311.1 pg/ml, giving sensitivity=100%, specificity=87%, and statistically significant (p-value p=0.000) with a confidence interval of 95% running between 0.958 and 1.0. It means results having been attained suggested neopterin to possess very strong discriminative abilities in identifying those T2DM patients who have hypothyroidism.

The ROC curve analysis for neopterin as a predictive marker in T2DM patients without hypothyroidism indicates fairly moderate diagnostics. It is shown that the area under the curve is 0.698. The optimal cut-off value was identified as 405.5 pg/ml, sensitivity was 60% and with a specificity of 100%. These findings are summarized in figure 2 and they imply that though neopterin has limited sensitivity it remains highly specific in detecting T2DM cases without coexisting hypothyroidism (Fig. 2., Table 6).

DISCUSSION

Endocrine dysfunction is the root cause of both diabetes and thyroid disease, and both conditions have been shown to influence each other [12]. Patients with thyroid disorders have a higher prevalence of diabetes mellitus. This trend may be explained by increased medical sur-

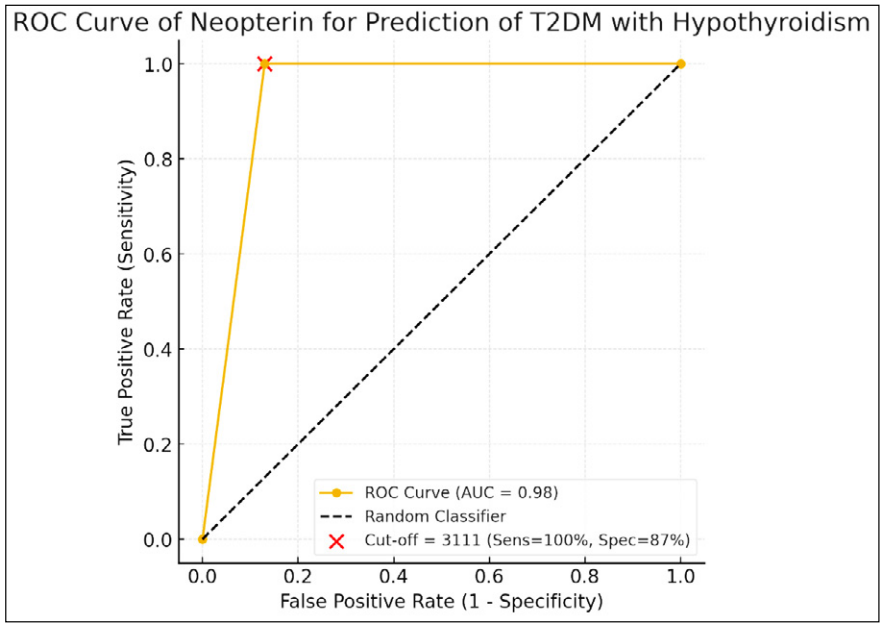

Fig. 1. ROC curve analysis of neopterin for the prediction of T2DM with hypothyroidism
Source: Own material

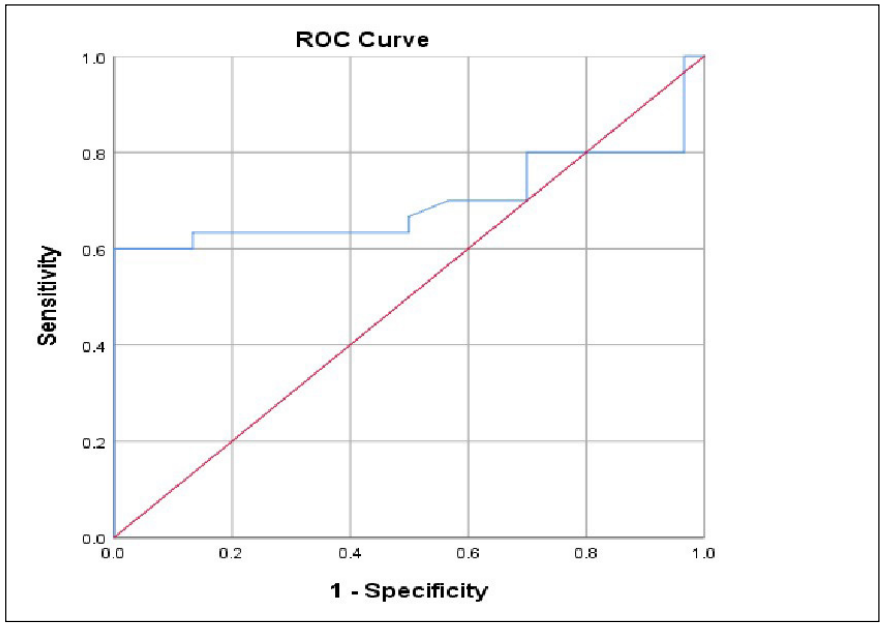

Fig. 2. ROC curve analysis of neopterin for the prediction of T2DM without hypothyroidism
Source: Own material

veillance of these patients, but there are also possible pathophysiological mechanisms that could explain why thyroid disorders develop in DM patients and why people with thyroid disorders are more likely to develop DM themselves [13]. Thyroid hormone (TH) increases gastrointestinal motility, which improves the absorption of glucose [14]. High levels of GLUT2 in the liver increase glucose output by the liver. Thus, it triggers endogenous glucose production, including gluconeogenesis and glycogenolysis [15]. Overactivated metabolic pathways cause hyperinsulinemia and impaired glucose tolerance, which also lowers insulin sensitivity within peripheral tissues [14]. Thyroid hormones act directly by enhancing the secretion of insulin by β-cells of the pancreas and α-cell-mediated glucagon release. At the same time, it promotes the breakdown of fat in adipose tissue; this increases the amount of free fatty acids in circulation that further support gluconeogenesis in the liver [16]. The amount of cellular immunological activity can be determined by looking at the production of neopterin. In patients with thyroid disorders, neopterin level measurement may provide offer prognostic and predictive information [17]. The migration of mononuclear cells in thyroid disorders is regulated by adhesion molecules and inflammatory cytokines [18]. The production of cytokines and autoantibodies by B cells and extracellular matrix leads to the expansion of T-cells. It is known that neopterin is a biochemical indicator of activation of cellular immunity, since neopterin, a particular indicator of monocyte activity, and other cytokines make monocytes in healthy people inactive [19]. Significantly higher levels of neopterin were observed among the of patients with T2DM and hypothyroidism, patients with T2DM without hypothyroidism, and the control group;

Table 4. Correlation coefficient for the correlation between neopterin and other biomarkers

Variables	Pearson's Correlation Coefficient (r)	
	Group I	Group II
BMI	0.357*	0.371*
FBS	0.502**	0.586**
Insulin level	0.037	0.119
HOMA-IR	0.655**	0.547**
HbA1c %	0.359*	0.339*
TC	0.308*	0.388*
TG	0.369*	0.363*
HDL-C	0.029	-0.148
LDL-C	0.687**	0.621**
AIP	0.350*	0.317*
T_3	0.124	0.185
T_4	0.182	0.146
TSH	0.399*	0.234

*: significant correlation at p <0.05; **: high significant correlation at p <0.01

Source: Own material

Table 5. ROC curve analysis of neopterin for the prediction of T2DM with Hypothyroidism

AUC	Cutt-off	SE	p-value	95% CI		Sensitivity	Specificity
				Lower bound	Upper bound		
0.98	311.1	0.12	0.000	0.958	1.0	100	87

Source: Own material

Table 6. ROC curve analysis of neopterin for the prediction T2DM without hypothyroidism patients

AUC	Cutt-off	SE	p-value	95% CI		Sensitivity	Specificity
				Lower bound	Upper bound		
0.698	405.5	0.076	0.008	0.549	0.847	60	100

Source: Own material

similar results were observed by previous articles. [20, 21]. Elevated levels of neopterin are a consequence of the autoimmune response characterized by a considerable infiltration of macrophages in the thyroid gland. This infiltration results in a marked production of neopterin, which in turn elevates its concentration in the peripheral blood. It has been suggested that the interplay between neopterin levels and the titer of TSH-receptor stimulatory antibodies may serve as an indicator of autoimmune activity that is specific to the thyroid [21]. Previous studies have also reported a positive associations between neopterin and BMI [22-24]. They postulated that in obese people with thyroid disorders, insulin resistance is caused by inflammation of the adipose tissue mediated by an activated immune system, rather than just an increase in adipose tissue mass, which directly results in attenuation of insulin action [25]. The neopterin level has a positive correlation coefficient with HbA1c ($p<0.05$) as well as with FBS and HOMA- ($p<0.01$) in T2DM with hypothyroidism patients, as well as T2DM without hypothyroidism patients, which is consistent with the results of several study [26]. In the development of type 2 diabetes, serum neopterin seems to be linked to both insulin resistance and decreased insulin production. Elevated blood glucose levels may cause the pancreatic beta cells to become more stimulated. In hypothyroidism, there is an increase in the amount of insulin secreted in response to a glucose stimulation. Hypothyroidism also slows the breakdown of insulin. This may be the cause of elevated HOMA-IR index and elevated serum insulin levels in hypothyroid people [27]. Furthermore, the positive correlation between neopterin level and TC, TG and AIP (at $p<0.05$), as well as the high positive correlation between neopterin level and LDL-C ($P<0.01$) in patients with T2DM and hypothyroidism, as well as in patients with T2DM without hypothyroidism, and this is agreement with several study [28-30]. All of the aforementioned alterations add up to higher levels of total cholesterol, triglycerides, and LDL, which is a risk agent for the occurrence of "nonalcoholic fatty liver disease"

(NAFLD). Another factor that links hypothyroidism to NAFLD is hepatic insulin resistance, which is exacerbated by increased triglyceride accumulation in the liver [31]. Furthermore, lipoprotein lipase enzyme activity is reduced in overt hypothyroidism, which prevents the clearance of TG-rich lipoproteins and raises serum TG levels. Neopterin and AIP showed a strong positive connection in patients with type 2 diabetes who also had hypothyroidism. It has already been shown that the primary atherogenic component of LDL, serum LDL level, has a substantial correlation with AIP. However, it has been demonstrated that thyroid conditions are linked to highly atherogenic pattern B of LDL-C subtractions. According to reports, AIP is a better predictor of cardiovascular danger than a traditional lipid profile and offers predictive value beyond that of personal lipids as a marker of lipoprotein particle size [32]. Lipid profiles are greatly impacted by hypothyroidism, which raises the risk of cardiovascular disease. Thyroid hormone is essential for controlling lipid metabolism and cholesterol levels. Serum levels of LDL-c, TC and may be TG rise with hypothyroidism. Atherosclerosis and other cardiovascular diseases are facilitated by this changed lipid profile [33]. Neopterin levels have a positive correlation coefficient with TSH in hypothyroidism patents with T2DM patients ($p<0.05$), and this is in agreement with other study [34]. It can be believed that many internal cascade reactions may be triggered with TSH inhibition in thyroid illnesses and this might depress neopterin release by the hypothalamus pituitary axis [35]. Total neopterin and HDLC have an inverse relationship; this is because HDLC helps to transfer extra cholesterol to the liver for excretion after removing it from peripheral tissue [36]. HDL's anti-inflammatory and antioxidant properties are among its many uses. In peripheral tissue, cholesterol builds up and leads to atherosclerosis and inflammation if the function is compromised [37, 38]. ROC curve analysis of neopterin as a prognostic marker in patients with type 2 diabetes mellitus without hypothyroidism shows a rather moderate diagnostic value. It was reported that neopterin, a key molecule taking part in organization of immune response, energy expenditure and the continued rise levels of neopterin are considered a risk indicator for cardiovascular disease and its complications.

CONCLUSIONS

The elevated levels of neopterin in type 2 diabetic patients with hypothyroidism and without hypothyroidism play as a regulator of energy consumption, leading to the hypothesis that thyroid gland disease may influence its level. In addition, the potential for use as a diagnostic marker for diabetics with thyroid disease due to the occurrence of complications of diabetes, including cardiovascular diseases.

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CONFLICT OF INTETEST
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