https://doi.org/10.46389/rjd-2021-1016
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2021; volume 28, issue 1, pages 105-111

Case Report

Metabolic changes of lipids in patient with subclinical hypothyroidism

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Received: 10 June 2020 / Accepted: 19 February 2021

Abstract

Background and Aims: the effect of subclinical hypothyroidism on the dynamics of lipid spectrum during lipid-tolerance test was studied. Subclinical hypothyroidism (SH) is the earliest thyroid dysfunction and is the most common. However, data on the presence of dyslipidemia in subclinical hypothyroidism are controversial. The aim of this study was the early detection of lipid metabolism disorders in patients with subclinical hypothyroidism on the basis of lipid-tolerance testing. **Materials and Methods:** the study involved 96 people. The main group included 37 patients with subclinical hypothyroidism, but seven of them had fasting hypercholesterolemia, dyslipidemia, and they were excluded from further study. Thus, 30 patients with SH formed the main group 1. Two comparison groups were presented by 59 comparisons by main characteristics (age, sex, exclusion criteria) of individuals without thyroid pathology (group 2) - 30 people, and with overt hypothyroidism (group 3) - 29 people. An oral fat tolerance test was used to evaluate postprandial lipemia. **Results and Conclusions:** As a result of the study, data were obtained according to which fat load stimulated the development of different levels of postprandial hyperlipidemia, depending on the thyroid status of patients. Patients with subclinical hypothyroidism had postprandial hypertriglyceridemia, which was combined with an increase in low-density lipoprotein levels and a decrease in high-density lipoprotein levels. The proposed method allows the detection of early disorders of lipid metabolism in patients with subclinical hypothyroidism.

Keywords: Lipidotolerance test, postprandial hypertriglyceridemia, subclinical hypothyroidism.

Background

According to a large-scale meta-analysis of N. Rodondi, which involved more than 55,000 patients, a correlation of cardiovascular morbidity (CVM) with thyroid-stimulating hormone (TSH) was found. A significant increase in the risk of CVM was established at TSH> 7 mU/l [1–3]. According to WHO data, hypercholesterolemia in patients with hypothyroidism is one of the significant manifestations of the disease, and is found in 93.4% of patients. As in patients with ischemic heart disease, hypertriglyceridemia and dyslipoproteinemia are observed in patients with hypothyroidism [1-–3]. Along with the increase in total cholesterol in patients with hypothyroidism, there is a decrease in high-density cholesterol-lipoprotein (HDL-lipoprotein) and an increase in low-density lipoprotein (LDL-lipoprotein) cholesterol, while decrease in LDL/HDL ratio.

Thyroid hormones affect the synthesis of lipids, but to a much greater extent

the processes of their degradation. They are involved in the utilization of fats, mobilization of triglycerides from adipose tissue through activation of enzymes, liver lipase (LL), lecithin-cholesterol-acetyltransferase (LCAT) and cholesterol-ether transport protein HETP [1–3]. LL participates in the processes of remodeling of various lipoproteins, LCAT esterifies free cholesterol, HETP mediates the exchange of cholesterol esters between lipoproteins and is a key factor in reverse cholesterol transport. If long-term hypothyroidism persists, there may be a significant decrease in HETP and LL activity [3–5].

In the study of the processes of atherogenesis, much attention is paid to the influence of oxidized forms of LDL cholesterol on the formation of atherosclerotic plaque. Increasing their level is an important marker of the activity of the atherosclerotic process [5]. Oxidized LDL cholesterols have been found to be crucial in endothelial damage, as they stimulate lipid migration into the subendothelial space and their capture by macrophages leading to the formation of foam cells [6–8]. In addition, under conditions of thyroid hormone deficiency, there is a decrease in the number of LDL receptors in the liver, which leads to a decrease in the excretion of cholesterol by hepatocytes and, as a consequence, an increase in the level of LDL and HDL [8]. Thus, a decrease in thyroid function contributes to the development of atherosclerosis. The level of hypercholesterolemia in patients with hypothyroidism correlates with the severity of hypothyroidism, and therefore the highest cholesterol figures are observed in patients with myxedema [8].

Subclinical hypothyroidism (SH) is the earliest thyroid dysfunction and is the most common. However, data on the presence of dyslipidemia in subclinical hypothyroidism are controversial [3–5].

Lipidogram does not always allow an objective assessment of cardiovascular risk, as it is known that in about one third of patients with clinically pronounced atherosclerosis, including coronary arteries (CA), indicators of atherogenic fractions of lipids and lipoproteins (LP) are within the normal values [7–9]. However, in this group of patients there are certain disorders of the blood lipid transfer system (LTS). In normal clinical practice, the effect of prandial fats on lipid metabolism is not studied, as the effects of exogenous fats on lipid spectrum (LS) values are not tested. Post-prandial lipemia, which is defined as the degree and duration of the increase in triglyceride (TG) levels, is generally known to occur after the consumption of fatty foods.

According to the studies [7–9], exogenous fats which cause the phenomenon of postprandial hyperlipemia (PPH), have the most adverse atherogenic effect. In the postprandial period, absorption of chylomicrons and LDL by the arterial wall occurs [9]. Postprandial hyperlipidemia lasts for several hours after each meal, so the person is in this state for most of the day [9–13]. Recent studies have confirmed the atherogenic nature of postprandial dyslipidemia as an independent risk factor for cardiovascular disease. Data on the state of lipid metabolism in subclinical hypothyroidism are controversial, since studies of lipidogram were performed on an empty stomach, namely postprandial lipidemia and the effect of fat loading in patients with subclinical hypothyroidism was not studied [13–15].

Aim of this study was the early detection of lipid metabolism disorders in patients with subclinical hypothyroidism on the basis of lipid-tolerance testing.

Materials and Methods

The study conducted at the Department of Endocrinology of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine" involved 96 people. The criteria for inclusion in the study were: confirmed diagnosis of SH (twice with an interval of three months detecting TSH level> 4.0 μME/ml at normal fT4 level - 12–22 pmol/l); age of patients under 45; voluntary consent to participate in the study. Exclusion criteria were: presence of cardiovascular pathology (ischemic heart disease, hypertension); chronic liver and kidney diseases with impaired function; oncological, rheumatic diseases; autoimmune diseases (except Hashimoto's disease); diabetes; hypertension; smoking; taking hypolipidemic drugs; pregnancy. Thyrotropic hormone (TSH) and free thyroxine (fT4) fraction

https://doi.org/10.46389/rjd-2021-1016

were determined as screening. The etiologic factor of hypothyroidism was predominantly autoimmune thyroiditis (elevated antibody titer to thyroid peroxidase was detected in 48 patients out of 59 patients with hypothyroid status of varying severity). The main group included 37 patients with subclinical hypothyroidism, but seven of them had fasting hypercholesterolemia, dyslipidemia, and they were excluded from further study. Thus, 30 patients with SH formed the main group 1. Two comparison groups were presented by 59 comparisons by main characteristics (age, sex, exclusion criteria) of individuals without thyroid pathology (group 2), 30 people, and with overt hypothyroidism (group 3), 29 people.

To exclude atherosclerotic lesions of arteries, a color duplex scan of the brachiocephalic arteries was performed with calculation of the intima-media ratio (mean 0.57 mm ± 0.02 was obtained) and a treadmill test during which the ischemic type of reaction was excluded.

An oral fat tolerance test was used to evaluate postprandial lipemia using the J. Patch method, according to which a standard fat diet was carried out at the rate of 65 g of fat per 1 m^2 of body surface. 72.5% butter was used as the fat source, along with 50 g of white bread. Blood samples were taken on an empty stomach and three hours after fat load. Patients did not take food during the study. The following parameters were investigated: total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL-lipoproteins).

To determine the level of cholesterol and its fractions, the enzymatic colorimetric direct method was used, using reagents "HUMAN", Germany, on a SAPPHIRE 400 apparatus.

Statistical processing of the study materials was performed using the STATISTICA v.6.1 software package (Statsoft Inc., USA) (license number AGAR909E415822FA). Taking into account the law of quantitative data distribution (Liliefors and Shapiro-Wilk criteria), parametric and non-parametric methods were used. In the case of the normal distribution law, the statistical characteristics are represented as arithmetic mean (M), standard error of the mean (m), 95% confidence interval for the mean (95% CI), in other cases the values of median (Me) and interquartile variance are given [25%; 75%]. Comparisons of statistical characteristics in the different groups and in the dynamics of the observation were performed using the Student's t test for paired (T) and independent (t) samples, Mann-Whitney (U) and Wilcoxon (W) criteria; multiple comparison by ANOVA (F) and Kruskall-Wallis (H) analysis of variance; the likelihood of differences in the relative indices was estimated by Pearson's Chi-square test ($\chi 2$). Differences were considered statistically significant at $p<0.05$.

Results and Discussion

The main characteristics of the examined patients at the onset of the study are shown in Table 1. All selected study groups were statistically comparable ($p > 0.05$) by age and gender of patients, as well as BMI that met the criteria (18–24.9 kg/m^2). At the same time, the groups significantly ($p<0.001$) differed in the levels of TSH, fT4, fT3 and antibodies to thyroperoxidase (Ab-TPO). In particular, the TSH level in the serum of patients with SH was 4.2-times higher than in patients without thyroid pathology ($p<0.001$), but was 12.8-times reduced relative to patients with overt hypothyroidism ($p < 0.001$). The production of fT4, fT3 hormones in the blood of group one patients was normal ($p > 0.05$) and exceeded the same parameters in group 3 by 2.3 and 1.9-times, respectively ($p<0.001$).

The most specific marker of lipid tolerance disorder is the dynamics of the level of TG and LDL in three and six hours after fat loading [15–18]. In our study, we used the determination of postprandial lipid metabolism in three hours as this point is as informative as possible. In the first two hours after nutrition loading, the phase of early postprandial physiological hyperlipidemia continues. By the three-hour mark in healthy subjects without lipid metabolism, this phase is fully completed, which gives grounds for evaluation and comparison in patients with subclinical hypothyroidism.

Data on the results of the study of fasting lipidgram indices and after lipid-tolerance test are presented in table 2 and figure 1, 2, 3.

Table 1: Main characteristics of the examined patients at the onset of the study.

Characteristics	Group 1 – SH (n = 30)	Group 2 – without TG pathology (n = 30)	Group 3 – overt (n = 30) hypothyroidism	Significance of difference between groups as a whole*
Age, years, M±m	32.4 ± 1.6	31.8 ± 1.6	33.2 ± 1.5	F = 0.20, p > 0.05
Gender, n/ %:				
male	8/26.7	11/36.7	9/30.0	χ^2 = 0.73, p > 0.05
female	22/ 73.3	19/ 63.3	21/ 70.0	
BMI, kg/m^2, M±m	20.4 ± 0.5	21.2 ± 0.6	22.1 ± 0.7	F = 2.28, p > 0.05
TSH, μME /ml, M±m	7.43 ± 0.41 *p2, p3*	1.77 ± 0.09 *p1, p3*	95.18 ± 6.69 *p1, p2*	F = 183.2, p < 0.001
fT4, pmol/l, M±m	16.65 ± 0.57 *p3*	15.82 ± 0.53 *p3*	7.14 ± 0.55 *p1, p2*	F = 91.2, p < 0.001
fT3, nmol/l, M±m	2.04 ± 0.10 *p3*	2.20 ± 0.11 *p3*	1.10 ± 0.01 *p1, p2*	F = 45.5, p < 0.001
Antibodies to TPO, ME/ml, Me [25%;75%]	1426.6 [565.5; 2456.8] *p2*	15.5 [8.1; 27.1] *p1, p3*	1079.7 [544.3; 2291.6] *p2*	H = 55.8, p < 0.001

Notes: *p1, p2, p3* – $p < 0.001$ compared to the corresponding group 1,2,3; * - significance of differences between groups as a whole by one-way ANOVA (F), Kruskall-Wallis (H), Pearson Chi-square (χ2).

From the data in table 2 it is seen that in 3 hours there was a significant increase in levels of total cholesterol, triglycerides, and LDL cholesterol in patients with subclinical hypothyroidism (group 1) and group with overt hypothyroidism (group 3) at p<0,001. Thus, in patients with SH and normal fasting lipidogram after a load test a long-term postprandial hypercholesterolemia is noted, characterized by a probable (p<0.001) increase in the level of TC on average by 0.67 mmol/L or by 14.6%, TH – by 0.89 mmol/l (by 52.0%), the level of LDL cholesterol - by 1.28 mmol/L (by 50.2%).

Similar pronounced changes in lipidogram three hours after load were observed in overt hypothyroidism: the average level of TC was significantly (p<0.001) increased by 0.58 mmol/L, i.e. by 11.4%, TH level - by 0.73 mmol/L (by 31.7%), the content of LDL cholesterol - by 0.89 mmol/L (by 24.3%).

In the control group in the euthyroid status there were no statistically significant changes in the indices of the lipidogram, either fasting or three hours after fat load (p> 0.05).

Comparative analysis of lipid-tolerance test results between study groups showed that statistically comparable levels of TC and its fraction (LDL-cholesterol) in the serum of patients of the 1st and 2nd groups obtained on an empty stomach (p> 0.05) showed a significant difference of indices 3 hours after fat load (figure. 1, 2). In patients with SH index of TC was higher by 14.1%, and the level of LDL cholesterol - by 50.2% than in the group of patients with euthyroid status (p<0.001).

In the group of patients with overt hypothyroidism, lipidogram values were significantly higher than in patients with SH and euthyroid status at all stages of the study at $p < 0.001$ (figure 1, 2, 3).

Thus, at this stage of the study, it was demonstrated that the consumption of dietary fats in individuals with euthyroid status and in patients with subclinical hypothyroidism stimulated the development of different levels and duration of hyperlipemia by increasing fraction of TG-rich LP. This is likely to be due to a decrease in liver lipase activity and a cholesterol-ether transport protein under conditions of the least thyroid hormone deficiency, and a parallel decrease in the number of LDL receptors in the liver.

https://doi.org/10.46389/rjd-2021-1016

Table 2: Averaged TC, TG, LDL cholesterol according to lipid-tolerance test (M ± m).

Study groups	TC, mmol/L		p	TG, mmol/L		p	LDL cholesterol, mmol/L		p
	0*	3*		0*	3*		0*	3*	
Group 1 – SH (n=30)	4.58 ± 0.09	5.25 ± 0.08	<0.001	1.71 ± 0.01	2.60 ± 0,03	<0.001	2.55 ± 0.01	3.83 ± 0.04	<0.001
Group 2 – without TG pathology (n=30)	4.56 ± 0.10	4.60 ± 0.09	0.817	1.22 ± 0.05	1.30 ± 0,05	0.105	2.54 ± 0.01	2.55 ± 0.01	0.107
Group 3 – overt hypothyroidism (n=30)	5.11 ± 0.06	5.69 ± 0.06	<0.001	2.30 ± 0.06	3.03 ± 0,03	<0.001	3.66 ± 0.02	4.55 ± 0.04	<0.001

Notes: *time of blood taking, hours; p - level of significance of differences between indices before and after nutrition load (Student's T-test).

In some patients with high TSH, no clinical or laboratory evidence of hypothyroidism is observed. In addition, some ethnic groups have a genetically determined elevated TSH, which is not accompanied by a thyroid disorder. The lipidogram and lipid load test are cost-effective and simple laboratory studies to further evaluate cardiovascular risks in patients with hypothyroidism of varying severity and to make a clinical decision on adjustment of the corrective dosage of levothyroxine, the target level of TSH.

Conclusions

1. In patients of group 1 and 2 the mean levels of total cholesterol and LDL cholesterol were statistically comparable and in 3 hours after the fat load in patients of group 2 they remained unchanged, but probably increased by 14.6% and 50.2% in those of group 1. Thus, dyslipidemia in the postprandial period in individuals without additional risk factors was only found in individuals with thyroid disorders.
2. Subclinical hypothyroidism leads to lipid metabolism disorders, which are detected by the method of fat load test, and is a risk factor for the development of cardiovascular pathology resulted from long-term postprandial dyslipidemia.
3. Fat load test can be used as a marker of lipid metabolism disorder in patients with subclinical hypothyroidism and may be performed for early detection of dyslipidemia and timely correction.

Acknowledgments

The article was written as part of a dissertation for a Ph.D. degree in the subject "The effect of subclinical hypothyroidism on endothelial function, daily variability of blood pressure and lipid metabolism", based on the Department of Endocrinology of State Institution "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine". The authors are grateful for the assistance in conducting this study to collective of the

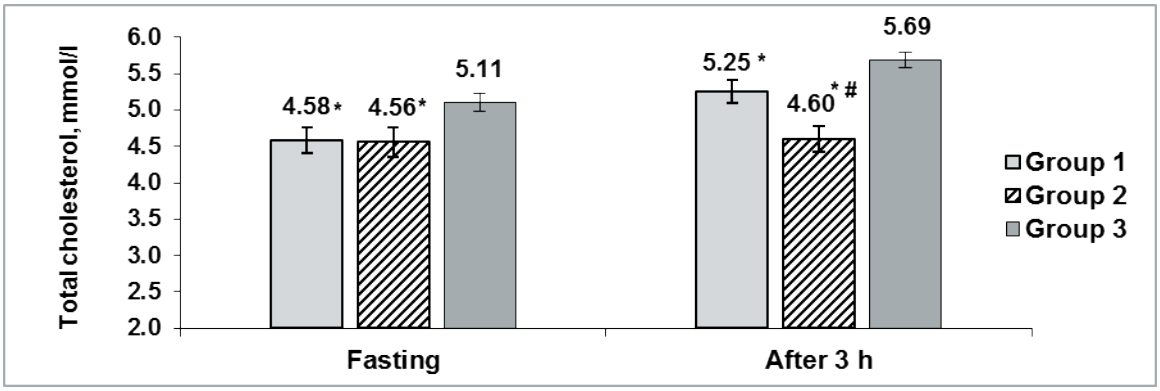

Figure 1: Average levels (M, 95% CI) of total fasting cholesterol and in three hours after fat load in groups 1, 2 and 3: * – $p < 0{,}001$ compared to group 3; # – $p < 0.001$ compared to group 1 (Student's t-test).

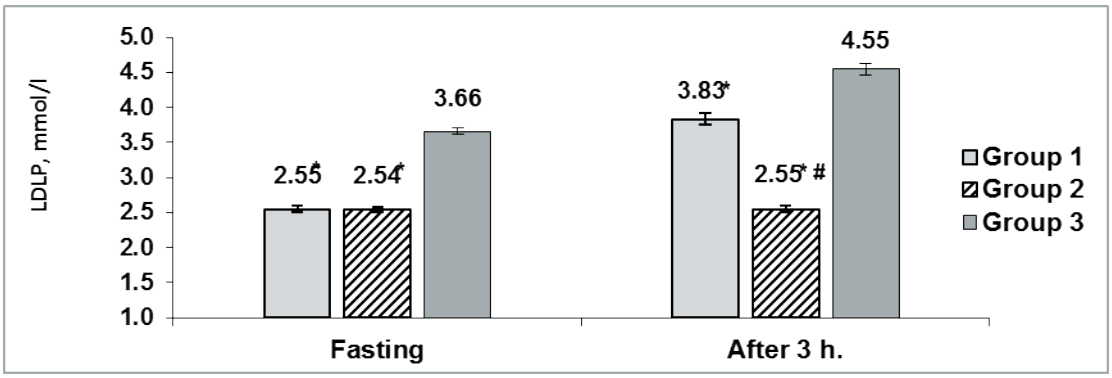

Figure 2: Average levels (M, 95% CI) of fasting LDL cholesterol and in three hours after fat load in groups 1, 2 and 3: * – $p < 0{,}001$ compared to group 3; # – $p < 0.001$ compared to group 1 (Student's t-test).

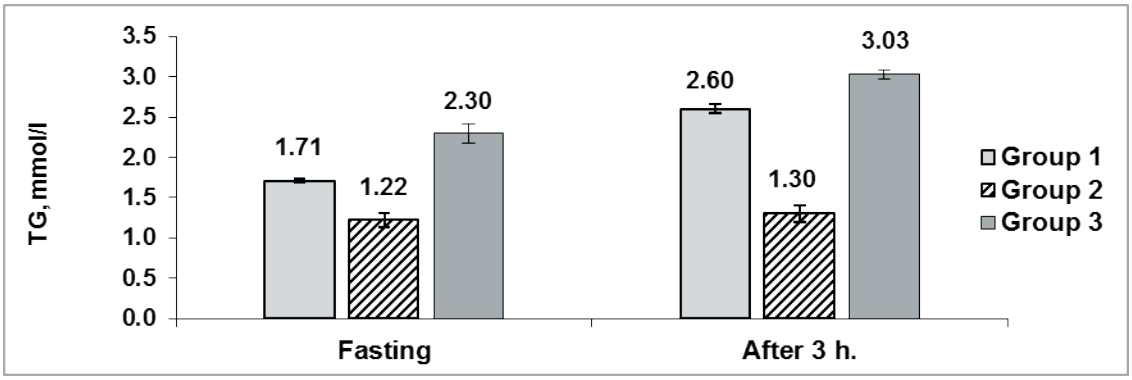

Figure 3: Average levels (M, 95% CI) of fasting triglycerides and in three hours after fat load in groups 1, 2 and 3: $p < 0.001$ for all comparisons between groups (Student's t-test).

«Laboratory of the Medical Diagnostic Center of the Medical Academy». The authors are grateful and offer deep appreciation to Dr. Irina Gubar and Dr. Yevgen Martsynik for the advice and valuable comments given while working on this article.

Conflict of Interest

The authors declare no conflict of interest.

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