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Original Article

Direct correlation between serum homocysteine level and insulin resistance index in patients with subclinical hypothyroidism: Does subclinical hypothyroidism increase the risk of diabetes and cardio vascular disease together?

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ABSTRACT

Background: Subclinical hypothyroidism known as mild thyroid disorder without significant sign and symptoms. The correlation between subclinical hypothyroidism and some of cardiovascular disease risk factors such as serum lipids, homocysteine levels and also insulin resistance index is not well established and the current study was conducted to clarify this issue.
Methods and materials: Seventy four patients with mild elevation in levels of thyroid stimulating hormone (TSH) along with normal levels of T3 and T4 were selected as patients group and 74 age and sex matched individuals were selected as healthy control group. Serum insulin, triglyceride, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol and homocysteine levels were measured. Obtained data compared between groups with independent sample *t*-test. For evaluation of the correlation between mentioned parameters Pearson correlation coefficient method was used.
Results: Serum levels of LDL-C and total cholesterol significantly increased in SCH group compared to healthy control group. Homeostatic Model Assessment of Insulin Resistance (HOM-IR) and serum homocysteine level significantly elevated in patients with SCH compared to control group. There was a significant direct correlation between HOM-IR and serum homocysteine levels in SCH patients.
Conclusion: Subclinical hypothyroidism likely have significant effect on insulin resistance as major diabetes risk factors and also cardiovascular disease risk factors such as homocysteine. The direct correlation between HOM-IR with serum homocysteine level indicate the possible role of insulin resistance in elevation of serum homocysteine in SCH patient group.

1. Introduction

Subclinical hypothyroidism (SCH) known as mild hypothyroidism. In SCH, the serum level of T4 is usually normal but the serum thyrotropin (TSH) levels is mildly increased and in majority of SCH patients has less than 10 mi/u/l [1]. Prevalence of SCH is from 3% to 8% in general population [2]. SCH has not obvious clinical sign and symptoms, therefore, this is highly possible that this disease remained undiagnosed for the many years, because of that detection of SCH adverse effects on cardiovascular or diabetes risk factors is highly necessary. Cardiovascular diseases are one of the most common causes of death worldwide. As many as 17 million people died of cardiovascular disease in 2015, in the other word about 32% of deaths are due to this disease [3]. However, the disease is completely preventable and researchers believed that 90% of cases can be preventable [4]. Cardiovascular disease is one

Abbreviation: HOM-IR, homeostatic model assessment of insulin resistance; SCH, Subclinical hypothyroidism; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol.

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of the diseases with significant biochemical bases and numerous biochemical risk factors suggested for it. One of this risk factors is serum homocysteine level which is an α-amino acid that not involved in proteinogenesis. Homocysteine produced from the methionine in the body. Folate and vit B12 have essential roles in homocysteine metabolism. Homocysteine have significant clinical importance and well known as important cardiovascular disease risk factor [5–7]. Relationship between thyroid dysfunction and cardiovascular risk factors such as serum lipids and homocysteine levels were investigated [8–12]. In addition, association between thyroid dysfunction and insulin resistance, as major diabetes and metabolic syndrome risk factor, were evaluated. In some of this studies association between metabolic syndrome and thyroid dysfunction specially SCH was not accepted [13], but some studies demonstrated a significant association between thyroid function and metabolic syndrome components [14,15]. In specially some of studies reported that the insulin resistance had increased in patients with thyroid dysfunction specially SCH [16,17], on the other hand this is well known that insulin resistance involved in atherosclerosis pathogenesis [18], therefor likely relationship between SCH and insulin resistance has significant importance.

The correlation between this risk factors in patients with SCH is not well established. In addition the likely correlation between thyroid hormones particularly TSH, homocysteine, serum lipids and Homeostatic Model Assessment of Insulin Resistance (HOM-IR) need to further investigation, therefor we designed the current clear and simple clinical study with sufficient sample size to investigate the mentioned correlations properly.

1.1. Patients and methods

The current study was approved by Babol University of Medical Science student research committee (NO: 4899) and also ethical committee (NO:1396.128). This study was conducted on patients whose referred to Valiasr medical laboratory, Babol, Iran, for thyroid hormones levels checkup during 2017–2018. The complete medical history were taken from all of the patients and after that 5 ml fasting blood sample were taken from the patients. We applied the strict inclusion and exclusion criteria for the patients and controls selection which described below.

1.2. Inclusion criteria

Mild elevation of serum TSH level (higher than 5 mlu/l) and normal T4 levels that repeated for the three times without significant clinical presentation and have age higher than 18 are inclusion criteria.

1.3. Exclusion criteria

Medical history of thyroid dysfunction, cardiovascular disease, diabetes, any type of cancers, infection disease, inflammatory disease, pregnancy, renal and liver disease, regular use of lipid lowering drugs, NSAIDS and steroids, use of drugs that inducted thyroid function such as lithium, have age less than 18 and more than 60, smoking, alcohol consumption and significant obesity are the exclusion criteria.

1.4. Subject's selection

Among the all patients with subclinical hypothyroidism, 74 patients (37 men and 37 women) were selected as patient group according to inclusion and exclusion criteria. Control group were included of 74 (37 men and 37 women) healthy sex and age matched with case group. This is should be noted that the informed consent were taken from all of the study subjects.

1.5. Laboratory analysis

The serum homocysteine level were measured by ELISA method according to kit instruction (Axis Shield, UK). The serum levels of TSH and T4 were measured with chemiluminescence method by Abbot instrument (USA), insulin serum levels were measured with ELISA method with using commercial kit (Diametra, Italy), FBS, TG, CHOL,HDL and LDL serum levels were measured with use commercial kits (Parsazmoon, Iran) by means of auto analyzer instrument (Hitachi 704, Japan). Insulin resistance index were calculated according to below formula:

$$\boldsymbol{HOM-IR} = \frac{\text{fasting plasma glucose}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{fasting insulinemia}\left(\frac{\mu\text{U}}{\text{mL}}\right)}{405}$$

1.6. Statistical analysis

Obtained data were saved and analyzed by using SPSS version 17 software. For comparison means of parameters between groups independent sample *t*-test were used. For evaluation of correlation between variable we use of pearson correlation coefficient. P-value < 0.05 considered as statistical significant.

2. Results

As shown in Table 1, the findings of current study demonstrated that the serum level of homocysteine and insulin increased in patients with SCH compared to healthy control group. Serum level of LDL-C and total cholesterol increased significantly in patients with SCH compared to healthy subjects, while the level of serum triglyceride and HDL-C not significantly different between two groups. Serum fasting glucose level has not differ between two group but the Homeostatic model of insulin resistance (HOM-IR) increased significantly in patients with SCH compared to healthy control group. Table 2 demonstrated the correlation between Homeostatic model of insulin resistance with serum homocysteine, lipid profile and thyroid hormones levels in patients with SCH. As shown in Table 2 HOM-IR was positively correlated with serum LDL-C and negatively correlated with serum T4 levels in patients with SCH but this correlations is not statistical significant but serum TSH level were significantly correlated with HOMA-IR in patients with SCH (Fig. 1). There was significant correlation between serum homocysteine and HOMA-IR levels in patients with SCH (Fig. 2).

3. Discussion

As we noted in introduction section, hyper-homocysteinemia is one of the major cardiovascular disease risk factors. Previous study has shown that there is relation between serum total

Table 1
Comparison of mean ± SD of variables between SCH patients and healthy subjects.

parameters	SCH patients n = 74	Healthy controls n = 74	p-value
Age(years)	40 ± 12	41 ± 11	0.708
Homocysteine(μm/l)	8.7 ± 3.1*	6.9 ± 2.5	0.000
FBS(mg/dl)	94 ± 13	94 ± 15	0.842
TG(mg/dl)	166 ± 64	170 ± 68	0.730
Total cholesterol(mg/dl)	208 ± 38*	189 ± 31	0.001
HDL-C(mg/dl)	46 ± 7	48 ± 8	0.111
LDL-C (mg/dl)	129 ± 37*	107 ± 30	0.000
TSH (μIU/ml)	7.5 ± 1.8*	2 ± 1	0.000
T4(μg/dl)	6.7 ± 1.3	6.5 ± 1.1	0.538
Insulin(μIU/ml)	8.9 ± 2.7*	7.1 ± 2.9	0.000
HOM-IR	2.08 ± 0.8*	1.6 ± 1	0.010

* statistical significant.

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