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The Effects of Thyroid Dysfunctions on Insulin Resistance in Patients with Hepatosteatosis

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Hepatosteatosis can develop due to insulin resistance. The effect of thyroid function status on insulin sensitivity and resistance is of great interest but the data is still conflicting.
Objectives. The aim of this study was to evaluate the effects of thyroid dysfunctions on insulin resistance in patients with hepatosteatosis.
Material and Methods. A total of 407 patients with hepatosteatosis were divided into three groups: 102 subjects with hypothyroidism, 103 with hyperthyroidism and 202 with normal thyroid function (control group). We measured serum thyroid stimulating hormone (TSH), free T4 (FT4) and free T3 (FT3) concentrations, blood glucose and insulin levels, serum lipid levels, hepatic transaminases and the homeostasis model assessment of insulin resistance (HOMA IR).
Results. Neither hypothyroidism patients nor hyperthyroidism patients showed significant differences in HOMA IR, glucose and insulin levels ($p > 0.05$ for each). The frequency of insulin resistance was similar in all groups ($p > 0.05$).
Conclusions. Based on our findings, hypothyroidism and hyperthyroidism are not correlated to insulin resistance in patients with hepatosteatosis. Different causes which are associated with insulin resistance should be investigated in patients with thyroid dysfunction and hepatosteatosis (**Adv Clin Exp Med 2014, 23, 6, 913–918**).

Key words: insulin resistance, hepatosteatosis, hypothyroidism, hyperthyroidism.

Insulin resistance has a key role in the development of hepatic steatosis and, potentially, steatohepatitis [1]. Strong epidemiological, biochemical, and therapeutic evidence supports the premise that the primary pathophysiological derangement in most patients with hepatosteatosis is insulin resistance [2]. Increases in visceral adipose tissue and intrahepatic fat correlate with increased gluconeogenesis, increased free fatty acid levels, and insulin resistance [3].

Carbohydrate metabolism disorders have been found to be associated with thyroid dysfunctions and, therefore, thyroid disease prevalence in patients with diabetes is significantly higher than in the general population [4, 5]. This indicates a possible interplay between thyroid status and insulin resistance.

In hyperthyroidism, decreased, normal, or even increased levels of plasma insulin have been reported [6]. However, the increased degradation of insulin in hyperthyroid subjects was a consistent finding [6, 7]. In thyrotoxicosis, glucose absorption from the gastrointestinal tract increases due to the higher rate of stomach emptying and increased blood flow of the portal vein. It has been also postulated that severe thyrotoxicosis can lead, in the long run, to irreversible pancreatic damage [8].

Hypothyroidism is an established risk factor for insulin resistance, hyperlipidemia, hypercoagulability and low grade inflammation [9, 10]. In this type of thyroid dysfunction, adrenergic activity and intestinal glucose absorption decrease and lead to a decrease in liver and muscle glycogenolysis, gluconeogenesis and also basal insulin secretion [11].

There are many studies which have investigated the association between thyroid dysfunctions and insulin resistance. The results of these studies are inconsistent and furthermore, hepatosteatosis, which is strongly associated with insulin resistance, was not investigated in these studies [6, 12–15].

In the present study, we aimed to evaluate the effects of thyroid dysfunctions on insulin resistance in patients with hepatosteatosis.

Material and Methods

The study was arranged in an internal medicine department of a tertiary hospital from September 2011 to June 2012. A total of 407 patients with hepatosteatosis were included and separated into three groups. One of the study groups was comprised of 102 patients with hypothyroidism and the other one was comprised of 103 patients with hyperthyroidism. The control group included 202 patients with normal thyroid function. The institution review board of the hospital approved the study and informed consent was obtained from all the study participants. The study was conducted in accordance with the Declaration of Helsinki. Inclusion criteria were age of 18–65 years, newly diagnosed and untreated patients with thyroid dysfunction and hepatosteatosis. Patients with diabetes, hypertension, obesity, dyslipidemia, atherosclerosis, polycystic ovarian disease, liver disorders, renal disorders, congestive cardiac failure, other systemic illnesses, pregnancy, malignancies, alcoholism, intake of oral contraceptive pills, other medications that alter thyroid functions or insulin resistance, and subclinical forms of thyroid dysfunction were excluded.

Non-alcohol fatty liver disease (NAFLD) was defined as hepatosteatosis and it was evaluated by experienced radiologists with a Toshiba Xario SSA-790 model ultrasound (2006, Japan). The diagnosis of NAFLD was based on increased liver echogenicity on ultrasonography compared to the kidneys, vascular blurring and deep attenuation [16]. Four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) are used to diagnose NAFLD [17]. Long-axis images of the right lobe of the liver including the right kidney and a dual image of the liver and spleen for direct comparison of echogenicity were obtained. The liver was considered to be normal if there was normal hepatic echogenicity and normal beam attenuation.

We measured serum TSH, FT4 and FT3 concentrations, blood glucose and insulin levels, serum lipid levels (LDL, HDL, triglycerides), hepatic transaminases (AST, ALT) and homeostasis model assessment of insulin resistance (HOMA IR). Patients with a high TSH level with low FT4 level and patients with a low TSH level with high FT4 or FT3 level were considered to have hypothyroidism and hyperthyroidism, respectively. Blood samples were collected after an overnight fasting. Thyroid function profile (TSH, FT3 and FT4) and insulin levels were measured by an Abbott Architect I 2000 SR analyzer system (Illinois, USA). Serum glucose, lipids, AST, ALT, urea and creatinine were analyzed on a Beckman Coulter LX 20 (Massachusetts, USA) using commercially available kits. Weight, height and body mass index (BMI) were documented. A body mass index (kg/(height,m)^2) $\geq$ 30 kg/m^2 was considered as an exclusion criterion. Insulin resistance was measured using homeostasis model assessment using the Oxford HOMA calculator (http://www.dtu.ox.ac.uk/homa/index.html).

The SPSS 19.0 package program (SPSS Inc., Chicago, Illinois) was used for statistical analysis. The data was reported as the mean ± standard deviation (SD). Chi square and Kolmogorov-Smirnov tests were used to compare categorical measures between the groups and to show the normal distribution of quantitative measurements, respectively. ANOVA or Kruskal Wallis tests were used for comparison of quantitative measurements between the three groups. The level of statistical significance was considered as $p \leq 0.05$ in all tests.

Results

Average age was 50.8 ± 14.1 years. Sex, mean age and mean BMI were not significantly different between the control and study groups ($p = 0.116$, 0.319 and 0.168, respectively, Table 1). The female sex was preponderant (266 [65%] females vs. 141 [35%] males). Not surprisingly, mean serum TSH was normal (2.97 ± 1.1), high (18.2 ± 7.4) and low (0.01 ± 0.08) in the control, hypothyroidism and hyperthyroidism groups, respectively. The difference between the groups according to the serum TSH levels was statistically significant ($p = 0.001$, Table 2). Correspondingly, mean serum FT3 and FT4 were normal, low and high in the control, hypothyroidism and hyperthyroidism groups, respectively. The difference was statistically significant ($p = 0.001$) for both FT3 and FT4. The mean serum insulin levels of the control, hypothyroidism and hyperthyroidism groups were 14.7 ± 11.2, 13.4 ± 14.3 and 12.8 ± 10.4, respectively. The groups were comparable according to the serum insulin levels ($p = 0.638$). Insulin resistance frequency and HOMA-IR were comparable

Table 1. Baseline characteristics of the subjects

Parameter	Total	Groups			
		control	hypothyroidism	hyperthyroidism	p
n	407	202	102	103	
Sex: males, n (%) females, n (%)	 141 (35%) 266 (65%)	 73 (36%) 129 (64%)	 33 (32%) 69 (68%)	 35 (34%) 68 (66%)	0.116
Age yrs (mean ± SD)	50.8 ± 14.1	49.4 ± 13.7	51.8 ± 11.5	49.7 ± 15.2	0.319
BMI kg/m^2 (mean ± SD)	26.6 ± 2.8	26.9 ± 2.6	27.2 ± 1.5	25.1 ± 2.4	0.168

BMI – body mass index.

in the control and two study groups. There were 97 (48%), 43 (43%) and 41 (40%) patients with insulin resistance in the control, hypothyroidism and hyperthyroidism groups, respectively. There was no statistically significant difference between the groups (p = 0.497, Fig. 1, Table 2).

The mean levels of HOMA-IR were 3.5 ± 3.7, 3.2 ± 2.1 and 3.3 ± 3.1 in the control, hypothyroidism and hyperthyroidism groups, respectively (p = 0.394, Table 2, Fig. 2). LDL cholesterol levels were significantly higher in the hypothyroidism group compared to both the control and hyperthyroidism groups (p < 0.001). Other biochemical tests (glucose, triglyceride, HDL cholesterol, AST, ALT, urea and creatinine) were not statistically different (p > 0.05, respectively, Table 2).

Discussion

In the present study, we investigated the effects of thyroid dysfunction on insulin resistance in patients with hepatosteatosis. The effect of thyroid function status on insulin sensitivity is of great interest but the data is still conflicting [5]. Several studies were performed to elucidate the association between insulin resistance and hypothyroidism or hyperthyroidism [12–14, 18]. However, hepatosteatosis was not evaluated in these studies.

It is well known that insulin resistance is strongly related to hepatosteatosis pathogenesis [19]. The frequency of insulin resistance in healthy individuals with normal glucose tolerance is nearly 25% of the populations [19, 20]. In the current study, the frequency of insulin resistance in the control group was higher, up to 48%. This difference can be ascribed to hepatosteatosis present in all subjects including the control group.

Of particular interest is the influence of thyroid hormone action on insulin levels. The data on insulin levels in patients with thyroid dysfunction is conflicting [5, 14]. For example, patients with hypothyroidism can experience hypoglycemia. This phenomenon can be attributed to reduced gluconeogenesis leading to decreased liver glucose output [11, 21]. On the other hand, previous studies in hypothyroid animal models demonstrated that insulin resistance is present in peripheral tissues [22, 23].

In contrast to the aforementioned studies, no association between overt hypothyroidism and

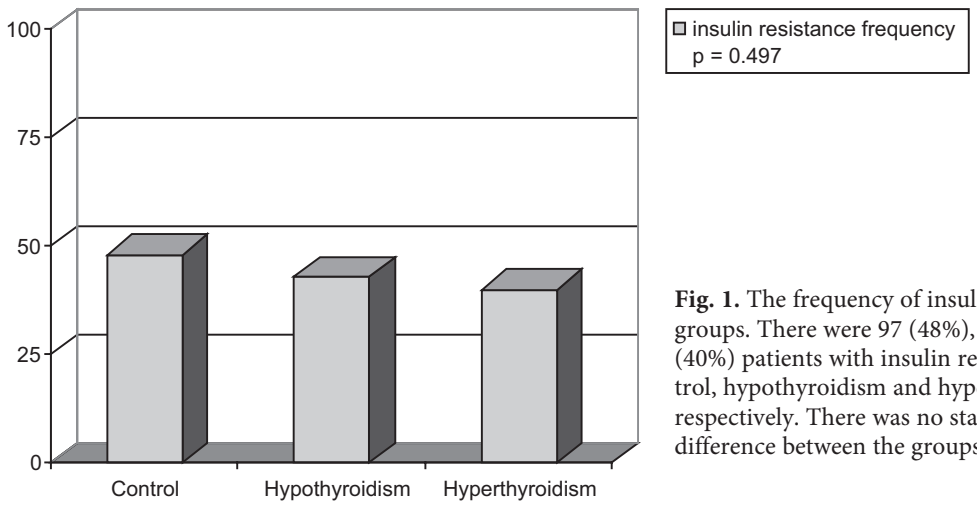

Fig. 1. The frequency of insulin resistance of the groups. There were 97 (48%), 43 (43%) and 41 (40%) patients with insulin resistance in the control, hypothyroidism and hyperthyroidism groups, respectively. There was no statistically significant difference between the groups (p = 0.497)

Table 2. Biochemical parameters and HOMA-IR of the subjects

Parameter	Normal	Control	Hypothyroidism	Hyperthyroidism	p
Insulin resistance frequency	HOMA-IR < 2.5	97 (48%)	43 (43%)	41 (40%)	0.497
HOMA-IR	< 2.5	3.5 ± 3.7	3.2 ± 2.1	3.3 ± 3.1	0.394
Insulin (mcU/mL)	1.4–14	14.7 ± 11.2	13.4 ± 14.3	12.8 ± 10.4	0.638
Glucose (mg/dL)	70–110	92.1 ± 12.3	89.6 ± 14.2	94.3 ± 12.0	0.097
FT3 (pg/mL)	2.3–4.2	3.3 ± 0.47	1.19 ± 0.29	6.26 ± 1.27	0.001
FT4 (ng/dL)	0.88–1.72	1.19 ± 0.19	0.69 ± 0.22	4.71 ± 1.2	0.001
TSH (mcIU/mL)	0.57–5.56	2.97 ± 1.1	18.22 ± 7.4	0.01 ± 0.08	0.001
HDL (mg/dL)	35–55	46.1 ± 13.4	46.3 ± 8.1	46.8 ± 9.7	0.947
LDL (mg/dL)	0–130	123.5 ± 29.2	141.5 ± 28.3	111.7 ± 32.4	< 0.001
Triglyceride (mg/dL)	0–200	164.7 ± 30.0	173.1 ± 29.3	161.0 ± 68.7	0.217
ALT (IU/L)	0–35	37.4 ± 21.0	34.2 ± 18.8	32.3 ± 20.0	0.450
AST (IU/L)	0–35	24.6 ± 22.5	26.4 ± 18.6	25.5 ± 14.5	0.069
Urea (mg/dL)	15–45	25.2 ± 8.4	27.4 ± 8.6	26.6 ± 11.6	0.089
Creatinine (mg/dL)	0.6–1.2	0.97 ± 0.19	0.79 ± 0.35	0.77 ± 0.26	0.271

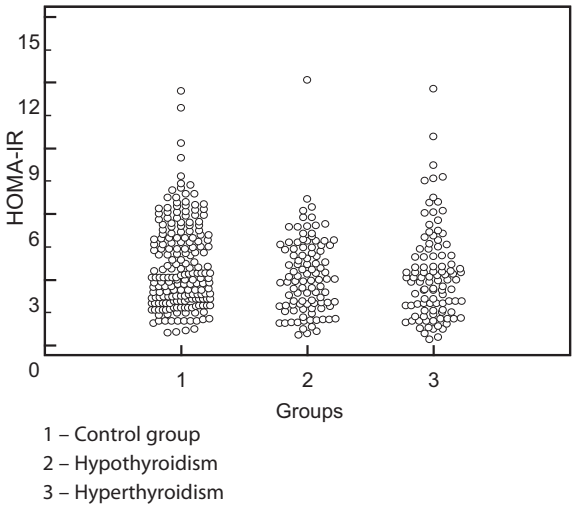

Fig. 2. The mean level of HOMA-IR of the groups. The mean levels of HOMA-IR were 3.5 ± 3.7, 3.2 ± 2.1 and 3.3 ± 3.1 in the control, hypothyroidism and hyperthyroidism groups, respectively (p = 0.394)

HOMA-IR was found by Owecki et al. [15]. Consistently, patients with hypothyroidism treated with levothyroxine had no impairment of insulin-stimulated glucose disposal in the forearm [24]. Concordant with these last studies, we found that the frequency of insulin resistance in hypothyroidism was comparable to both the control and hyperthyroidism groups.

Next, we tested a possible correlation between insulin resistance in patients with hepatosteatosis and hyperthyroidism. As discussed extensively in the review by Dimitriadis and Raptis [5], impaired glucose tolerance is a frequent finding in thyrotoxic subjects. Insulin binding at low insulin concentrations was reduced in thyrotoxic patients and was accompanied by impaired insulin sensitivity of glucose transport and oxidation and lipogenesis. Shen et al. [25] demonstrated decreased peripheral insulin sensitivity in hyperthyroidism.

Unlike other studies, we found that insulin resistance frequency and HOMA-IR in patients with hyperthyroidism were comparable to both the control and hypothyroidism groups. This result may be related to hepatosteatosis.

Regarding the association of the lipid profile with insulin resistance, fasting and postprandial lipoprotein lipase activity has been reported to be significantly reduced in patients with insulin resistance and hyperinsulinemia [26, 27]. In the present study, triglyceride levels were comparable despite thyroid dysfunction. This condition might be a result of lipoprotein lipase activity that was affected by insulin resistance as described above. Fasting insulin levels in the different groups were concordant to the lipid profile and previous reports [26, 27].

Our results suggest that hypothyroidism and hyperthyroidism have no severe effect on insulin resistance in patients with hepatosteatosis.

Our study has some limitations. First, it would have been beneficial if the groups had been compared with similar groups without hepatosteatosis. Second, in addition to hepatosteatosis, genetic

factors, body fat distribution, new endogenous hormones, inflammatory mediators and differences in lifestyle should be investigated for best results. Third, we do not have any idea about the duration of thyroid disease. Fourth, evaluation of hepatosteatosis with ultrasound can be another limitation, but we accepted the ultrasound results for diagnosis of hepatosteatosis because of the high sensitivity, specificity and predictive values of ultrasound in the diagnosis of hepatosteatosis [28, 29].

In conclusion, we can say that insulin resistance may not be sufficiently affected by thyroid dysfunctions due to the other strong etiologic causes in patients with hepatosteatosis (like genetic factors, body fat distribution, new endogenous hormones, inflammatory mediators, differences in lifestyle, etc.). In hepatosteatosis, the abnormalities in other liver-related metabolic factors are so severe that they presumably minimize any other influencing factor, like thyroid dysfunctions here.

Finally, thyroid dysfunctions may have no effect on insulin resistance in patients with hepatosteatosis. Further studies with greater sample sizes, and with or without hepatosteatosis are needed for clear information.

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