Thyroid dysfunction in obese adults in relation to nonalcoholic fatty liver disease

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Background
Hormones of the thyroid gland play an important role in the regulation of various metabolic processes. Disturbances in thyroid hormone concentrations may lead to hyperlipidemia and obesity, thus contributing to nonalcoholic fatty liver disease (NAFLD).
Aim
To evaluate thyroid dysfunction and determine its possible relationship to NAFLD in obese adults.
Patients and methods
Our cross-sectional study recruited 100 obese patients, who were subjected to full medical history, physical examination, abdominal ultrasonography, and routine laboratory tests in addition to liver function and thyroid function tests. NAFLD was recognized on the basis of ultrasonographic findings, and in the absence of other causes of liver disease.
Results
The patients were divided into two groups: group 1 (65 patients) with NAFLD and group 2 (35 patients) without NAFLD. Out of 100 patients recruited into the study, the most common thyroid dysfunction was overt hypothyroidism (22%), followed by (9%) subclinical hypothyroidism. Twenty-six (40%) patients with NAFLD were found to have thyroid dysfunction, of them eight (12.3%) NAFLD patients had subclinical hypothyroidism, and 18 (27.7%) NAFLD patients had overt hypothyroidism. Although prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) was 22 and 9%, respectively, among patients with obesity, there was nonsignificant positive correlation between BMI and thyroid-stimulating hormone (r=0.051 and P=0.612). Multivariate regression analysis showed that fatty liver, obesity index, and dyslipedemia were predictors of thyroid dysfunction in obese patients.
Conclusion
Thyroid hypofunction is common in obese patients with NAFLD, which has implications for screening for hypothyroidism in patients with NAFLD and for the administration of appropriate therapy for hypothyroidism.

Keywords:
hypothyroidism, nonalcoholic fatty liver disease, obesity

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is an important health problem. It is considered one of the most common causes of chronic liver disease [1]. NAFLD includes a wide range of pathology from simple steatosis to nonalcohol steatohepatitis (NASH), fibrosis, cirrhosis, and is identified by excessive free fatty acids and triglyceride accumulation in the liver. Although type 2 diabetes mellitus and obesity contribute as risk factors for NAFLD, other endocrine disorders such as thyroid dysfunction, adrenal insufficiency, growth hormone deficiency, and polycystic ovary syndrome also play a role in the occurrence of NAFLD [2].

The thyroid gland is significantly involved in the regulation of energy expenditure, adipogenesis, carbohydrate, and lipid metabolism, thereby playing an important role in the development of metabolic abnormalities [3,4]. Thyroid hormones affect hepatic fat accumulation through multiple pathways, including stimulation delivery of free fatty acid to the liver for reesterification to triglycerides, and increasing β-oxidation fatty acid.

Several studies have shown an association between thyroid dysfunction and NAFLD, but have

demonstrated inconsistent results. Therefore, to better characterize this association, we conducted our study to evaluate thyroid dysfunction and determine its possible relationship to NAFLD in obese adults.

Patients and methods

This cross-sectional study recruited 100 obese patients (BMI≥30 kg/m^2) followed up at the obesity outpatient clinic of Internal Medicine Department at Assiut University Hospitals during the period between May 2017 and May 2018.

Exclusion criteria

Patients with any liver diseases such as viral-induced hepatitis or liver cirrhosis, liver malignancy, diabetic patients, patients with history of thyroid disease, or other endocrinal disorders.

All participants in the study were subjected to:

(1) Full history taking and clinical examination: BMI was calculated as weight divided by squared height (kg/m^2), waist circumference, and waist-to-hip ratio was calculated as the ratio of the circumference of the waist to that of the hips.
(2) Ultrasonographic examination of the liver: liver ultrasound was performed by an experienced consultant by using conventional B-mode with a convex 2.5–5 MHz probe (logiq p5 GE Ultrasound; USA). NAFLD was defined according to four ultrasonographic criteria for fatty liver : hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring [5], in the absence of other causes of liver disease, alcohol consumption, or seropositivity to antibody to hepatitis C virus or hepatitis B surface antigen.
(3) Laboratory investigations: blood samples were obtained from each participant after overnight fasting. Laboratory studies included fasting blood sugar (mg/dl), urea, and creatinine; lipid profile, liver function test; and hepatitis B virus surface antigen, hepatitis B surface antibody, and antihepatitis C antibody. Thyroid function tests [free T3, free T4, and thyroid-stimulating hormone (TSH)] were assessed by enzyme-linked immunosorbent assay technique.

The study was approved by Assiut University ethics committee and review board. All the patients who participated in the study provided written informed consents.

Statistical analysis

Data were collected and analyzed by computer program SPSS, version 24 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean±SD; categorical variables were expressed as number and percentage. Student's t test and one-way analysis of variance were used to compare continuous variables. χ^2 test was used to compare categorical variables. Correlations between parameters measured were calculated using Spearman's correlation coefficient. Multivariate regression analysis was used to determine the predictors of thyroid dysfunction in obese, adult patients. P value was significant if less than 0.05.

Results

This cross-sectional study involving 100 obese patients, 55 (55%) men and 45 (45%) women, mean age 30±4 years. Sixty-five (65%) patients have NAFLD versus 35 (35%) patients with normal liver ultrasound. As regards thyroid dysfunction in the study group; 22 (22%) patients have overt hypothyroidism, nine (9%) patients had subclinical hypothyroidism, and 69 (69%) patients had normal thyroid function test; comparison between different grades of thyroid dysfunction showed a significant difference in obesity index, total cholesterol, triglycerides, low-density lipoprotein (LDL) (P=0.02, 0.01, 0.04, 0.03, respectively) (Table 1, Fig. 1).

According to obesity index WHO classification in 2014 [6], the patients were divided into three groups; 31 (31%) patients were of obese class 1 (with BMI ranging from 30 to <35); 23 (23%) patients were of obese class 2 (with BMI ranging from 35 to <40), and 46 (46%) patients were of obese class 3 (with BMI ≥40). Prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) was 22 and 9%, respectively, among patients with obesity. There was nonsignificant positive correlation between BMI and TSH (r=0.051 and P=0.612) (Fig. 2).

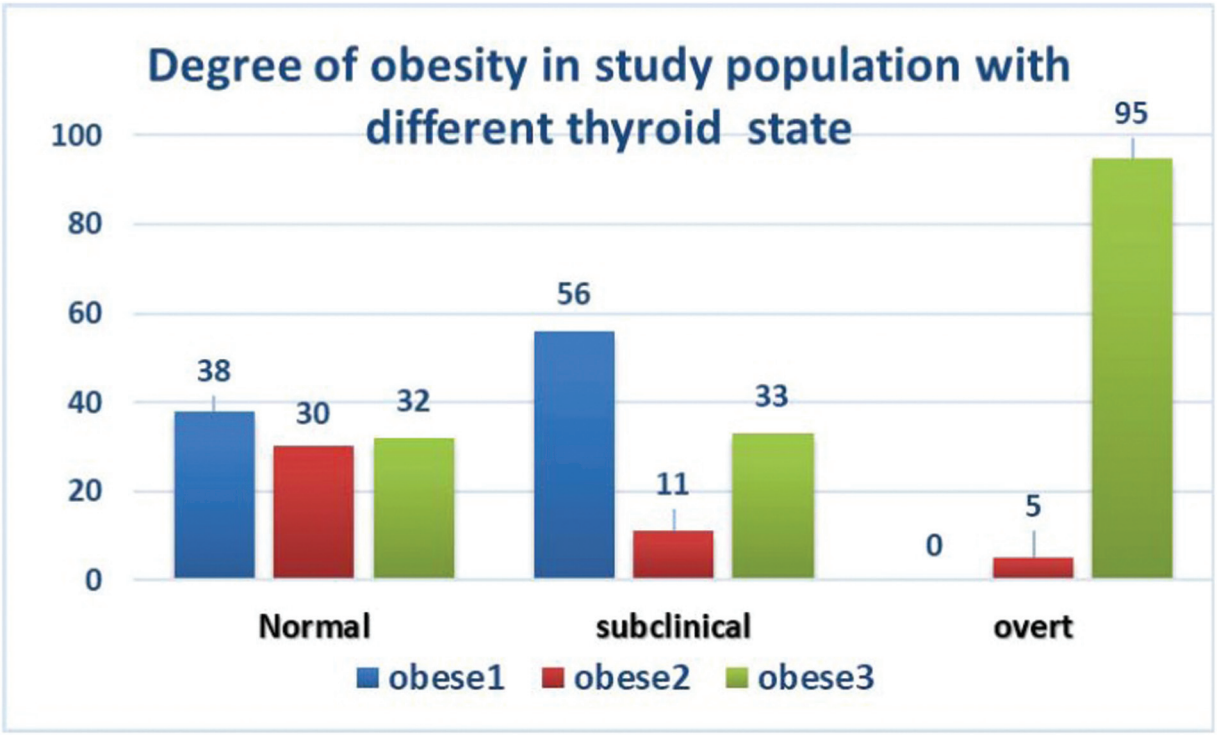
The comparison between patients with and without NAFLD is described in Table 2, with higher significant difference in the mean levels of each of BMI, alanine aminotransferase, aspartate aminotransferase, FT3 (P=0.001, <0.001, <0.001, 0.008, respectively) in patients with NAFLD than in those with normal liver ultrasound findings. The prevalence of thyroid dysfunction (whether overt hypothyroidism or subclinical hypothyroidism) among

Table 1 Comparison of clinical and laboratory findings between different grades of thyroid dysfunction

Parameters	Normal (*N*=69)	Subclinical hypothyroidism (*N*=9)	Overt hypothyroidism (*N*=22)	*P* value
Age (years)	30±4	32±5	29±3	0.21
Sex (male)	39 (56)	6 (67)	10 (48)	0.63
Body weight (kg)	98±8	103±10	98±8	0.21
Height (m^2)	1.6±0.06	1.6±0.07	1.5±0.6	0.44
BMI (kg/m^2)	38±3	40±4	39±3	0.23
WC (cm)	92±13	104±21	95±15	0.08
WHR	0.8±0.01	0.8±0.02	0.8±0.02	0.60
Systemic hypertension	18 (26)	5 (55)	5 (24)	0.12
Obesity index				
Obese class 1	26 (38)	5 (56)	0 (0)	**0.02**
Obese class 2	21 (30)	1 (11)	1 (5)	
Obese class 3	22 (32)	3 (33)	21 (95)	
ALT (IU/l)	41±16	53±32	42±12	0.20
AST (IU/l)	20±7	25±9	21±8	0.16
Albumin (g/dl)	1.9±0.06	1.8±0.07	1.8±0.06	0.90
Total cholesterol (mg/dl)	147±46	205±40	202±30	**0.01**
Triglycerides (mg/dl)	120±44	148±66	146±42	**0.04**
HDL (mg/dl)	63±17	61±28	54±17	0.23
LDL (mg/dl)	62±23	108±41	86±35	**0.03**

Data are presented as mean±SD and *n* (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference; WHR, waist-to-hip ratio. Bold values is significant and non bold values is non significant.

Figure 1



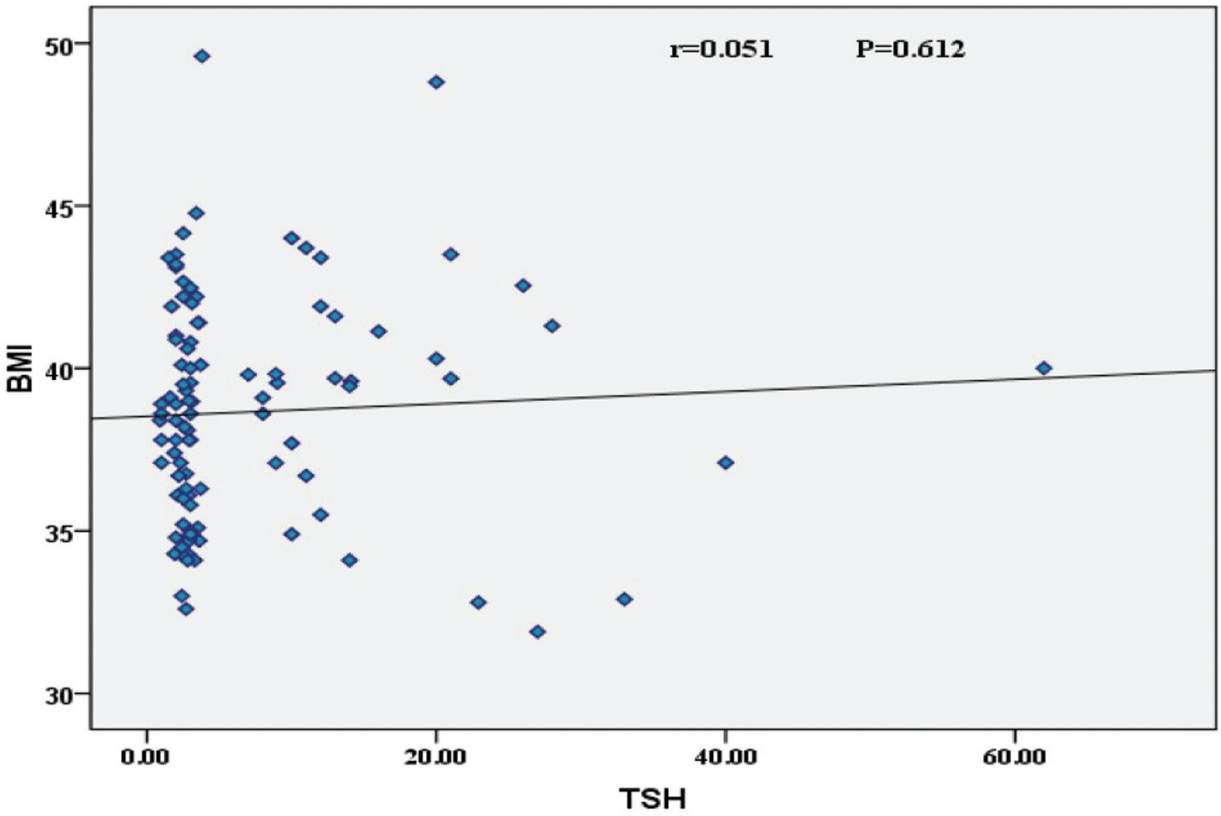
Degree of obesity in the study group with different thyroid states.

patients with and without NAFLD is presented in Table 3. The current study showed that obesity index, dyslipidemia, and fatty liver was independent factors for thyroid dysfunction in obese adult patients (Table 4).

Discussion

In this study, 100 obese patients were recruited with a mean age of 30±4 years, 55 (55%) men, and 45 (45%) women. In this study, the mean BMI was 39±3 with

Figure 2



Correlation between TSH and BMI. TSH, thyroid-stimulating hormone.

Table 2 Clinical and laboratory data in patients with nonalcoholic fatty liver disease versus patients without nonalcoholic fatty liver disease

	Patients with NAFLD (*N*=65) (mean±SD)	Patients without NAFLD (*N*=35) (mean±SD)	*P* value
Age (years)	30.18±4.49	29.94±3.51	0.817
BMI (kg/m^2)	39.38±3.47	37.31±3.17	**0.001**
WC (cm)	92.69±14.05	94.73±15.72	0.896
ALT (IU/l)	47.91±13.66	32.75±19.95	<**0.001**
AST (IU/l)	22.67±6.23	16.27±7.52	<**0.001**
Albumin (g/dl)	1.87±0.06	1.87±0.06	0.561
Total cholesterol (mg/dl)	165.29±50.27	161.77±48.92	0.508
TGs (mg/dl)	124.90±41.04	134.11±57.23	0.859
LDL (mg/dl)	72.66±34.62	68.36±25.72	0.851
HDL (mg/dl)	59.48±16.01	64.33±22.04	0.299
FT3 (pg/dl)	3.36±1.04	3.9257±0.83	**0.008**
FT4 (ng/dl)	3.44±3.44	4.69±4.42	0.190
TSH (μIU/ml)	9.07±3.09	3.69±2.88	0.114

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; TG, triglycerides; TSH, thyroid-stimulating hormone; WC, waist circumference.

three grades of obesity and a statistically significant difference between the three groups in the mean level of TSH ($P<0.05$). The association between TSH and BMI was clarified by Chen *et al.* [7] to be under the impact of adipose tissue signals and leptin may have significant effects on thyroid function by central regulation of thyroid-releasing hormone. Although 22 patients had overt hypothyroidism, 21(95%) of them were obese grade 3 with a BMI equal to or more than 40. There was nonsignificant positive correlation between BMI and TSH ($r=0.051$ and $P=0.612$). These findings came in contrast with Solanki *et al.* [8] who reported a significant positive association between participants' BMI and their mean serum TSH levels. Moreover, Knudsen *et al.* [9] showed that serum TSH is positively correlated with BMI.

This study showed that the prevalence of NAFLD increases with higher obesity index ($P<0.05$), as out of 46 patients of obese grade 3, 39 (85%) were reported to had NAFLD which highlights the importance of weight reduction strategies for the prevention and management of NAFLD. Also the Loomis *et al.* [10] study showed a strong association between BMI and prospectively recorded diagnoses of NAFLD/NASH.

Table 3 Prevalence of thyroid dysfunction in patients with and without nonalcoholic fatty liver disease

Parameters	Patients with NAFLD (*N*=65)	Patients without NAFLD (*N*=35)	*P* value
Subclinical hypothyroidism	8 (12.3)	1 (2.8)	0.028
Overt hypothyroidism	18 (27.6)	4 (11.4)	
Euthyroid state	39 (60)	30 (85.7)	

Data are presented as *n* (%). NAFLD, nonalcoholic fatty liver disease.

Table 4 Multivariate regression analysis for the prediction of thyroid dysfunction in obese patients

Variables	Odd's ratio	95% confidence interval	*P* value
Obesity index	3.45	2.56–5.68	0.03
Dyslipidemia	1.94	1.87–3.33	0.04
Fatty liver	2.67	2.04–6.09	0.01

Over the past decade, the relationship between thyroid dysfunction and NAFLD has become an important research topic. After controversial reports, many studies have confirmed an association between thyroid function and NAFLD [11].

The association between hypothyroidism and NAFLD may due to may underlying mechanisms. Hypothyroidism has been associated with insulin resistance [12], obesity [3], dyslipidemia [13], all of which are significant components of the metabolic syndrome. Furthermore, hypothyroidism is also related to metabolic syndrome [14], which plays vital role in the development of NAFLD [15].

In this study, there was a significant (*P*=0.028) higher prevalence of thyroid dysfunction in the form of overt and subclinical hypothyroidism (27.6 and 12.3%, respectively) among patients with NAFLD. Of the nine patients who were diagnosed to be subclinical hypothyroid, eight had fatty liver with a percentage of 89%, and from the 22 patients who were diagnosed to have overt hypothyroidism 18 patients had fatty liver with a percentage of 82%. Concordant with our result, the Chung *et al.* [16] study showed a higher prevalence of NAFLD in patients with hypothyroidism. Bano *et al.* [17] revealed that primary hypothyroidism was independently associated with an increased risk of NAFLD. Also He *et al.* [18] in a review involving 13 observational studies showed that primary subclinical and overt hypothyroidism were associated with an nearly 50% higher risk of NAFLD, even after adjustment for numerous metabolic confounders. Inversely, Lee *et al.* [19] reported that both subclinical and overt hypothyroidism were not independently associated with an increased risk of NAFLDs.Hypothyroidism may worsen preexisting lipid abnormalities in patients with NAFLD, leads to elevated cholesterol and low-density lipoproteins, and affects the synthesis, mobilization, and degradation of all features of lipid metabolism [13]. In our study, there is a significant increase in cholesterol, triglycerides, and LDL levels in hypothyroid patients than euthyroid patients which came in agreement with the Canaris *et al.* [20] study which showed that patients with subclinical hypothyroidism had higher total cholesterol and LDL level in comparison to the euthyroid population. Another study in Austria did not find those differences [21]. A sample analysis of the National Health and Nutrition Survey (NHANES III) showed higher serum cholesterol and triglyceride levels in patients with subclinical hypothyroidism compared with euthyroid participants. However, this difference disappeared after adjusting for variables such as sex, age, and race [22]. Also Erem [23] established the occurrence of hypercholesterolemia and hypertriglyceridemia in overt hypothyroidism.

In conclusion, according to our study, hypothyroidism independently increases the risk of NAFLD, which has implications for screening for hypothyroidism in patients with NAFLDs. In the meantime, it may also be useful to identify hypothyroidism in patients with NAFLD and to administer appropriate treatment for hypothyroidism. Therefore, the results of this study are of great importance for the preventive medicine of hypothyroidism and NAFLD.

One of the limitations of our study is that the diagnosis of NAFLD was made on an ultrasound examination, while liver biopsy is considered as the reference method for the detection of mild steatosis or hepatic fibrosis. However, liver biopsies are not routinely performed in the diagnosis of NAFLD because of their invasiveness and potential complications. In addition, abdominal ultrasound has a sensitivity of 80–90% for liver detection by other imaging modalities.

We recommend further research by using prospective studies to assess the prevalence of hypothyroidism in NAFLD. In addition, the efficacy of using thyroid-related drugs to prevent steatosis and the development of NASH must be explored in animal and cellular culture models.

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Conflicts of interest
There are no conflicts of interest.

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