Research Article

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Non-alcoholic fatty liver disease across the spectrum of hypothyroidism

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Background & Aims: The aim of this study was to characterize the relationship between the broad spectrum of hypothyroidism and NAFLD.

Methods: A cross-sectional study with 4648 health check-up subjects (2324 cases with hypothyroidism *vs.* age- and sex-matched controls) was conducted. The subjects were categorized as having either subclinical [thyroid-stimulating hormone (TSH) $\geqslant$4.1 mIU/L and normal free thyroixine (T_4) level (0.7–1.8 ng/dl)] or overt hypothyroidism [free T_4 <0.7 ng/dl]. NAFLD was diagnosed on the basis of typical ultrasonographic findings, and alcohol consumption of less than 20 g/day in the absence of other causes of liver disease.

Results: The mean age of the subjects was 48.6 ± 11.8 years and 62.4% were female. NAFLD was significantly associated with hypothyroidism (30.2% patients *vs.* 19.5% control, p <0.001). The prevalence of NAFLD and abnormal liver enzyme levels (ALT >33/25 IU/L) increased steadily with increasing grades of hypothyroidism (for NAFLD, subclinical: 29.9% and overt: 36.3%; for abnormal ALT, 20.1% and 25.9%, p <0.001, respectively). Multivariate regression analysis showed that NAFLD was statistically significantly associated with hypothyroidism (odds ratio (OR) 1.38, 95% confidence interval (CI), 1.17–1.62) and the grade of hypothyroidism in a dose-dependent manner (OR 1.36, 95% CI, 1.16–1.61 in subclinical hypothyroidism and OR 1.71, 95% CI, 1.10–2.66 in overt hypothyroidism).

Conclusions: Subclinical hypothyroidism, even in the range of upper normal TSH levels, was found to be related to NAFLD in a dose-dependent manner. Hypothyroidism is closely associated with NAFLD independently of known metabolic risk factors, confirming a relevant clinical relationship between these two diseases.

Keywords: Hypothyroidism; Non-alcoholic fatty liver disease; Metabolic syndrome; Hepatic steatosis.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; TSH, thyroid-stimulating hormone; T_4, thyroxine; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high density lipoprotein; OR, odds ratio; CI, confidence interval.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has been recognized as the most common liver disease, and it includes a spectrum of hepatic dysfunctions ranging from simple steatosis to non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma [1,2]. Because the mechanism underlying the development of NAFLD has been linked to insulin resistance and metabolic syndrome, NAFLD is considered to be the hepatic manifestation of metabolic syndrome [3–5], and the associations with many predictors of cardiovascular disease have been reported [6–9].

Thyroid dysfunction is a common condition that affects lifelong health [10]. Subclinical hypothyroidism, which refers to an elevated thyroid-stimulating hormone (TSH) level and a normal free thyroxine (T_4) level, has been associated with metabolic syndrome, cardiovascular diseases and mortality [11–14]. Because thyroid hormones play a fundamental role in lipid metabolism [15], hypothyroidism may cause hypercholesterolemia and play an essential role in the pathogenesis of NAFLD [16,17]. Previous studies have reported that thyroid dysfunction is associated with liver diseases, including chronic hepatitis C [18], hepatocellular carcinoma [19], primary biliary cirrhosis, and primary sclerosing cholangitis [17]. Furthermore, a recent study showed that the prevalence of NAFLD is negatively correlated with free T_4 levels, and decreased free T_4 levels contribute to the risk of NAFLD [20]. Although a relationship between thyroid function and NAFLD has been suggested in an elderly euthyroidic population [20], associations between NAFLD and the full spectrum of hypothyroidism in the general population have not been well studied.

Therefore, we conducted a cross-sectional study to evaluate the prevalence and association of NAFLD according to the spectrum of hypothyroidism in a large healthy population.

Patients and methods

Study population

A total of 71,780 subjects visited Seoul National University Hospital, Healthcare System Gangnam Center, Seoul, South Korea for a routine health check-up between October 2006 and October 2009. Among the total screenees, subjects with thyroid dysfunction, including both subclinical and overt hypothyroidism, were included as cases. Eighty-four subjects who take medications, such as thyroid hormone or antithyroid drugs, were excluded. Three hundred and twenty-one subjects with excessive alcohol intake (>20 g/day) and 195 subjects with underlying liver disease were excluded. In addition, five subjects with type 1 diabetes were excluded because this may be a confounder for the association between auto-immune thyroid disease and NAFLD. To reduce the effects of confounding factors, controls with normal-range TSH levels and T_4 levels were randomly matched to the cases by age and sex. This study was approved by the Institutional Review Board of the Seoul National University Hospital with a waiver of informed consent.

Clinical and laboratory assessments

Each participant completed a past medical history questionnaire, an anthropometric assessment, and laboratory tests on the same day. Height and body weight were measured using a digital scale, and body mass index (BMI) was calculated as follows: BMI = body weight (kg)/height squared (m^2). Waist circumference was measured to the nearest millimeter at the midpoint between the lower costal margin and the anterior superior iliac crest by a well-trained examiner using a tape. Systolic blood pressure and diastolic blood pressure were measured twice during the same day, and mean values were used for the study. The laboratory tests included the following: baseline thyroid function (TSH and free T_4 levels) measured using a commercial immunoradiometric assay (Abbott, North Chicago, IL, USA), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, glucose, hepatitis B surface antigen and antibody to hepatitis C virus. Blood samples were taken from all participants after a 12-h overnight fast. All laboratory tests were carried out using standard laboratory methods.

Definitions

The presence of diabetes mellitus was defined as either a fasting serum glucose level equal to or over 126 mg/dl or as taking anti-diabetic medication. The presence of hypertension was defined as having a systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg or taking anti-hypertensive medication. Euthyroidism was defined as a serum TSH level between 0.4 and 4.1 mIU/L with normal T_4 levels (0.7–1.8 ng/dl). Subclinical hypothyroidism was defined as a serum TSH level over 4.1 mIU/L with a normal free T_4 concentration, and overt hypothyroidism was defined as a free T_4 level less than 0.7 ng/dl. Conventionally, cut-off levels of 4–5 mIU/L TSH have been used to diagnose subclinical hypothyroidism, however, a much lower TSH cut-off with an upper limit of 2.5 mIU/L was recently suggested [21,22]. Additionally, to investigate dose-dependent relationship TSH and NAFLD, we classified TSH into quartiles according to TSH levels.

Abnormal liver enzyme levels were based on ALT elevation over the cut-off of the reference laboratory (ALT >40 IU/L), and the strict cut-off was based on the updated Asian definition of Lee *et al.* (ALT >33 IU/L for men, and >25 IU/L for women) [23].

NAFLD was defined as the presence of fatty liver disease as determined by ultrasonography in the absence of the following: (1) seropositivity for hepatitis B surface antigen or antibody to hepatitis C virus, (2) excessive alcohol intake (>20 g/day), (3) other causes of liver disease, and (4) medications known to produce fatty liver disease.

Metabolic syndrome was diagnosed when three or more of the five components were present, that is, (1) central obesity [waist circumference as defined by the Regional Office for the Western Pacific Region of the World Health Organization (WPRO) criteria, >90 cm (men) or >80 cm (women)]; (2) a triglyceride level $\geqslant$150 mg/dl; (3) HDL-cholesterol <40 mg/dl (men) or <50 mg/dl (women); (4) fasting glucose $\geqslant$100 mg/dl or treatment for diabetes; (5) arterial pressure $\geqslant$130/85 mmHg or treatment for hypertension [24].

Ultrasonographic assessments

Ultrasonographic examination of the liver was performed by experienced radiologists who were unaware of the clinical and laboratory information. The diagnosis of fatty liver was performed by ultrasonography (Acusion, Sequioa 512, Siemens, Mountain View, CA) using previously described standardized criteria [25].

Statistical analysis

Comparisons of continuous variables between the two groups were performed with the Student's *t*-test or Mann–Whitney *U* test, and categorical variables were compared using the Chi-square test. Variables that were statistically significant by univariate analysis and known risk factors were added to a multiple logistic regression model to identify independent predictors of the presence of NAFLD. Statistical analysis was performed with SPSS 17.0 (SPSS Inc.; Chicago, IL, USA). *p* values of <0.05 were considered statistically significant. Age and sex matching and statistical analysis were supported by the Seoul National University Hospital, Medical Research Collaborating Center.

Results

Baseline characteristics

A total of 2324 pairs of subjects with thyroid dysfunction and age- and sex-matched controls (1450 pairs of females and 874 pairs of males) were finally enrolled. The mean age was 48.6 ± 11.8 years and 62.4% were female. The anthropometric, clinical, and laboratory characteristics of the subjects are shown in Table 1. The BMI, waist circumference, serum ALT, AST, glucose, triglyceride, systolic blood pressure, and diastolic blood pressure were all significantly different between the hypothyroidism and the euthyroidism. Hypothyroidism was statistically significantly associated with NAFLD and metabolic syndrome (30.2% *vs.* 19.5% and 23.1% *vs.* 14.6%, p <0.001, respectively, Table 1). There was no difference in the comparison between patient with subclinical and with overt hypothyroidism except age, AST, and HDL-cholesterol. The prevalence of abnormal liver enzyme levels (ALT >40 IU/L) was significantly higher in the subjects with hypothyroidism than in the subjects with normal thyroid function (9.7% *vs.* 6.1%, p <0.001). The prevalence of elevated ALT using a strict cut-off point (ALT >33 IU/L for men, and >25 IU/L for women) was significantly higher in the subjects with hypothyroidism than in the subjects with normal thyroid function (20.5% *vs.* 15.8%, p <0.001, Table 2).

Prevalence of NAFLD and abnormal ALT according to the spectrum of hypothyroidism

Among subjects with hypothyroidism, 2189 (94.2%) with subclinical hypothyroidism and 135 (5.8%) with overt hypothyroidism were analyzed along with their matched controls. Fig. 1 illustrates that the prevalence of NAFLD and abnormal liver enzyme levels (ALT >33/25) increased steadily with increasing hypothyroidism grade (for NAFLD, subclinical: 29.9% and overt: 36.3%; for abnormal ALT (>33/25), 20.1% and 25.9%, *p*-value (*vs.* matched control) <0.001, respectively).

Among the subjects with ultrasonographically diagnosed NAFLD, the prevalence of abnormal liver enzyme levels (ALT >33/25) was 36.8%. Table 2 shows that the prevalence of