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Higher free triiodothyronine is associated with non-alcoholic fatty liver disease in euthyroid subjects: the Lifelines Cohort Study

Eline H. van den Berg[a,*,1], Lynnda J.N. van Tienhoven-Wind[b,1], Marzyeh Amini[c], Tim C.M.A. Schreuder[a], Klaas Nico Faber[a], Hans Blokzijl[a], Robin P.F. Dullaart[b]

[a] Department of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, The Netherlands
[b] Department of Endocrinology, University of Groningen and University Medical Center Groningen, The Netherlands
[c] Department of Epidemiology, University of Groningen, and University Medical Center Groningen, The Netherlands

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ABSTRACT

Objective. Overt hypothyroidism confers an increased risk of non-alcoholic fatty liver disease (NAFLD). The liver plays a crucial role in the metabolism of cholesterol and triglycerides; thyroid hormones interact on hepatic lipid homeostasis. Thyroid function within the euthyroid range affects a number of health issues, including atherosclerosis development and biochemical markers of increased cardiovascular risk. However, the association of thyroid hormones with NAFLD in euthyroid subjects has not been unequivocally established. We therefore determined associations of thyroid hormone parameters with NAFLD among euthyroid subjects.

Methods. The study was conducted in the Lifelines Cohort Study, a population-based cohort study of participants living in the North of the Netherlands. Only euthyroid subjects (thyroid-stimulating hormone (TSH) 0.5–4.0 mU/L, free thyroxine (FT4) 11–19.5 pmol/L and free triiodothyronine (FT3) 4.4–6.7 pmol/L) older than 18 years were included. Exclusion criteria were participants with excessive alcohol use, known hepatitis or cirrhosis, liver functions ≥ three times the upper limit, current cancer, non-white ancestry, previous or current use of thyroid medication and current use of lipid or glucose lowering medication. A priori defined liver biochemistry, thyroid function parameters and metabolic syndrome (MetS) were studied. NAFLD was defined by using the validated Fatty Liver Index (FLI); FLI ≥ 60 was categorized as NAFLD. A $P < 0.01$ was considered significant.

Results. FLI ≥ 60 was found in 4274 (21.1%) of 20,289 individuals (62.1% male, median age 46 years) with increased prevalence of MetS ($P < 0.0001$). In age- and sex-adjusted analysis FLI ≥ 60 was independently associated with a higher FT3 (OR 1.34, 95% CI 1.29–1.39, per SD increment, $P < 0.0001$) and a lower FT4 (OR 0.73, 95% CI 0.70–0.75, $P < 0.0001$) but not by TSH.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DIO, iodothyronine deiodinase; FLI, Fatty Liver Index; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IQR, interquartile range; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NFS, NAFLD fibrosis score; OR, odds ratio; SD, standard deviation; TG, triglycerides; TSH, thyroid-stimulating hormone; VLDL, very low density lipoproteins.

* *Corresponding author at:* Department of Gastroenterology and Hepatology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3616161; fax: +31 50 3619306.
E-mail address: e.h.van.den.berg@umcg.nl (E.H. van den Berg).
[1] Contributed equally to the manuscript.

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The strongest association was found for the FT3/FT4 ratio (OR 1.44, 95% CI 1.39–1.49, $P < 0.0001$). These associations remained similar after additional adjustment for the presence of MetS. In subjects with enlarged waist circumference, TSH and FT4 were lower while FT3 was higher, resulting in an increased FT3/FT4 ratio ($P < 0.0001$).

Conclusions. Euthyroid subjects with suspected NAFLD are characterized by higher FT3, lower FT4 and higher FT3/FT4 ratio, probably consequent to central obesity.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis in the absence of excessive alcohol consumption [1]. NAFLD includes a broad spectrum of pathology ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, while it also predisposes to hepatocellular carcinoma. NAFLD is considered to reflect the hepatic component of the metabolic syndrome (MetS), since there is a strong association with insulin resistance, (central) obesity, dyslipidemia and hypertension [2]. As a consequence of the obesity epidemic, NAFLD is the leading cause of chronic liver disease in the Western world. It is estimated that NAFLD occurs in 20%–30% of European adults [3]. Therefore, it is expected that subjects with NAFLD will require further identification of concurrent NASH and/or fibrosis to be a prominent target for lifestyle modification and pharmacological intervention in the near future [4].

The liver plays a crucial role in the metabolism of cholesterol and triglycerides [5], with hepatic fat accumulation being regarded as the driving force of elevated plasma triglycerides [6]. Importantly, thyroid hormones interact on hepatic lipid homeostasis through multiple pathways, including stimulation of free fatty acid delivery to the liver for re-esterification to triglycerides, and increasing fatty acid β-oxidation, thereby affecting hepatic fat accumulation [5,7–10].

Several studies have demonstrated an association between overt thyroid dysfunction and NAFLD. Subjects with hypothyroidism are about 1.5 to 2 times more likely to have biopsy-proven or ultrasonography-confirmed NAFLD [11,12]. Accordingly, a recent longitudinal study demonstrated that (subclinical) hypothyroidism is associated with NAFLD risk [13]. A systematic review indeed suggested a relation between NAFLD and hypothyroidism, although such an effect has not consistently been reported [14]. There are, however, only a few small studies, which aimed to assess the association of NAFLD with variations in thyroid function within the euthyroid range [15–19]. Higher thyroid-stimulating hormone (TSH) levels within the euthyroid range were found in subjects with NAFLD but may also relate to attenuated serum alanine aminotransferase (ALT) elevations in the context of MetS and insulin resistance [15,16]. In euthyroid subjects with NAFLD, lower free thyroxine (FT4) levels were found in some studies [15,17,18], whereas a higher free triiodothyronine (FT3) level was found in middle-aged Chinese subjects [19].

Given the importance of variations in thyroid function within the euthyroid range for a considerable number of health issues, including (subclinical) atherosclerosis and altered levels of pro-atherogenic biochemical markers [5,20], it is relevant to examine the relationship of NAFLD with thyroid function parameters in an euthyroid population. In the present cross-sectional study, we aimed to determine the relationship of NAFLD with TSH, FT4 and FT3 among participants of the Lifelines Cohort Study, representative of the general population from the North-Eastern region of the Netherlands.

2. Material and Methods

2.1. Study Design

The present cross-sectional study is conducted in the framework of the Lifelines Cohort Study. The Lifelines Cohort Study is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North-Eastern region of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics [21]. All participants provided written informed consent. The medical ethics committee of the University of Groningen, the Netherlands, approved the study conforming to the Declaration of Helsinki.

2.2. Participants

We included subjects of Western-European origin and all participants were aged between 18 and 85 years at time of enrollment. Only euthyroid subjects participated in the present study. Euthyroidism was defined as a TSH level between 0.5 and 4.0 mU/L, FT4 level between 11 and 19.5 pmol/L and FT3 level between 4.4 and 6.7 pmol/L, i.e. within their respective institutional reference ranges. Eligible subjects had liver enzyme values <3 times the upper reference limit, i.e. for aspartate aminotransferase (AST) < 120 U/L, alanine aminotransferase (ALT) < 135 U/L, gamma-glutamyl transferase (GGT) < 165 U/L and alkaline phosphatase (ALP) < 360 U/L. Additional exclusion criteria were: missing data required to calculate the Fatty Liver Index (FLI, as outlined below) and to determine the presence of metabolic syndrome (MetS) and its components and non-white ancestry (participants were assumed to be immigrant if his/her birth country or that of one or both parents was outside the Netherlands). The representativeness of the Lifelines cohort for the North Netherlands population has