Impact of hypothyroidism on the development of non-alcoholic fatty liver disease: A 4-year retrospective cohort study

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Background/Aims: Hypothyroidism is reported to contribute to the development of nonalcoholic fatty liver disease (NAFLD). We compared the risk of the development of NAFLD among three groups with different thyroid hormonal statuses (control, subclinical hypothyroidism, and overt hypothyroidism) in a 4-year retrospective cohort of Korean subjects.

Methods: Apparently healthy Korean subjects without NAFLD and aged 20–65 years were recruited (n=18,544) at health checkups performed in 2008. Annual health checkups were applied to the cohort for 4 consecutive years until December 2012. Based on their initial serum-free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels, they were classified into control, subclinical hypothyroidism (TSH >4.2 mIU/L, normal fT4), and overt hypothyroidism (TSH >4.2 mIU/L, fT4 <0.97 ng/dL) groups. NAFLD was diagnosed on the basis of ultrasonography findings.

Results: NAFLD developed in 2,348 of the 18,544 subjects, representing an overall incidence of 12.7%: 12.8%, 11.0%, 12.7% in the control, subclinical hypothyroidism, and overt hypothyroidism groups, respectively. The incidence of NAFLD did not differ significantly with the baseline thyroid hormonal status, even after multivariate adjustment (subclinical hypothyroidism group: hazard ratio [HR]=0.965, 95% confidence interval [CI]=0.814–1.143, P=0.67; overt hypothyroidism group: HR=1.255, 95% CI=0.830–1.899, P=0.28).

Conclusions: Our results suggest that the subclinical and overt types of hypothyroidism are not related to an increased incidence of NAFLD. (Clin Mol Hepatol 2015;21:372-378)

Keywords: Hypothyroidism; Nonalcoholic fatty liver disease

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic accumulation of triglycerides and free fatty acids in the liver.1 The incidence of NAFLD is increasing rapidly, and it is the most common cause of abnormal liver function results worldwide.2 The increase in the prevalence of NAFLD has been attributed to the global increase in the prevalence of obesity and other metabolic risk factors. Advanced age and metabolic disorders such as type 2 diabetes mellitus, impaired glucose tolerance, and...
central obesity, are among the risk factors for NAFLD.\textsuperscript{3} Cryptogenic cirrhosis is a term used for patients with liver cirrhosis who lack any identifiable viral, alcoholic, autoimmune or drug-related causes for the condition. Many clinicians now believe that a considerable number of these patients have cirrhosis due to nonalcoholic steatosis hepatitis (NASH).\textsuperscript{4}

NAFLD has broad pathological spectrum, ranging from simple steatosis to NASH, and potentially progressing to fibrosis and cirrhosis.\textsuperscript{5} After fat infiltrates the liver, progression to hepatocellular inflammation and fibrosis may occur.

The thyroid gland is significantly involved in energy homeostasis, lipid and carbohydrate metabolism, regulation of body weight and adipogenesis. Subclinical and overt hypothyroidism has been associated with metabolic syndrome, cardiovascular mortality and disturbance in lipid metabolism.\textsuperscript{6}

Several clinical studies have investigated the role of hypothyroidism as a predictor for NAFLD in cross-sectional analyses,\textsuperscript{7,10} but the results have been contradictory. No longitudinal study has demonstrated a relationship between hypothyroidism and NAFLD.

Therefore, in this study, we investigated the relationship between baseline thyroid hormonal status and the incidence of NAFLD in a 4-year follow-up of a cohort of 18,544 apparently healthy Korean subjects.

**MATERIALS AND METHODS**

1. Participants

This was a retrospective cohort study, and the subjects were participants in the Kangbuk Samsung Health Study, a large database of participants in a medical health check-up program at the Health Promotion Center of Kangbuk Samsung Hospital. The purpose of the medical health check-up program is to promote the health of employees through regular health check-ups and to enhance early detection of disease. Most of the examinees were employees of various companies. The cost of the medical examinations is largely paid for by employers, and a considerable proportion of the examinees undergo examinations.

Initial data were obtained from 28,861 subjects in whom annual health check-ups were performed for 5 consecutive years between January 2008 and December 2012. Among these subjects, 7,317 were excluded (5,835 due to initial fatty liver disease, 1,266 due to positive serological marker for chronic viral hepatitis, 1,436 unclassified by thyroid hormonal status, and 1,780 consuming alcohol more than 20 gram per day (Fig. 1).

Finally, 18,544 apparently healthy subjects without NAFLD aged 20-65 years were included. Questionnaires were used to determine alcohol consumption (gram per day). Alcohol intake and smoking habits were assessed by chart review and a standardized questionnaire. Based on initial serum free thyroxine (fT4) and thyroid-stimulating hormone (TSH), the subjects were classified into euthyroid control [TSH 0.27~4.2 mIU/L, fT4 0.97~1.68 ng/dL], subclinical hypothyroidism [TSH >4.2 mIU/L, fT4 0.97~1.68 ng/dL] and overt hypothyroidism [TSH >4.2 mIU/L, fT4<0.97 ng/dL] groups. NAFLD was diagnosed based on the results of abdominal ultrasonography, after excluding heavy alcohol consumption, and viral, or other liver diseases.

This study protocol was approved by the Institutional Review Board and Ethics Committee of Kangbuk Samsung Hospital. The participants provided written informed consent for their medical check-up data to be used in this study.

2. Biochemical assays

Blood samples were obtained after a 12 hour overnight fast and used to measure fasting plasma glucose (FBG), total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), fasting insulin, creatinine, direct bilirubin, and the following liver function parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP). As a marker of insulin resistance (IR), homeostatic model assessment (HOMA) of IR was calculated as follows: $\text{HOMA-IR} = \frac{\text{fasting insulin (\muU/mL)}}{\text{fasting glucose (mmol/L)}} \times 22.5$. Baseline thyroid function (fT4 and TSH levels) was measured using commercial immunoradio-
metric assays.

### 3. Ultrasonography

Abdominal ultrasonography (Logic Q700 MR, GE, Milwaukee, WI, USA) was performed in all subjects. Fatty liver was diagnosed based on standard criteria, including hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring, using a 3.5 MHz probe. Several experienced radiologists, who were blinded to the clinical status of the subjects, performed the ultrasounds. However, we did not assess inter-observer reliability.

### 4. Statistical analysis

Normality was tested using the Kolmogorov-Smirnov test. The chi-squared test was used to compare categorical variables between groups. For continuous variables, parameters that followed a normal distribution were analyzed with a t-test or analysis of variance (ANOVA) and described as the mean±SD. Parameters that did not follow a normal distribution were analyzed with the Mann-Whitney U test or the Kruskal-Wallis test and expressed as the median. Kaplan-Meier survival analyses were performed for incident NAFLD for 4 years according to baseline thyroid hormonal status. Cox proportional hazards regression models were used after adjusting for several confounders. Statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as \( P < 0.05 \).

### RESULTS

The study cohort included 18,544 subjects. Among them, 2,348 (12.7%) developed NAFLD within 4 years. The median duration to develop NAFLD was 2.92 years. The subjects were divided into two groups: those who developed NAFLD (NAFLD) and those who did not (Non-NAFLD). The baseline clinical characteristics of the subjects are shown in Table 1.

**Table 1.** Baseline clinical characteristics of the subjects recruited in 2008 and grouped according to the development of nonalcoholic fatty liver disease (NAFLD) during 2009–2012

| Characteristics                  | NAFLD (n=2,348) | Non-NAFLD (n=16,196) | \( P \)-value |
|----------------------------------|-----------------|----------------------|--------------|
| Age, year                        | 39.2±5.9        | 37.8±5.7             | <0.001       |
| Men, n (%)                       | 1,701 (72)      | 8,177 (50)           | <0.001       |
| Smoker, n (%)                    | 1,195 (51.2)    | 5,927 (36.8)         | <0.001       |
| BMI (kg/m\(^2\))                 | 24.2±2.4        | 22.3±2.5             | <0.001       |
| Cholesterol (mg/dL)              | 196.2±31.6      | 185.7±30.7           | <0.001       |
| Triglyceride (mg/dL)             | 135.2±77.2      | 100.1±55.9           | <0.001       |
| LDL-cholesterol (mg/dL)          | 114.5±27.3      | 102.1±26.4           | <0.001       |
| Fasting glucose (mg/dL)          | 96.3±10.9       | 93.5±9.8             | <0.001       |
| Fasting insulin (mIU/L)          | 5.9±2.8         | 4.6±2.4              | <0.001       |
| HOMA-IR (mIU/L)                  | 1.4±0.7         | 1.0±0.6              | <0.001       |
| AST (IU/L)                       | 22.2±9.6        | 21.2±7.9             | <0.001       |
| ALT (IU/L)                       | 23.3±12.9       | 18.7±10.4            | <0.001       |
| T4 (ng/dL)                       | 1.28±0.16       | 1.26±0.15            | 0.988        |
| TSH (mIU/L)                      | 2.3±4.3         | 2.3±2.6              | 0.8          |
| Bilirubin (mg/dL)                | 0.9±0.3         | 0.9±0.3              | 0.39         |
| Diabetes mellitus, n (%)         | 46 (2.0)        | 178 (1.1)            | <0.001       |
| Hypertension, n (%)              | 313 (13.3)      | 1250 (77)            | <0.001       |
| BUN (mg/dL)                      | 13.5±3.7        | 13.0±3.3             | <0.001       |
| Serum creatinine (mg/dL)         | 1.0±0.2         | 0.9±0.1              | <0.001       |

NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; LDL, low density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T4, free thyroxine; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen. Quantitative variables are presented as the mean±SD. Smoker: past + current smoker.
two groups for follow up, such as those who developed NAFLD (n=2,348) and those who did not (n=16,196). Table 1 shows a comparison of the baseline characteristics between the subjects according to the development of NAFLD. The NAFLD group was older than that of the non-NAFLD group (39.2±5.9 vs. 37.8±5.7 years). The NAFLD group had a significantly higher proportion of males, and a higher body mass index (BMI). Additionally, baseline serum levels of total cholesterol, triglycerides, LDL, FPG, fasting insulin, AST, ALT, blood urea nitrogen (BUN), and creatinine were significantly higher in the NAFLD group than those in the non-NAFLD group. However, TSH and free T4 were not associated with the development of NAFLD.

The subjects were divided into three groups according to initial thyroid hormonal status. (17,052 in the euthyroid control, 1,303 in the subclinical hypothyroidism, and 189 in the overt hypothyroidism groups). The clinical and laboratory characteristics of the subjects are shown in Table 2. Among them, 2,181 (12.8%) euthyroid subjects, 143 (11%) subclinical hypothyroidism subjects and 24

Table 2. Baseline characteristics and prevalence of NAFLD according to thyroid functional status

| Variable          | Euthyroidism (n=17,052) | Hypothyroidism |          |          |
|-------------------|-------------------------|----------------|----------|----------|
|                   |                         | Subclinical (n=1,303) | Overt (n=189) |          |
| Age, year         | 34.6±4.9                | 34.2±5.1        | 35.2±6.2 |          |
| Female, n (%)     | 7,697 (45.1)            | 805 (61.8)      | 164 (86.8) |          |
| BMI (kg/m²)       | 22.6±2.6                | 22.3±2.6        | 22.4±2.8 |          |
| Obesity, n (%)    |                         |                |          |          |
| Normal (BMI<23)   | 9,743 (57.2)            | 806 (61.9)      | 124 (66.3) |          |
| Overweight (23≤BMI<25) | 4,381 (25.7)     | 282 (21.7)      | 31 (16.6) |          |
| Obese (BMI≥25)   | 2,917 (17.1)            | 214 (16.4)      | 32 (17.1) |          |
| AST (IU/L)        | 20 (18-23)              | 20 (18-23)      | 21 (18-23.5) |          |
| ALT (IU/L)        | 17 (13-22)              | 16 (13-20)      | 16 (13-20) |          |
| Fasting glucose (mg/dL) | 94±10               | 93±4.9         | 91±8.6 |          |
| Diabetes mellitus, n (%) | 214 (1.3)                | 13 (1.0)       | 2 (1.1) |          |
| Hypertension, n (%) | 1,453 (8.5)                | 91 (7.0)       | 19 (10.1) |          |
| Total cholesterol (mg/dL) | 187±30               | 187±31         | 194±37.8 |          |
| Triglyceride (mg/dL) | 104.8±60                | 102.5±60       | 101±5.2 |          |
| LDL-cholesterol (mg/dL) | 103.7±26.9             | 103±26.1       | 106±30.5 |          |
| T4 (ng/dL)        | 1.27±0.15               | 1.19±0.14      | 0.82±0.15 |          |
| TSH (mIU/L)       | 1.78 (1.25-2.47)        | 5.2 (4.6-6.3)  | 7.4 (5.6-14.4) |          |
| NAFLD, n (%)      | 2,181 (12.8)            | 143 (11.0)     | 24 (12.7) |          |

Quantitative variables are presented as the mean±SD or median (interquartile range).
NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low density lipoprotein cholesterol; T4, free thyroxine; TSH, thyroid stimulating hormone.

*P*-value<0.05.

Table 3. Cox proportional-hazards ratio analysis for the development of NAFLD during 2009–2012 grouped according to the thyroid hormonal status in 2008

| Variables          | Crude analysis | Adjusted analysis |
|--------------------|----------------|------------------|
|                    | HR 95% CI      | P-value          | HR 95% CI    | P-value |
| Euthyroidism       | 1 95% CI 1.00  | 0.156            | 1 95% CI 1.00 | 0.506  |
| Hypothyroidism     |                |                  |               |        |
| Subclinical        | 0.85 0.72-1.00 | 0.054            | 0.97 0.81-1.14 | 0.678  |
| Overt              | 0.97 0.65-1.45 | 0.873            | 1.26 0.83-1.90 | 0.282  |
Cumulative incidence of nonalcoholic fatty liver disease in the
three groups with different thyroid hormonal statuses. Overt, overt
data thyroidism; Sub, subclinical hypothyroidism; Euthyroid, euthyroid
status.

(12.7%) overt hypothyroidism subjects developed NAFLD during
the 4 year of follow-up (Table 2). However, this result was not
statistically relevant (P=0.132).

Cox proportional hazards regression analyses were used to esti-
mate hazard ratios (HRs) for the incidence of NAFLD due to hypo-
thyroidism during the follow-up. Our analysis showed that sub-
clinical and overt hypothyroidism were not risk factors for
developing NAFLD in the crude model (subclinical: HR, 0.847;
95% CI, 0.647–1.447). Metabolic syndrome was strongly associated
with this relationship. Therefore, we further adjusted the Cox pro-
portional hazards regression analysis for indicators of metabolic
syndrome. However, even after adjusting for sex, age, BMI, TGs
and HDL, the relationship between subclinical and overt hypo-
thyroidism and incident NAFLD was not significant. The adjusted
HRs (95% CI) were 0.965 (0.814–1.143) and 1.255 (0.83–1.89), re-
spectively (Table 3). The Kaplan-Meier survival curve (cumulative
incidence of NAFLD) showed no difference among the three
groups (P=0.15) (Fig. 2). These results indicate that hypothyroid-
ism is not an independent factor predicting the development of
NAFLD.

DISCUSSION

We did not demonstrate an association between thyroid hor-
monal status and the incidence of NAFLD, and the incidence of
NAFLD did not increase with hypothyroidism.

Several studies have investigated the association between hy-
pothyroidism and NAFLD. Chung et al. showed that subclinical
hypothyroidism, even in the range of upper normal TSH levels, is
closely associated with NAFLD in a dose-dependent manner.
However, a causal relationship between hypothyroidism and
NAFLD was not detected in their cross-sectional study.1 In addi-
tion, three studies have indicated that hypothyroidism is an inde-
pendent risk factor for developing NAFLD/NASH.2-4 Several stud-
ies have reported that lower free T4 is an independent risk factor
for NAFLD.5-7 Several other studies have shown that increased
serum TSH is an independent risk factor for NAFLD/NASH.8,9 In
contrast, similar to our finding, three studies could not find an as-
sociation between hypothyroidism and NAFLD. Mazo et al. did
not find an association between hypothyroidism, simple steatosis,
and NASH.10 Ittermann et al. reported no association between hy-
per- or hypothyroidism and hepatic steatosis in a population-
based study.11 And Eshraghian et al. showed that thyroid hormone
abnormalities in patients with NAFLD may be due to changes in
thyroid hormones due to other non-thyroid illnesses.12

An explanation for the association between hypothyroidism and
NAFLD is that hypothyroidism is associated with metabolic syn-
drome. Several studies have reported that hypothyroidism is relat-
ed to obesity and metabolic syndrome.13-15 Thyroid hormones
stimulate the expression of uncoupling proteins in the mitochon-
dria of fat and skeletal muscle, through modulate adrenergic re-
ceptor numbers by enhancing responsiveness of catecholamine.16
Thus, thyroid hormones influence body weight, thermogenesis, li-
polysis, and cholesterol metabolism. Patients with NAFLD have
abnormal lipid profiles, such as elevated total cholesterol, LDL and
TG levels.17 Among these, TGs is a one of metabolic syndrome
components. Hypertriglyceridemia increases importation of TGs
into the liver and is therefore associated with the development of
NAFLD.18 For this reason, some studies have suggested that hypo-
thyroidism may contribute to the development of NAFLD, or that
it may be associated with other NAFLD risk factors.

However, we found no association between hypothyroidism
with NAFLD, which conflicts with studies that have reported an
association between hypothyroidism and NAFLD. One study sug-
gested that thyroid hormone abnormalities in patients with
NAFLD may occur be due to other non-thyroid illnesses.19 This
concept may explain the absence of the association between hy-
pothyroidism and NAFLD observed in our study.

This study had some strength. Most of other studies have inves-
tigated the prevalence of NAFLD according to thyroid status
(cross-sectional study), but we report the incidence of NAFLD
through a 4 year follow-up (longitudinal cohort study). As most of

Figure 2. Cumulative incidence of nonalcoholic fatty liver disease in the
cross groups with different thyroid hormonal statuses. Overt, overt
hypothyroidism; Sub, subclinical hypothyroidism; Euthyroid, euthyroid
status.
our participants were healthy young people, we thought that the relationship between hypothyroidism and NAFLD would be less affected by other variables.

This study had several limitations. First, the NAFLD diagnosis was not histologically confirmed, after ultrasound, which has reported sensitivity of 67-89% and specificity of 77-89%. Second, alcohol intake was determined by a self-reported questionnaire; therefore, we cannot rule out the possibility of misreporting or recall bias. In addition, lifestyle risk factors, which can affect future development of NAFLD, including exercise and dietary habits, were not considered. Thus, the data were subject to potential under or over-estimation. Third, our cohort was consisted of relatively young people, so it may not represent general population. Fourth, our study excluded baseline NAFLD patients. This may bias the results, leading to underestimation of NAFLD incidence in the overall course of hypothyroidism. Lastly, our cohort was comprised of participants who had volunteered for health check-ups, which may have introduced selection bias.

In conclusion, although a high prevalence of hypothyroidism has been reported in with NAFLD, we found no significant correlation between hypothyroidism and the incidence of NAFLD. Further studies are needed to clarify the exact role of hypothyroidism in the progression of NAFLD.

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Conflicts of Interest
The authors have no conflicts to disclose.

REFERENCES

1. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis 2001;21:17-26.
2. Angulo P. GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2007;25:883-889.
3. Yamada T, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. J Gastroenterol Hepatol 2010;25:352-356.
4. Caldwell SH, Lee VD, Kleiner DE, Al-Osaimi AM, Argo CK, Northup PG, et al. NASH and cryptogenic cirrhosis: a histological analysis. Ann Hepatol 2009;8:346-352.
5. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413-1419.
6. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365-1374.
7. Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, et al. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol 2012;57:150-156.
8. Liangpunsakul S, Chalasani N. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? J Clin Gastroenterol 2003;34:340-343.
9. Pagadala MR, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in nonalcoholic fatty liver disease. Dig Dis Sci 2012;57:528-534.
10. Parikh P, Phadke A, Sawant P. Prevalence of hypothyroidism in non-alcoholic fatty liver disease in patients attending a tertiary hospital in western India. Indian J Gastroenterol 2015;34:169-173.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.
12. Ittermann T, Haring R, Wallachofski H, Baumeister SE, Nauck M, Dörr M, et al. Inverse association between serum free thyroxine levels and hepatic steatosis: results from the Study of Health in Pomerania. Thyroid 2012;22:568-574.
13. Xu C, Xu L, Yu C, Miao M, Li Y. Association between thyroid function and nonalcoholic fatty liver disease in euthyroid elderly Chinese. Clin Endocrinol (Oxf) 2011;75:240-246.
14. Moustafa AH, Ali EM, Mohamed TM, Abdou H. Oxidative stress and thyroid hormones in patients with liver diseases. Eur J Intern Med 2009;20:703-708.
15. Canulli L, Ballestrì S, Lonardo A, Lami F, Violi F, Losi L, et al. Is non-alcoholic steatohepatitis associated with a high-though-normal thyroid stimulating hormone level and lower cholesterol levels? Intern Emerg Med 2013;8:297-305.
16. Mazo DF, Lima VM, Stefano JT, Rabelo F, Faintuch J, Oliveira CP. Gluco-lipidic indices in treated hypothyroidism associated with non-alcoholic fatty liver disease. Arq Gastroenterol 2011;48:186-189.
17. Eshraghian A, Dabbaghmanesh MH, Eshraghian H, Fattahi MR, Omrani GR. Nonalcoholic fatty liver disease in a cluster of Iranian population: thyroid status and metabolic risk factors. Arch Iran Med 2013;16:584-589.
18. Pearce EN. Thyroid hormone and obesity. Curr Opin Endocrinol Diabetes Obes 2012;19:408-413.
19. Pacifico L, Anania C, Ferraro F, Andreoli GM, Chiesa C. Thyroid function in childhood obesity and metabolic comorbidity. Clin Chim Acta 2012;413:396-405.
20. Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, Milanovic I, et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study. Clin Endocrinol (Oxf) 2012;76:911-918.

21. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism 2005;54:1524-1528.

22. Musso G, Gambino R, Cassader M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD). Prog Lipid Res 2009;48:1-26.

23. Goldberg IJ, Ginsberg HN. Ins and outs modulating hepatic triglyceride and development of nonalcoholic fatty liver disease. Gastroenterology 2006;130:1343-1346.