Prevalence of Elevated TSH and its Association with Dyslipidemia and NAFLD Among Filipino Adult Executive Check-Up Patients in a Tertiary Hospital

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Abstract

Objectives: The study examined the prevalence of elevated thyroid stimulating hormone (TSH) and its association with dyslipidemia and non-alcoholic fatty liver disease (NAFLD) among Filipino adults undergoing executive check-up.

Methods: Clinical characteristics such as age, vital signs, anthropometrics, FBS, lipid profile, liver function tests, TSH and hepatobiliary ultrasound were reviewed from the charts of 580 patients to determine the prevalence of elevated TSH, NAFLD, and dyslipidemia. Binary logistic regression analysis was performed to determine association between TSH levels, NAFLD, and dyslipidemia.

Results: The prevalence of elevated TSH was 3.10%. Patients with increased total cholesterol was approximately 4.18 times as likely (95% CI 1.20 to 14.61%, p = 0.025) to have elevated TSH. However, after adjusting for age and sex, we had insufficient evidence to demonstrate an association between NAFLD and lipid levels with elevated TSH levels.

Conclusion: The prevalence of elevated TSH in this group of patients from a highly urbanized area was 3.1%. We had insufficient evidence to demonstrate an association between NAFLD, lipid levels, and elevated TSH levels after adjusting for age and sex.

Keywords: thyroid stimulating hormone, dyslipidemia, non-alcoholic fatty liver disease, subclinical hypothyroidism

Introduction

For years, it was demonstrated in numerous studies that there is a clear association between overt hypothyroidism and metabolic abnormalities- dyslipidemia, and non-alcoholic fatty liver disease (NAFLD) that translates to higher cardiovascular risks.[1,2,3,4] With this, there is a growing interest to its precedent conditions:- asymptomatic patients with mildly elevated thyroid stimulating hormone (TSH) and subclinical hypothyroidism (SH)- defined as having elevated TSH and normal Free T4 levels, as the latter is more prevalent than overt hypothyroidism even in our country, with the PhilTiDes study showing SH to be the second most common form of thyroid dysfunction in Filipinos at 2.18%.[5]

On population studies looking at elevated TSH alone, like the Colorado Thyroid Prevalence Study, the prevalence of elevated TSH level is 9.5%.[6] The TROMSO study data, on the other hand, showed the prevalence of elevated TSH (initial 5th TROMSO study without concurrent FT4 determination) to be only 2.0%.[7]

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In an unpublished study done in our institution year 2007, investigating executive check-up patients at Makati Medical Center, the prevalence of elevated TSH levels is as high as 8.28%. Mean total cholesterol, LDL and triglyceride were found to be greater in the group with high TSH, with most of the patients being female and considered obese by BMI category. However, patients with a prior history of thyroid disorders, surgery and those taking medicines that may affect thyroid function were not excluded in this study.

Although it is well-established how overt hypothyroidism, that is with the combined influence of elevated TSH and low free T4, can cause elevated cholesterol and LDL, it is only recently that evidence were presented on the possible mechanism on how TSH alone can cause abnormal lipid levels. According to Tian et al, TSH acts on hepatocyte cell membrane TSH receptors causing an upregulation in the expression of HMG-CoA Reductase (the rate-limiting enzyme in cholesterol synthesis) and stimulates the cyclic adenosine monophosphate / protein kinase A / cyclic adenosine monophosphate-responsive element binding protein (cAMP/PKA/CREB) signaling system. They concluded that TSH elevates cholesterol levels both in vivo and in vitro by promoting liver cholesterol synthesis.[8] Furthermore, other studies provided evidence that TSH can cause preadipocyte differentiation and adipogenesis,[9] stimulates metabolism and breakdown of lipids leading to increased serum free fatty acid levels in vivo[10] and has effects on leptin.[11]

Hence numerous studies attempted to test the relationship between TSH alone with lipid profile, ranging from population based surveys to the more recent cross sectional studies, however results are conflicting and studies reported disparate results.[7,14-18]

Looking at TSH, a study investigated its association with serum lipid concentrations despite being in the "Normal" range and the study found that even within the normal range of TSH, a higher (high normal) level of TSH was associated with less favorable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH.[12] And on the 11th year follow-up of the HUNT study, participants with a higher TSH levels at baseline have higher non-HDL cholesterol and triglyceride levels and lower HDL cholesterol levels at follow-up, but the associations were very modest and not consistent between the sexes.[13]

In the analysis of the data of the fifth TROMSO study, it was noted that in both genders, there were significant correlations between serum TSH levels and serum Total cholesterol and serum LDL-C.[7] Also in a study done in Korea, TSH was positively associated with total cholesterol in both the subclinical hypothyroid and euthyroid overweight participants.[14]

In a study done in an older biracial population, a TSH higher than 5.5 mIU/mL was associated with a 9.0 mg/dL (0.23 mmol/L) higher cholesterol level.[15] Similarly, a community-based study in Australia showed that total cholesterol and LDL is associated with elevated TSH (≤ 10 mU/l), as well as it is positively correlated with triglyceride.[16] Chao Xu et. al. evaluated the relationship between TSH and lipid profile independent of thyroid hormone in coronary heart disease patients and found that TSH can increase the total cholesterol level in CHD patients independent of FT4, FT3 and reverse T3 and that for each 1.0 mIU/L increase in the TSH level might be linked to a 0.015580712mmol/L elevation of the serum total cholesterol value.[17]

In the study of Sarzosa Teran, V. et al. (2012) a statistical association was shown between dyslipidemia and altered TSH levels. However, they added that the strength of this association was very weak, and they concluded that TSH has no value as a clinical predictor of dyslipidemia.[18]

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic entity increasingly being recognized as a major health burden. Being the most common liver disease, worldwide it has a reported prevalence of six to 35% with a median of 20 percent and it is at five to 30% in the Asia-Pacific regions.[19,20,21] Locally, in a retrospective study done at Philippine General Hospital via review of case records from January 1999 to December 2004, from a total of 1102 patients with fatty liver, 134 patients (12.2%) were diagnosed with NAFLD, based on clinical and histopathological findings or ultrasound findings suggestive of fatty liver.[22]

If dyslipidemia and metabolic diseases like diabetes are linked with hypothyroidism, it is not unlikely that NAFLD is also prevalent in patients with thyroid hypofunction. In a scientific review done in an effort to clarify the mechanism for the relationship of NAFLD and thyroid dysfunction, the role of leptin and Fibroblast growth factor (FGF-21) in hepatic insulin resistance and overproduction of damaging reactive oxygen species (ROS) from accumulation of free fatty acid in hepatocytes due to elevated cholesterol and triglyceride from decreased lipoprotein lipase activity were the possible mechanisms found to be involved in the association of NAFLD and thyroid hypofunction.[23]

In a case-control study in a Chinese population by Xu et. al., the incidence of NAFLD increased in patients across different TSH subgroups (from euthyoid level to severely elevated) and they noted that subjects with higher baseline TSH levels were more likely to develop NAFLD during the follow-up period and the association is significant even after adjustment for indicators of metabolic syndrome. [24] In a study of euthyroid patients, NAFLD prevalence increased gradually with increasing quartiles of TSH levels and that TSH is an independent risk factor for NAFLD (odds ratio (OR): 2.21, 95% confidence interval (CI): 1.21–4.02, p = 0.01, for TSH levels). [25] However, the result of the study done by Zhang et. al., TSH was not seen as an independent risk factor of NAFLD, hence they concluded that a change of TSH level would not influence the prevalence of NAFLD. [26] Furthermore, in a study done in an Iranian population, no significant difference was seen in TSH and even in free T4, and free T3 levels between the participants with NAFLD and without NAFLD.[27]

In a systematic review of 11 studies investigating on NAFLD and thyroid dysfunction (2014), the authors concluded that the results of current studies are conflicting about the association between thyroid abnormalities and NAFLD and that physicians caring for patients with NAFLD may be led to test thyroid hormone profiles as part of initial clinical assessment of patients with NAFLD because some of the reviewed studies still propose thyroid dysfunction as a risk factor for NAFLD.[28]

Guidelines on thyroid diseases suggest the use of TSH as a screening test to detect thyroid dysfunction.[29,30] These are the guiding principles which are used as the basis of its incorporation of TSH in the diagnostic work-up of essentially healthy patients that avails of standard tests to assess their over-all health like the Executive Check-up package. Yearly, approximately 800 patients are admitted under Executive Check-Up Plans A and B in Makati Medical Center. The package includes laboratory testing to assess

metabolic problems and screening for thyroid function abnormalities (TSH determination using radioimmunoasay). Ultrasound of the whole abdomen, a sensitive screening tool for fatty liver, is also included, as well as HBsAg (Hepatitis B antigen) which is used to rule out occult hepatitis B infection. Hence clinicians, even in our institution, are often faced with a patient with elevated lipid tests alongside the finding of fatty liver disease in which the TSH is elevated. With only these tests on-hand, without the benefit of a free T4 result, is there an association between dyslipidemia and fatty liver disease with the elevated TSH?. Also, if in case faced with an elevated TSH in an asymptomatic patient, would it be enough to justify work-up for dyslipidiemia and fatty liver disease even without yet the benefit of a Free T4 result? To help answer these questions, this study aims to determine the prevalence of elevated TSH among patients who availed the Executive Check-Up Plans from January 1, 2013 to December 31, 2013 in Makati Medical Center and its association with dyslipidemia and fatty liver disease.

This is the first local study looking at the association of non-alcoholic fatty liver disease and elevated TSH in essentially healthy Filipino adult patients with/without stable comorbid disease. Data that will be generated from this research has the potential for clinical utility by revealing the prevalence of elevated TSH in executive check-up patients in a Tertiary hospital and their metabolic profile, to prove if it is indeed worthwhile to continue screening this subset of patients for possible thyroid hypofunction using only TSH. In addition, the study can also validate if screening of patients with mildy elevated TSH for dyslipidemia and fatty liver disease must be recommended and advocated for Filipino patients, similar to some international recommendations. This is a timely study due to the current increasing prevalence of the metabolic disorders of interest, namely dyslipidemia and fatty liver disease, in the Filipino population.

Methodology

Study design and population

This is a cross-sectional analytic study utilizing a retrospective review of charts. We included Filipino adults aged 18 years or older, admitted at Makati Medical Center under Executive Health Package A or B from January until December 2013, and who finished all diagnostic tests covered by their package. We excluded patients with hepatitis and hepatobiliary infections, hepatic malignancy, biliary tract disease, portal hypertension, previously known thyroid disease, pituitary disease, previous radioactive therapy or intake of thyroid hormones or anti-thyroid medications, and surgeries that may lead to secondary NAFLD such as gastropexy, jejunoileal bypass, extensive small bowel resection, biliopancreatic diversion, and small bowel diverticulosis).

Sample size estimation

We required a minimum of 467 adults for this study using 95% confidence interval and a desired confidence width of 5%. We assumed the prevalence of elevated TSH to be at 8.28% based on MMC records (Aquino et al, 2007, unpublished).

Data collection

A record review of all eligible patients was conducted after procurement of the Institutional Review Board approval for the study granted September 2014. Information was noted on a data collection tool. All efforts to maintain the anonymity and confidentiality of all data was exercised. The "within normal" results of all laboratory tests in this study were based on Makati Medical Center laboratory reference values.

Study Variables/Operational Definition

1. Executive Check-up patient defined as healthy adult patients, with or without stable or controlled comorbid disease/s who in their own volition was admitted for general work-up

2. High TSH defined as having a TSH value above 4.5 mIU/L without previous history of thyroid disease and not taking levothyroxine or anti-thyroid medications. For this study mildly elevated TSH is between 4.51 mIU/L and 10 mIU/L.

3. Dyslipidemia defined as elevated values of Total Cholesterol, LDL, or Triglyceride or low HDL compared to the reference normal value/s of the following lipid parameters: total cholesterol (above 200mg/dl), triglyceride (above 150mg/dl), and LDL (above 100mg/dl); values below reference normal for HDL (less than 40mg/dl for both men and women)

4. Fatty Liver Disease as documented by ultrasound done in the Makati Medical Center Ultrasound Section, described as diffuse increase in hepatic echogenicity, or "bright liver", due to increased reflection of ultrasound from the liver parenchyma, which is caused by intracellular accumulation of fat vacuoles [31]

5. Demographic data: age and gender

6. Comorbid diseases: Impaired fasting glucose (IFG)/ impaired glucose intolerance (IGT)/ diabetes mellitus (DM), hypertension/ cardiovascular disease (CVD)/ coronary artery disease (CAD)

7. Anthropometric measures: height, weight, Body Mass Index (BMI) and classification based on WHO Asia-Pacific definitions (32):

- Underweight: <18.5
- Normal: 18.5-22.9
- Overweight: 23-24.9
- Obese Class 1: 25-29.9
- Obese Class 2: 30-40
- Morbidly Obese: >40

8. Liver function tests namely SGPT and SGOT and abnormal levels defined as high if levels are above 35 mg/dl.

9. Other metabolic parameters: Fasting blood sugar (an abnormal high value falling at 100mg/dl and above) and blood uric acid (an abnormal high value for females that is above 5.7 mg/dl and for men it is above 7 mg/dl)

STATISTICAL ANALYSIS

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, and mean and SD for interval/ratio variables. Independent Sample T-test, and Chi-square/Fisher's Exact test was used to determine the difference of means and proportions between elevated and normal TSH level groups, respectively. Odds ratios and corresponding 95% confidence intervals were determined. We conducted a binary logistic regression to determine the association of fatty liver disease, lipid levels, and TSH levels, adjusted for age and sex. All valid data was included in the analysis. Missing variables was neither replaced nor estimated. Null hypotheses were rejected at 0.05 -level of significance. STATA 12.0 was used for data analysis.

Results

A total of 917 patients were admitted for routine Executive Check-Up under package A or B from January 1, 2013 to December 31, 2013. While most exclusions were due to incomplete data, a number of patients were also excluded for HbsAg positivity and having a history of heavy alcohol drinking, thyroid disorder (namely goiter, thyroid nodule, hypothyroidism, hyperthyroidism and Hashimoto's thyroiditis) and thryoid surgery. Only 580 patients remained for analysis. Of these, 18 patients (3.10%) had elevated TSH levels. The average TSH value of the elevated TSH group was 5.61 + 0.90 (units). The normal and elevated TSH groups were comparable in terms of age, gender, weight, height, BMI and comorbidities (Table I).

Fatty liver disease on ultrasound, abnormal lipid profile and liver enzymes, elevated fasting blood sugar and high serum uric acid were compared between groups of patients with elevated TSH and normal TSH (Table II). Elevated total cholesterol, triglyceride, low density lipoprotein, fasting blood glucose and serum uric acid were more common in the elevated TSH group, while fatty liver disease and deranged liver enzymes were more frequent among those with normal TSH. However, only total cholesterol was significantly increased in the elevated TSH group (83% versus 55%, p = 0.015).

We determined whether age, sex, BMI, fatty liver disease, liver function tests, lipid profile, fasting blood glucose, and uric acid had an association with elevated TSH levels (Table III). On bivariate analysis, we had insufficient evidence to demonstrate an association for these parameters except for total cholesterol > 200. Patients with increased total cholesterol was approximately 4.18 times as likely (95% CI 1.20 to 14.61%, p = 0.025) to have elevated TSH.

We conducted a binary logistic regression to determine whether NAFLD and lipid levels are associated with elevated TSH levels. On adjusting for age and sex, we had insufficient evidence to demonstrate an association between NAFLD and lipid levels with elevated TSH levels (Table IV).

Discussion

For this study, the rate of elevated TSH is 3.1%, near the estimated prevalence of elevated TSH in the Tromso study. [7]

There is a higher frequency of high Total Cholesterol, Triglyceride and LDL in the elevated TSH group, in the frequency of 83%, 44% and 89%.. The same is not seen for low HDL and fatty liver disease, showing a slightly higher frequency of these conditions in patients with normal TSH.

The association of high or higher TSH (high-normal) with total cholesterol, as well as other lipid parameters has been seen in several studies.[12-17] For the association of total cholesterol with elevated TSH, the same relationship is seen in our study (Table III), in that total cholesterol was significantly higher in the elevated TSH group wherein patients with increased total cholesterol was approximately 4.18 times as likely (95% CI 1.20 to 14.61%, p = 0.025) to have elevated TSH. However, on adjusting for age and sex, the said association was not significant. The said result maybe because part of the association between TSH and total cholesterol is explained by age and gender. In the study by Lu et. al., on initial analysis, total cholesterol, LDL and triglyceride were not different between the two groups after adjusting for age, sex and BMI. However after further analysis, they found that the relationship of TSH and lipids levels were different in the overweight and normal weight populations, along with those in men and women, wherein the said lipid parameters were

Table I. Clinical profile of 580 executive check-up patients admitted in MMC from January to December 2013 (n=580)

	Elevated TSH (n=18)	Normal TSH (n=562)	P-Value
	Frequency (%); Mean + SD		
Age	46.67 + 9.89	48.58 + 11.36	0.480*
TSH level	5.61 + 0.90	1.66 + 0.85	**0.000***
BMI	25.36 + 4.28	26.32 + 5.17	0.434*
Height (cm)	162.72 + 7.97	163.27 + 12.29	0.851*
Weight (kg)	67.64 + 14.47	72.21 + 17.10	0.263*
Sex			0.851ł
Male	11 (61.11)	331 (58.90)	
Female	7 (38.89)	231 (41.10)	
BMI category			0.265§
Underweight	1 (5.56)	2 (0.36)	
Normal	3 (16.67)	113 (20.11)	
Overweight	5 (27.78)	114 (20.28)	
Obese 1	7 (38.89)	216 (38.43)	
Obese 2	2 (11.11)	103 (18.33)	
Morbid Obese	0	14 (2.49)	
Comorbidities			
IFG, IGT or overt diabetes	2 (11.11)	102 (18.15)	0.754§
Hypertension	5 (27.78)	207 (36.83)	0.432ł
CAD or CVD	0	22 (3.92)	1.000§

*Statistical test used: * – Independent T-test; ł – Chi-square analysis; § – Fisher's exact test*

Table II. Diagnostic and laboratory parameters of 580 patients by TSH levels

	Elevated TSH (n=18)	Normal TSH (n=562)	P-Value
	Frequency (%)		
Fatty liver disease	46.67 + 9.89	48.58 + 11.36	0.480*
Liver function tests (U/L)	25.36 + 4.28	26.32 + 5.17	0.434*
SGOT > 35	162.72 + 7.97	163.27 + 12.29	0.851*
SGPT > 35	67.64 + 14.47	72.21 + 17.10	0.263*
BMI category			
Total cholesterol > 200	15 (83.33)	306 (54.45)	**0.015**
Triglyceride > 150	8 (44.44)	154 (27.40)	0.113
LDL ≥ 100	16 (88.89)	443 (78.83)	0.301
HDL < 40	3 (16.67)	98 (17.44)	1.000§
Fasting blood glucose ≥ 100 mg/dL	5 (27.78)	150 (26.69)	1.000§
Uric acid (mg/dL): male: ≥ 7; female ≥ 5.7	13 (72.22)	304 (54.09)	0.128

Statistical test used: Chi-square analysis; § – Fisher's exact test

Table III. Association of clinical profile, diagnostic, and laboratory parameters of 580 patients to elevated TSH level

	Elevated TSH (n=18)	Normal TSH (n=562)	Unadjusted Odds Ratio (95% CI)	P-Value
	Frequency (%)			
Aged > 50 years old	6 (33.33)	255 (45.37)	0.60 (0.22 to 1.63)	0.317
Male	11 (61.11)	331 (58.90)	1.10 (0.42 to 2.87)	0.851
BMI > 23	14 (77.78)	445 (79.18)	0.92 (0.30 to 2.85)	0.885
Fatty liver disease	8 (44.44)	307 (54.63)	0.66 (0.26 to 1.71)	0.396
Liver function tests (U/L)				
SGOT > 35	0	70 (12.46)	-	-
SGPT > 35	3 (16.67)	195 (34.70)	0.37 (0.11 to 1.32)	0.126
Lipid profile tests (mg/dL)				
Total cholesterol > 200	15 (83.33)	306 (54.45)	4.18 (1.20 to 14.61)	**0.025**
Triglyceride > 150	8 (44.44)	154 (27.40)	2.12 (0.82 to 5.47)	0.120
LDL ≥ 100	16 (88.89)	443 (78.83)	2.15 (0.49 to 9.48)	0.312
HDL < 40	3 (16.67)	98 (17.44)	0.95 (0.27 to 3.33)	0.932
Fasting blood glucose ≥ 100 mg/dL	5 (27.78)	150 (26.69)	1.06 (0.37 to 3.01)	0.918
Uric acid (mg/dL): male: ≥ 7; female ≥ 5.7	13 (72.22)	304 (54.09)	2.21 (0.78 to 6.27)	0.138

Table IV. Association of non-alcoholic fatty liver disease and lipid levels with elevated TSH levels in Filipino adults, adjusted to age and sex (n = 580)

	Elevated TSH (n=18)	Normal TSH (n=562)	Unadjusted Odds Ratio (95% CI)	P-Value
	Frequency (%)			
Aged > 50 years old	6 (33.33)	255 (45.37)	0692 (0.24 to 1.97)	0.490
Male	11 (61.11)	331 (58.90)	1.03 (0.37 to 2.91)	0.952
BMI > 23	14 (77.78)	445 (79.18)	0.92 (0.30 to 2.85)	0.885
Non-alcoholic fatty liver disease	8 (44.44)	307 (54.63)	0.53 (0.18 to 1.55)	0.243
Lipid profile tests (mg/dL)				
Total cholesterol > 200	15 (83.33)	306 (54.45)	4.29 (0.90 to 20.58)	0.069
Triglyceride > 150	8 (44.44)	154 (27.40)	2 (0.68 to 5.89)	0.211
LDL ≥ 100	16 (88.89)	443 (78.83)	0.71 (0.11 to 4.53)	0.717
HDL < 40	3 (16.67)	98 (17.44)	0.97 (0.24 to 3.85)	0.965
Fasting blood glucose ≥ 100 mg/dL	5 (27.78)	150 (26.69)	1.28 (0.39 to 4.20)	0.689

found to be positively associated with TSH when their relationship was analyzed per population e.g. overweight population vs. normal weight and overweight female population vs. overweight male population. The said study illustrates that the combination of serum TSH, sex, and BMI has important effects on serum lipid parameters. In this light, in our study the non-association of triglyceride and LDL with TSH can also be a result of the relatively homogenous population of our study in terms of BMI, because for both high and normal TSH about 70% of the patients are overweight or obese (BMI >23), making the effects of TSH on these lipid parameters to be not significantly different between two groups (high vs. normal TSH) derived from a relatively homogenous population in terms of BMI.

In our study, fatty liver disease was not found to be more prevalent in the elevated TSH group. Conditions related to insulin resistance, like prediabetes, diabetes and body fat or obesity are well studied and documented risk factors for NAFLD.[33] Aside from most of the patients in both the high and normal TSH group having a BMI above normal, the patients in the normal TSH group, also have a higher mean BMI and higher number of prediabetic or diabetic patients than in the elevated TSH group. This setting may have put the patients in both groups at already high risk for having NAFLD, the normal TSH group more than the high TSH because of higher prevalance of elevated BMI and insulin resistance state in the normal TSH group. In the same light, the group of Lee et al. conducted a four-year retropective cohort study on the impact of differing levels of thyroid dysfunction on the development of NAFLD and found that both TSH and free T4 were not associated with the development of NAFLD. In the same study, the NAFLD group has significantly higher BMI, plasma glucose, plasma insulin and HOMA-IR (a marker of insulin resistance, computed as fasting insulin(μIU/mL) × fasting glucose (mmol/L))/22.5). [34]

Conclusion

For this study, the rate of elevated TSH is 3.1%, and when tested for its relationship with lipid parameters and NAFLD, only total cholesterol was significantly higher in the elevated TSH group compared to those with normal TSH wherein increased total cholesterol was approximately 4.18 times as likely (95% CI 1.20 to 14.61%, p = 0.025) to have elevated TSH. However, on adjusting for confounding factors like age and sex, we have insufficient evidence to demonstrate an association between lipid levels (including total cholesterol) and NAFLD with elevated TSH levels. These findings illustrates that serum TSH, sex, and BMI has important effects on serum lipid parameters and NAFLD and that part of the association between TSH with lipid parameters and NAFLD is modified by gender and BMI as seen by some recent studies.

With this, we recommend for future studies to investigate the effect of TSH on lipid parameters and NAFLD in a population and study design wherein their relationship can be observed in mutually exclusive groups of varying BMI or levels of insulin resistance and gender.

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