The Risk of Developing Non-Alcoholic Fatty Liver Disease in Adult Patients with Subclinical Hypothyroidism Compared to Euthyroid: An Evidence-based Case Report

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ABSTRAK

Latar belakang: *hipotiroidisme merupakan penyakit penyerta yang sering ditemukan pada pasien dengan penyakit perlemakan hati non-alkoholik (non-alcoholic fatty liver disease [NAFLD]). Penelitian-penelitian terdahulu mengenai hubungan antara hipotiroidisme subklinis dan NAFLD memperlihatkan hasil yang bertentangan, mulai dari hubungan kuat hingga asosiasi yang tidak signifikan. Laporan kasus ini bertujuan untuk menginvestigasi risiko berkembangnya NAFLD pada pasien hipotiroidisme subklinis.* ***Metode:*** *penelusuran literatur menggunakan basis data ScienceDirect, PubMed, ProQuest, dan Scopus. Penapisan judul dan abstrak dengan kriteria inklusi dan eksklusi menghasilkan 4 artikel (1 telaah sistematis, 1 kohort prospektif, 1 kohort retrospektif, dan 1 studi kasus-kontrol) yang sesuai untuk menjawab pertanyaan klinis. Telaah kritis dilakukan dengan menggunakan lembar kerja dari Centre for Evidence-Based Medicine, University of Oxford.* ***Hasil:*** *telaah sistematis dianggap tidak valid karena memiliki penelusuran yang kurang komprehensif terhadap studi-studi terkait, seleksi artikel yang kurang tepat untuk menyimpulkan hubungan kausal antarpenyakit, dan heterogenitas statistik. Kohort retrospektif dinilai tidak penting karena memiliki risiko relatif 0,85 (interval kepercayaan [IK] 95%, 0,72—1,00) yang batas atas IK-nya meliputi 1,00. Dua artikel lainnya valid serta memiliki risiko relatif dan rasio odds yang penting (1,27 [IK 95%, 1,09—1,47], 3,41 [IK 95%, 1,16—9,98]; berturut-turut). Number needed to harm (5—17) mengindikasikan bahaya yang bermakna secara klinis dari pajanan hipotiroidisme subklinis karena hanya sedikit pasien dengan hipotiroidisme subklinis yang dibutuhkan untuk memperoleh tambahan satu insidens NAFLD. Kedua artikel tersebut juga memiliki kemamputerapan yang baik untuk kasus ini.* ***Kesimpulan:*** *pasien dengan hipotiroid subklinis, dibandingkan dengan pasien eutiroid, berisiko lebih tinggi untuk mengalami NAFLD.*

Kata kunci: *eutiroid, hipotiroidisme subklinis, penyakit perlemakan hati non-alkoholik.*

ABSTRACT

Background: *hypothyroidism is a common concomitant disease of non-alcoholic fatty liver disease (NAFLD). Previous studies regarding the relationship between subclinical hypothyroidism and NAFLD showed conflicting results, ranging from a strong association to not significant one. This case report aimed to investigate the risk of developing NAFLD in subclinical hypothyroidism patients.* ***Methods:*** *literature searching used ScienceDirect, PubMed, ProQuest, and Scopus. Filtering process of titles and abstracts by using inclusion and exclusion criteria yielded 4 eligible articles (1 systematic review, 1 prospective cohort, 1 retrospective cohort, and 1 case-control*

study) for answering the clinical question. Critical appraisal was conducted by using worksheets from Centre for Evidence-Based Medicine, University of Oxford. ***Results:*** *the systematic review was considered invalid due to its less comprehensive search for relevant studies, inappropriate article selection to find a causal relationship between diseases, and statistical heterogeneity. The retrospective cohort was decided unimportant because it possessed a relative risk of 0.85 (95% confidence interval [CI], 0.72--1.00) which the upper limit of its CI included 1.00. The rest were valid and had important risk relative and odds ratio (1.27 [95% CI, 1.09--1.47], 3.41 [95% CI, 1.16--9.98]; respectively). The number needed to harm (5—17) indicated the clinically meaningful harm of the exposure since only a few patients with subclinical hypothyroidism is needed to obtain one additional NAFLD incidence. Those two articles were also suitable to be applied in our case.* ***Conclusion:*** *patients with subclinical hypothyroidism, compared to euthyroid patients, are at higher risk of developing NAFLD.*

Keywords: *euthyroid, non-alcoholic fatty liver disease, subclinical hypothyroidism.*

INTRODUCTION

Subclinical hypothyroidism is a condition characterized by an elevated levels of thyroid stimulating hormone (TSH) with a normal free thyroxine (FT4) levels.[1] This is a quite common condition found across various populations. The Colorado Thyroid Disease Prevalence Study found that the prevalence of subclinical hypothyroidism in United States is 9.0%, whereas the prevalence in India is 8.9% according to the South Indian Population Study.[2,3] Its prevalence in Indonesia is still undetermined.[4] The risk factors associated with subclinical hypothyroidism comprises female sex, advancing age, and suboptimal iodine status.[2] In the other hand, non-alcoholic fatty liver disease (NAFLD) has been recognized as the most common cause of abnormal liver function worldwide. The global prevalence of NAFLD is 24%, with the highest rates are reported from South America, the Middle East, and Asia.[5]

NAFLD is a wide spectrum of liver clinicopathologic conditions, varying from a benign condition called pure fatty steatosis (fatty infiltration in >5% of hepatocytes) to a heavier condition called non-alcoholic steatohepatitis (NASH). NASH may progress to cirrhosis, liver failure, and hepatocellular carcinoma. The key characteristic of NAFLD is excessive fat accumulation in the liver parenchyma of patients without any history of alcohol abuse (<20 g per day in men and <10 g in women).[6] NAFLD is strongly associated with metabolic syndrome, which is also linked to subclinical hypothyroidism.[7,8] Considering the important role of thyroid hormone in lipid metabolism, hypothyroidism may cause hyperlipidemia which plays a crucial role in the pathogenesis of NAFLD.[9]

The prevalence of hypothyroidism was higher among NAFLD patients compared to controls (21% vs 9.5%, p <0.01), indicating that hypothyroidism is a common concomitant disease of NAFLD and may have an association with the NAFLD development.[10] A recent study showed that the decreased levels of FT4, as happening in overt hypothyroidism, can escalate the risk of NAFLD.[11] However, previous studies regarding the relationship between subclinical hypothyroidism and NAFLD yielded conflicting results, varying from a strong association to no association.[9,12,13] Therefore, the causal relationship between them remains in dispute up to now. In this evidence-based case report, we aimed to determine the risk of developing NAFLD in patients with subclinical hypothyroidism.

CASE ILLUSTRATION

A 57-year-old female presented to a clinic, complaining of a progressive weight gain of around 15 kilograms over the past 6 months. She also reported cold intolerance and fatigue. Neither history of diabetes or of hypertension was identified. Family history was significant for an unclear thyroid disease in her mother, who passed away due to a liver disease. Vital signs were within normal limits. The body mass index was 26.3 kg/m^2. Thyroid enlargement was

not present. Other physical examination was unremarkable.

Complete blood count and serum electrolytes were normal. Serum cholesterol was 270 mg/dL (N < 200). The TSH levels was 9.1 mIU/mL (N = 0.4-4.3), and the FT4 concentration was 1.17 ng/dL (N = 0.8-1.7). She was suspected suffering subclinical hypothyroidism and was planned to repeat the laboratory tests in the following 3 months before the diagnosis could be established. The patient, as well as the medical doctor, would like to know whether subclinical hypothyroidism could raise the risk of developing NAFLD.

CLINICAL QUESTION

We formulated a clinical question based on the Patient, Indicator, Comparison, and Outcome (PICO) format as follows:

- Patient (P): Adults (aged 18 years or older);
- Indicator (I): Subclinical hypothyroidism;
- Comparison (C): Euthyroid;
- Outcome: Development of NAFLD.

Here is the clinical question: Are the adult patients with subclinical hypothyroidism, compared to euthyroid patients, at higher risk of developing non-alcoholic fatty liver disease?

Table 1. Searching strategy

Search Engine	Terms	Articles Found	Articles Used
Science Direct	(“subclinical hypothyroid“ OR “subclinical hypothyroidism“ OR “mild thyroid failure”) AND (euthyroid OR normal thyroixine) AND (“NAFLD” OR “non alcoholic fatty liver disease“ OR “nonalcoholic fatty liver disease“ OR “nonalcoholic steatohepatitis“)	2	0
PubMed	((((((((((subclinical hypothyroid[Title/Abstract]) OR subclinical hypothyroidism[Title/Abstract]) OR subclinical thyroid stimulating hormone deficiency[Title/Abstract]) OR subclinical thyroid stimulating hormone deficiencies[Title/Abstract]) OR subclinical thyroid-stimulating hormone deficiency[Title/Abstract]) OR subclinical thyroid-stimulating hormone deficiencies[Title/Abstract]) OR mild thyroid failure[Title/Abstract]) OR subclinical tsh deficiency[Title/Abstract]) OR subclinical tsh deficiencies[Title/Abstract])) AND (((((((euthyroid[Title/Abstract]) OR normothyroid[Title/Abstract]) OR normal thyroid[Title/Abstract]) OR normal thyroxine[Title/Abstract]) OR normal free thyroxine[Title/Abstract]) OR normal free t4[Title/Abstract]) OR normal ft4[Title/Abstract])) AND ((((((((((((((((NAFLD[Title/Abstract]) OR non alcoholic fatty liver disease[Title/Abstract]) OR non-alcoholic fatty liver disease[Title/Abstract]) OR nonalcoholic fatty liver disease[Title/Abstract]) OR non alcoholic fatty liver[Title/Abstract]) OR non-alcoholic fatty liver[Title/Abstract]) OR nonalcoholic fatty liver[Title/Abstract]) OR non alcoholic fatty livers[Title/Abstract]) OR non-alcoholic fatty livers[Title/Abstract]) OR nonalcoholic fatty livers[Title/Abstract]) OR nonalcoholic steatohepatitis[Title/Abstract]) OR non-alcoholic steatohepatitis[Title/Abstract]) OR nonalcoholic steatohepatitis[Title/Abstract]) OR nonalcoholic steatohepatitides[Title/Abstract]) OR non-alcoholic steatohepatitides[Title/Abstract]) OR non alcoholic steatohepatitides[Title/Abstract])	7	3
ProQuest	ab(subclinical hypothyroid OR subclinical hypothyroidism OR subclinical thyroid stimulating hormone deficiency OR subclinical thyroid stimulating hormone deficiencies OR subclinical thyroid-stimulating hormone deficiency OR subclinical thyroid-stimulating hormone deficiencies OR mild thyroid failure OR subclinical tsh deficiency OR subclinical tsh deficiencies) AND ab(euthyroid OR porphyroid OR normal thyroid OR normal thyroxine OR normal thyroxine OR normal free thyroxine OR normal free t4 OR normal ft4) AND ab(nafld OR non alcoholic fatty liver disease OR non-alcoholic fatty liver disease OR nonalcoholic fatty liver disease OR non alcoholic fatty liver OR non-alcoholic fatty liver OR nonalcoholic fatty liver OR non alcoholic fatty livers OR non-alcoholic fatty livers OR nonalcoholic fatty livers OR non alcoholic steatohepatitis OR nonalcoholic steatohepatitis OR non-alcoholic steatohepatitis OR non alcoholic steatohepatitis OR non-alcoholic steatohepatitis OR nonalcoholic steatohepatitis OR non alcoholic steatohepatitides OR nonalcoholic steatohepatides OR non-alcoholic steatohepatides)	15	1
Scopus	(TITLE-ABS-KEY ("subclinical hypothyroid" OR "subclinical hypothyroidism" OR "subclinical thyroid stimulating hormone deficiency" OR "subclinical thyroid-stimulating hormone" OR "mild thyroid failure" OR "subclinical tsh deficiency") AND TITLE-ABS-KEY (euthyroid OR normothyroid OR "normal thyroid" OR "normal thyroxine" OR "normal free thyroxine" OR "normal free t4" OR "normal ft4") AND TITLE-ABS-KEY (nafld OR "non alcoholic fatty liver disease" OR "non alcoholic fatty liver" OR "non alcoholic steatohepatitis" OR "non alcoholic hepatitides"))	6	0

METHODS

The article searching was performed in ScienceDirect, PubMed, ProQuest, and Scopus on July 14, 2018. The keywords of "subclinical hypothyroidism", "euthyroid", and "non-alcoholic fatty liver disease" along with their synonyms and related terms were used during the search. We omitted the keyword of "adult" because of the lack of results, yet it did not necessarily affect the finding and study analysis. The terminology applied in each of the databases is listed in **Table 1**.

Literature searching found several articles. The selection was conducted based on inclusion criteria, consisting of: (1) human; (2) comparative study; (3) meta-analysis/systematic reviews; (4) journal/research articles; (5) observational study; and (6) English. The yielded articles would be excluded if they were irrelevant to the clinical question, or their study design was cross-sectional.

Selection

There were 2 articles from ScienceDirect, 7 from PubMed, 15 from ProQuest, and 6 from Scopus yielded in literature searching. Limitation by using the inclusion criteria was then applied and there were 2 articles obtained from ScienceDirect, 4 from PubMed, 7 from ProQuest, and 6 from Scopus. After screening the title and abstract of each article, 6 articles with no double were found relevant to the clinical question. The full-text of those articles were available, and a thorough reading over them concluded that there were 4 useful articles to be reviewed for answering the clinical question. A flowchart summarizing the searching strategy and its results is shown in **Figure 1**.

Critical Appraisal

Four articles attained in literature searching were comprised of 1 systematic review, 1 prospective cohort, 1 retrospective cohort, and 1 case-control study. After the selection, critical

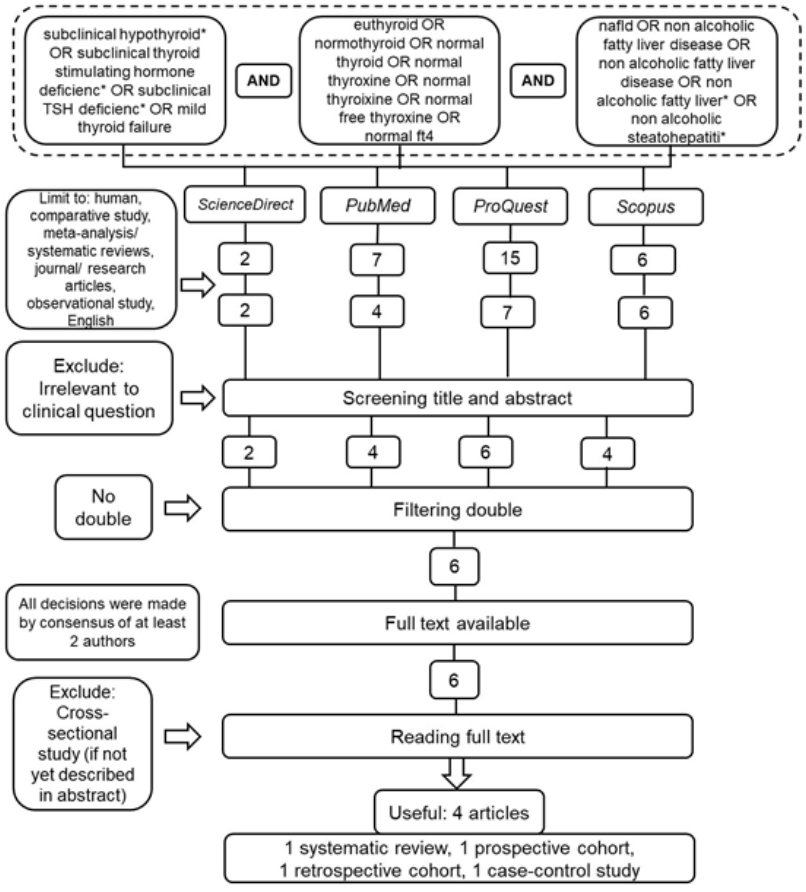

Figure 1. Flowchart of searching strategy.

appraisal was done by using worksheets from Center of Evidence-Based Medicine (CEBM), University of Oxford for etiologic studies or for systematic reviews.[14]

RESULTS

He et al.[15] conducted a systematic review of observational studies, aiming to evaluate the relationship between hypothyroidism and NAFLD. They searched PubMed, China Dissertation Database, and EMBASE. Thirteen studies were eventually included for the final study analysis. Those were consisted of 2 cohort, 4 case-control, and 7 cross-sectional studies. Subgroup analysis showed that the pooled odds ratio (OR) of NAFLD in patients with subclinical hypothyroidism is 1.40 (95% confidence interval [CI], 1.10-1.77). They drew a conclusion that subclinical hypothyroidism is independently associated with NAFLD.

A large population-based, prospective cohort study by Bano et al.[16] aimed to investigate the association between variations in thyroid function and NAFLD spectrum. This study was conducted at Ommoord district in Rotterdam, the Netherlands, and consisted of 3 periods of cohort (1990-1993, 2000, and 2006). A total of 14,926 subjects were enrolled and were comprised of 7,893 participants aged 55 years and over in the first cohort, 3,011 participants with same age limitation in the second cohort, and 3,932 participants aged 45 years or older in the last cohort. There were 9,419 participants eligible for study analysis. In this study, the relative risk (RR) of subclinical hypothyroidism, compared to euthyroid, in developing NAFLD is 1.27 (95% CI, 1.09–1.47) and the number needed to harm (NNH) is 17. They concluded that lower thyroid function is associated with an increased risk of NAFLD.

A 4-year retrospective cohort study by Lee et al.[17] aimed to compare the risk of developing NAFLD among three groups with different thyroid hormonal status (overt hypothyroidism, subclinical hypothyroidism, and control). They included 18,544 apparently healthy subjects without NAFLD aged 20-65 years who underwent annual health check-ups between 2008-2012 at the Health Promotion Center of Kangbuk Samsung Health Hospital, Korea. In this study, the RR of developing NAFLD in subclinical hypothyroid subjects is 0.85 (95% CI 0.72-1.00) and the NNH is -50. They suggested that both subclinical hypothyroidism and overt hypothyroidism are not related to an increased incidence of NAFLD.

Parikh et al.[18] conducted a case-control study, aiming to assess the prevalence of hypothyroidism in patients with NAFLD and to assess potential factors (dyslipidemia, obesity, diabetes) that could be linked with hypothyroidism. They entailed 800 adult patients in the Gastroenterology outpatient clinic of the Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, India. This study found that the prevalence of hypothyroidism in NAFLD is 16.8%. In this study, OR of NAFLD in subclinical hypothyroidism patients is 3.41 (95% CI 1.16-9.98) and the NNH is 5. They confirmed a significant clinical relationship between these two diseases.

The characteristics and relevant outcome of each yielded study are summarized in **Table 2**.

The critical appraisal result of the systematic review is provided in **Table 3**. Critical appraisal results of the cohort and case-control studies is reported in **Table 4**.

DISCUSSION

We appraised the validity of the systematic review by He et al.[15] In their title and abstract, they stated clearly the main research question being addressed, that is the relationship between hypothyroidism and NAFLD. The authors unfortunately carried out literature searching only in major bibliographic databases without any mentioned attempt to find related hand-searching journals, theses, conference proceedings, nor to contact experts for inquiring about unpublished articles. That is why we assessed that this review had less comprehensive search. In scrutinizing the inclusion of studies, we found that the authors kept including cross-sectional studies that makes this review lack of reliability to determine the causal relationship between subclinical hypothyroidism and NAFLD. Hence, we considered that this eligibility criteria makes us unable to rely on the results of this systematic

review to answer our clinical question. It is worth notice that the authors reported how they assess the quality of each study, that is by using Newcastle Ottawa Scale. This systematic review still had statistical heterogeneity and the study design was thought as the possible source. Overall, we decided that this systematic review is not valid to answer our clinical question. Therefore, we did not continue to further process of critical appraisal of this systematic review.

In the validity analysis of the prospective cohort study by Bano et al.[16], we found that the exposed groups and the controls were clearly defined. Both groups were similar because the authors had done adjustment for age, sex, follow-up time, use of hypolipidemic drugs, and cardiovascular risk factors. Thyroid function measurement and abdominal ultrasound for NAFLD diagnosis were performed in the same way in both groups. A single trained technician performed the abdominal ultrasonography and the images were reevaluated by an experienced hepatologist, though it was not mentioned whether the assessors were blinded to the thyroid status of participants. The median follow-up time was 10.04 (5.70-10.99) years and it is sufficiently long as Xu et al.[19] had found that 19.26% of subclinical hypothyroid subjects developed NAFLD during a median follow-up of 4.92 years. To make sure that the subclinical hypothyroidism preceded the onset of NAFLD, the authors had performed fatty liver index measurements at the beginning of study. The concept of "dechallange-rechallenge" is not applicable in this study. We found that the association in this study consistent with the study result of Kim et al.[20] which showed

Table 2. Characteristics and relevant outcome of the Yielded studies

Article	Country	Study Design	Participants (mean age [years old]; female %)	Definition of Subclinical Hypothyroidism	Diagnosis of NAFLD	Relevant Outcome
He et al.[15]	China	Systematic review	13 studies included: 2 cohort, 4 case-control, and 7 cross-sectional studies	Varying reference ranges among studies	11 studies by abdominal ultrasound, 2 studies by enzymatic procedures, 1 study by histological examination	Patients with subclinical hypothyroidism are at a higher risk for the development of NAFLD than euthyroid individuals (OR 1.40; 95% CI, 1.10-1.77)
Bano et al.[16]	Netherlands	Prospective cohort (median follow up time: 10.04 [5.70-10.88] years)	9,419 subjects (64.7; 56.5)	Serum TSH > 4.0 mIU/L and FT4 between 0.85-1.95 ng/dL	Abdominal ultrasound	Compared with euthyroid, subclinical hypothyroidism is associated with a 1.27-fold (95% CI, 1.087–1.469) higher risk of having NAFLD.
Lee et al.[17]	Korea	Retrospective cohort (follow up time: 4 years)	18,544 subjects (37.8 ± 5.7; 50)	TSH > 4.2 mIU/L and FT4 between 0.97-1.68 ng/dL	Abdominal ultrasound	Subclinical hypothyroidism is not a risk factor for developing NAFLD (hazard ratio [HR] 0.847; 95% CI, 0.715-1.003).
Parikh et al.[18]	India	Case-control	500 NAFLD patients (44.3 ± 3.2; 64.6), 300 controls (41.6 ± 3.89; 66)	TSH > 5.5 IU/mL but < 10 IU/mL, and FT4 levels within the reference range	Abdominal ultrasound	The odds ratio (OR) of NAFLD in subclinical hypothyroidism patients is 3.406 (95% CI, 1.162-9.981)

Table 3. Critical appraisal of systematic review

Article	Year	Study Design	Level of Evidence	Validity				
				Statement of the Main Question	Comprehensive Search	Appropriate Selection	Quality Assessment of Each Study	Homogenity
He et al.[15]	2017	Systematic review of cohort, case-control, and cross-sectional studies	3a	+	-	-	+	-

Table 4. Critical appraisal of cohort and case-control studies

	Bano et al.[16]	Lee et al.[17]	Parikh et al.[18]
Year	2016	2015	2015
Study Design	Prospective cohort	Retrospective cohort	Case-control
Level of Evidence	2b	2b	3b
Validity			
- Similarity between Two Groups	Yes	Yes	Yes
- Same Way of Measurement	Yes	Yes	Yes
- Adequate Follow Up	Yes	Yes	Yes
- Exposure Preceding Outcome	Yes	Yes	No
- Dose-Response Gradient	Yes	Yes	Yes
- Dechallenge - Rechallenge	Not applicable	Not applicable	Not applicable.
- Consistent Association	Yes	Yes	Yes
- Biological Sense	Yes	Yes	Yes
Importance	1.27 (1.09-1.47)	0.85 (0.72-1.00)	3.41 (1.16-9.98)
- RR (for Cohort Study)/ OR (for Case-Control Study) (95% CI)	0.28	0.11	0.85
- EER	0.22	0.13	0.62
- CER	0.27	- 0.15	0.37
- RRI	0.06	- 0.02	0.23
- ARI	17	- 50	5
- NNH			
Applicability			
- Applicable to Our Practice	Yes	-	Yes
- Potential Benefit and Harm from Agent	Not relevant	-	Not relevant
- Patient's Preferences and Concerns	Yes	-	Yes
- Availability of Alternative Treatments	Not relevant	-	Not relevant

ARI: absolute risk-increase; CER: control event rate; CI: confidence interval; EER: exposed event rate; NNH: number needed to harm; OR: odds ratio; RR: relative risk; RRI: relative risk-increase

the relationship between these diseases. The results of this study was also supported by the evidence of the physiological role of thyroid hormone in lipid metabolism.[9] Hence, we came to a decision that this evidence is valid to answer our clinical question.

We found in the cohort study by Bano et al.[16] that the NNH is 17, meaning that we need to have 17 patients with subclinical hypothyroidism to find 1 incidence of NAFLD. The RR in this study is 1.27, with 95% CI of 1.09-1.47. This confidence interval is narrow and stays within a clinically important increased risk. We considered that the valid results of this study are important.

Most of the patients enrolled in the cohort study by Bano et al.[16] were aged 55 years or older, and more than a half of them were female. So, our patient is not so different from those included in this study. The focus of interest in this study also resembles the concern of our patient. At last, we decided that this valid and important evidence about the risk of developing NAFLD in subclinical hypothyroidism individuals can be applied to our patient.

Appraisal of validity of the retrospective cohort study by Lee et al.[17] revealed that the exposed groups and the controls were clearly defined. The similarity of both groups was reassured by the adjustment for sex, age, body mass index, triglyceride and HDL levels. Assessment of initial levels of serum FT4, TSH, other biochemical indicators, as well as abdominal ultrasonography were performed in all subjects. The experienced radiologists were blinded to the clinical status of the subjects when they performed the ultrasounds. The follow-up time was 4 years and it is sufficiently long according to the finding in Xu et al.[19] The authors had excluded patients with initial fatty liver disease and only included healthy subjects without NAFLD, so we can have higher confidence that the subclinical hypothyroidism really preceded the onset NAFLD found in a later time. The concept of "dechallange-rechallenge" is not applicable in this study either. The negative association of subclinical hypothyroidism and NAFLD in this research is similar to the study by Mazo et al.[9] As a support for biological plausibility for this finding, Eshragian et al.[13] suggested that alterations in TSH levels in NAFLD patients is due to sick euthyroid syndrome, instead of subclinical hypothyroidism. Therefore, we reached a decision that the results of this study are valid.

The NNH in the cohort study by Lee et al.[17] is -50. This negative NNH indicates that the subclinical hypothyroid patients are less likely to develop NAFL than the euthyroid individuals. The RR in this study is 0.85, suggesting that subclinical hypothyroidism is the protective factor of NAFLD. The possible cause of this finding is that the participants included in this study were too young to develop NAFLD as the mean age of euthyroid group was 34.6 (SD 4.9) years old, while the mean age of subclinical hypothyroid group was 34.2 (SD 5.1) years old. It has been reported in another study that one of the risk factors of developing NAFLD is older age.[1]

However, the precision of these results is questionable since the 95% CI is 0.72-1.00. Because the upper limit of CI includes 1.00, there is a possibility that no significant relationship exists between those diseases in the actual population. Considering that the credibility of this study is not so fine, we decided that this evidence is valid, but not important. Thus, we did not continue appraising the applicability of this cohort study.

In the case-control study by Parikh et al.[18], validity appraisal found that the case group and the control group were well defined. Adjustment had been done for age, gender, alcohol use, and serum triglyceride levels to make both groups identical. All patients were evaluated in the same way for history, physical examination, thyroid profile, other laboratory tests, and abdominal ultrasound. It was not stated whether the assessors were blinded to the outcome and study hypothesis. No long follow-up period is needed because the outcome could be identified since the beginning of the case-control study. However, the study design makes it difficult to determine the temporal sequence between subclinical hypothyroidism as the exposure and NAFLD as outcome. The concept of "dechallange-rechallenge" is not applicable in this study. The association of subclinical

hypothyroidism and NAFLD in this study resembles the study result of Kim et al.[20] that showed a significant relationship between these diseases. The evidence of the fundamental role of thyroid hormone in lipid metabolism supported the results of this study.[9] Therefore, we reached a decision that this evidence is valid.

In the importance analysis of the case-control study by Parikh et al.[18], we found the NNH is 5, indicating that we need to have 5 patients with subclinical hypothyroidism to find 1 new incidence of NAFLD. The OR in this study is 3.41 (95% CI, 1.16-9.98). Although the confidence interval is not narrow, it stays within a clinically important increased risk. Thus, we decided that the valid results of this study are important.

The patients enrolled in the case-control study by Parikh et al.[18] were mostly women. The mean BMI of the NAFLD group was 29.15 (SD 0.56) kg/m^2, while the mean BMI of the control group was 27.14 (SD 0.54) kg/m^2. These characteristics resembles our patient's, so our patient is not so different from the subjects in this study. The focus of interest in this study also suites our patient's concern. Finally, we came to a decision that this valid and important evidence about the risk of NAFLD development in adults with subclinical hypothyroidism can be applied to our patient.

Overall, we had 2 valid, important, and applicable articles to answer our clinical question. Both articles highlighted the higher risk of developing NAFLD in patients with subclinical hypothyroidism. The foundation for our findings has been laid by several studies providing some possible explanations about the molecular mechanism underlying the causal relationship between subclinical hypothyroidism and NAFLD. Firstly, subclinical hypothyroidism is associated with insulin resistance.[21] At the same time, it has also been reported that insulin resistance represents the pathophysiological hallmark of NAFLD.[22]

Secondly, TSH can promote the hepatic expression of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR), a rate-limiting enzyme in cholesterol synthesis. The mechanism of action is that TSH bind to its receptors in hepatocyte membranes, stimulating the signaling system of cyclic adenosine monophosphate/protein kinase A/ cyclic adenosine monophosphate-responsive element binding protein (cAMP/PKA/CREB). This may be a potential mechanism for hypercholesterolemia involving direct action of TSH on the liver.[23]

Ultimately, patients with subclinical hypothyroidism may suffer secondary hypercholesterolemia which is associated with oxidative stress. Santi et al.[24] reported that subclinical hypothyroid patients, compared with the control group, are under increased oxidative stress which is characterized by lower activity of arylesterase, an enzyme with protective role against peroxidation of low-density lipoprotein (LDL) and other lipoproteins. They also found a significant correlation between lipids (triglyceride and LDL-C) and TSH.

CONCLUSION

Patients with subclinical hypothyroidism, compared to euthyroid patients, are at higher risk of developing NAFLD. Therefore, we can give an evidence-based answer to our patients about her greater risk of developing this liver disease if the diagnosis of subclinical hypothyroidism has been established. The screening of, as well as the preventive management (e.g. prescribing a reduced calorie, low-fat diet and regular exercises with the goal of controlling body weight) of NAFLD in subclinical hypothyroidism patients may be helpful to anticipate the poor outcome.

STATEMENT OF PRIOR PRESENTATION

This case report was presented in the form of scientific poster at the 16th Asia-Oceania Congress of Endocrinology (AOCE), September 27-30, 2018 in Yogyakarta, Indonesia.

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