



Greater Severity of Steatosis Is Associated with a Higher Risk of Incident Diabetes: A Retrospective Longitudinal Study

Ji Min Han^{1,*}, Jung Hwan Cho^{1,*}, Hye In Kim¹, Sunghwan Suh¹, Yu-Ji Lee², Jung Won Lee³, Kwang Min Kim³, Ji Cheol Bae¹

Divisions of ¹Endocrinology and Metabolism, ²Nephrology, ³Gastroenterology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Background: Fatty liver is associated with increased risk of developing type 2 diabetes. We aimed to evaluate whether the severity of hepatic steatosis is associated with incident diabetes.

Methods: We conducted a longitudinal analysis using data from 1,798 participants who underwent a comprehensive health check-up and abdominal computed tomography (CT). We assessed the association between baseline liver attenuation value on non-contrast CT images and risk of incident diabetes. All the participants were categorized into three groups based on the baseline liver attenuation value on non-contrast CT images: without hepatic steatosis (>57 Hounsfield unit [HU]), mild hepatic steatosis (41–57 HU), and moderate to severe hepatic steatosis (≤40 HU).

Results: During a median follow-up period of 5 years, 6.0% of the study participants progressed to diabetes. The incidence of diabetes was 17.3% in the moderate to severe hepatic steatosis group, 9.0% in the mild steatosis group, and 2.9% in those without hepatic steatosis. In a multivariate adjustment model, as compared with participants without hepatic steatosis, those with moderate to severe steatosis had a hazard ratio (HR) of 3.24 (95% confidence interval [CI], 1.64 to 4.2) for the development of diabetes, and those in the mild steatosis group had a HR of 2.33 (95% CI, 1.42 to 3.80). One standard deviation decrease in mean CT attenuation values of the liver was associated with a 40% increase in the development of diabetes (multivariate adjusted HR, 1.40; 95% CI, 1.2 to 1.63).

Conclusion: We found a positive association between severity of hepatic steatosis and risk of incident diabetes. Greater severity of steatosis was associated with a higher risk of incident diabetes.

Keywords: Fatty liver; Diabetes mellitus; Tomography, X-ray computed

INTRODUCTION

Ectopic fat is defined as excess fat deposition in non-adipose tissues, such as the liver, skeletal muscle, heart, and pancreas,

which normally contain only small amounts of fat [1]. It is well established that accumulation of ectopic fat is a major contributor to metabolic risk, with some depots having systemic effects [1,2]. As a key organ in systemic metabolism, the liver contrib-

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Corresponding author: Ji Cheol Bae

Division of Endocrinology and Metabolism, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea

Tel: +82-55-233-5831, Fax: +82-55-233-5109, E-mail: drkuri10@gmail.com

*These authors contributed equally to this work.

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utes substantially to the development of insulin resistance and type 2 diabetes [3]. Ectopic fat accumulation in the liver causes nonalcoholic fatty liver disease (NAFLD), encompassing simple steatosis, nonalcoholic steatohepatitis, fibrosis, and cirrhosis [2,4]. Accumulating evidence shows that NAFLD is associated with increased risk of incident diabetes, and this risk is independent of adiposity measures and other common metabolic risk factors [5].

There are still few large-scale studies on the quantitative relationship between NAFLD and type 2 diabetes, in terms of the severity of steatosis or NAFLD [5]. Liver biopsy is the gold standard for differentiating simple steatosis from steatohepatitis and evaluating the severity of hepatic steatosis and fibrosis. However, liver biopsy is invasive, expensive, and infeasible for population-based studies [6]. Therefore, studies based on histological findings were mostly small-scale and included patients in liver clinics [5,7,8]. Noninvasive modalities such as magnetic resonance imaging (MRI)-estimated proton density fat fraction (PDFF) and magnetic resonance elastography (MRE) are highly sensitive and specific for measuring liver fat contents; however, they are costly, time-consuming, and limited by technical feasibility [9]. Ultrasound is relatively limited in quantitatively measuring hepatic steatosis and distinguishing the severity of fatty liver. In most large-scale studies that examined the association between NAFLD and risk of developing diabetes, participants were recruited from general populations, and the diagnosis of NAFLD was based on ultrasonography [5].

In an observational cohort study of Korean adults, we carried out an analysis that examines the quantitative association between hepatic steatosis and risk of new-onset diabetes. In this study, we assessed the severity of hepatic steatosis using unenhanced hepatic computed tomography (CT). Although not as sensitive or specific as MRI-PDFF or MRE, unenhanced hepatic CT imaging correlates well with those measure by biopsy [10]. We aimed to investigate the association of hepatic steatosis with incident diabetes, and to determine if there are differences in these associations according to the severity of hepatic steatosis. The risk of diabetes may increase with alteration in glucose metabolism and insulin sensitivity that occurs as hepatic fat contents increase [11,12]. We hypothesized that the severity of hepatic steatosis is associated with incident diabetes.

METHODS

Study population

This study included 2,785 participants aged ≥ 20 years who un-

derwent a comprehensive health check-up and abdominal CT between January 2010 and December 2013 at the Samsung Changwon Hospital Healthcare Center. In the present study, a visit between 2010 and 2013 was termed a baseline visit. Among these participants, 996 were excluded based on the following criteria: (1) self-reported diabetes or undiagnosed diabetes (fasting glucose concentration ≥ 126 mg/dL or hemoglobin A1c [HbA1c] $\geq 6.5\%$) ($n=209$); (2) those who never underwent a follow-up examination after baseline visit ($n=731$); (3) those whose CT showed evidence of liver cirrhosis ($n=5$); (4) those with a history of malignant disease ($n=3$); and (5) missing data, including HbA1c and fasting plasma glucose (FPG) ($n=45$). After applying the above exclusion criteria, 1,798 participants were eligible for the analysis.

Study design and statistical analysis

This study was a retrospective, longitudinal, observational study of Korean adults without diabetes at baseline. We assessed hepatic steatosis and investigated associations with incident diabetes. We examined longitudinal associations between baseline liver attenuation value on non-contrast CT images and the risk of incident diabetes. All the participants were categorized into three groups using the baseline liver attenuation value on non-contrast CT images (>57 , $41-57$, and ≤ 40 Hounsfield unit [HU]). The incidence of diabetes was calculated in these groups, and the hazard ratio (HR) for the association of hepatic steatosis with incident diabetes was estimated using Cox proportional hazard regression analysis. The probability of developing diabetes, according to the baseline liver attenuation value, was estimated in multivariate logistic regression models using the margin command in Stata software. The median duration of follow-up for our study was 5 years (interquartile range, 4.2 to 5.3). All the models were adjusted for age, sex, body mass index (BMI), FPG, alcohol, triglyceride, and hepatitis B and C viral infections. A P value of <0.05 was considered statistically significant. All analyses were performed using Stata program version 15.1 (Stata Corp., College Station, TX, USA).

This study was approved by the Institutional Review Board (IRB) of the Samsung Changwon Hospital (IRB number: SMC201908003). Informed consent for this study was waived by the IRB because the researchers only accessed the database to obtain clinical data for the analyses, and personal information was not accessed.

Definition

The development of diabetes was assessed from the records of

participants at each follow-up visit through December 2018, and diabetes was diagnosed in participants who had FPG of ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ [13]. Additionally, participants who currently reported taking glucose-lowering medications based on a self-report questionnaire were defined as having diabetes. We used a mean liver attenuation cut-off value of 57 HU on unenhanced CT for mild hepatic steatosis (corresponding to hepatic fat contents $\geq 5\%$) and 40 HU for moderate to severe hepatic steatosis (corresponding to hepatic fat contents $\geq 30\%$) [10,14–16]. Significant alcohol consumption was defined as >21 standard drinks per week in men and >14 standard drinks per week in women. A standard alcoholic drink was any drink that contains 14 g of pure alcohol [17].

Measurement

Information on demographic characteristics and health-related history was obtained using self-reported questionnaires. The BMI was calculated as weight in kilogram divided by height in meters squared and then rounded to one decimal place. Blood samples were collected after an overnight fast. FPG concentration was determined on an automated chemistry analyzer (Hitachi Modular DPP, Roche Diagnostics, Tokyo, Japan) using a hexokinase method. HbA1c was measured using a non-porous

ion-exchange liquid chromatography with a HLC-723 Tosoh G8 automatic analyzer (Tosoh Corporation, Tokyo, Japan).

Computed tomography measurement of hepatic steatosis

Hepatic steatosis was assessed by measuring the liver attenuation value on non-contrast CT images expressed as HU. The unenhanced images were reviewed on a picture archiving and communication system (Marosis m-view, Marotech, Seoul, Korea) by researchers (J.C.B., J.M.H., H.I.K., J.W.L., K.M.K., and Y.J.L.) blinded to patient data. Details of the method have been described previously [18]. For each case, hepatic attenuation was measured by means of 12 circular regions of interests (ROIs) within three different transverse sections of the liver, with each section containing the umbilical portion of the left portal vein, confluence of the right hepatic vein, and posterior branch of the right portal vein. At each representative level, the liver was divided into four sectors (right anterior, right posterior, left medial, and left lateral sectors), and one ROI randomly drawn inside each sector, avoiding the large vessels, biliary structure, and any focal lesions, was considered representative of the sector [10]. The size of each ROI ranged between 1.0 and 1.1 cm². The abdominal CTs were performed using a 64-detector row helical scanner (SOMATOM Definition AS 64, Siemens Healthcare, Forchheim, Germany).

Table 1. Baseline Characteristics

Characteristic	All (n=1,798)	Mean liver attenuation on CT, HU ^a		
		>57 (n=1,025)	57–40 (n=669)	≤40 (n=104)
Age, yr	44.3±8.8	44.3±8.9	44.4±8.7	42.8±8.8
Male sex	1,245 (69.2)	625 (61.0)	524 (78.3)	96 (92.3)
BMI, kg/m ²	24.0±3.1	22.8±2.5	25.2±2.9	27.4±2.9
FPG, mg/dL	89.0±8.9	88.2±8.3	89.6±9.5	93.1±10.2
HbA1c, %	5.5±0.3	5.4±0.3	5.5±0.3	5.6±0.3
Triglyceride, mg/dL	100 (70–144)	88 (65–122)	113 (77–168)	148 (108–208)
HDL-C, mg/dL	57.4±14.2	60.7±14.1	53.5±13.3	49.8±9.8
AST, IU/L	22 (18, 28)	20 (17, 25)	23 (19, 30)	31 (26, 42)
ALT, IU/L	20 (14, 29)	16 (13, 23)	25 (19, 35)	49 (33, 66)
Alcohol	197 (11.0)	102 (9.9)	85 (12.7)	10 (9.6)
HBsAg positive	114 (6.3)	70 (6.8)	38 (5.7)	6 (5.8)
HCV Ab positive	5 (0.2)	3 (0.3)	2 (0.3)	0
Mean liver attenuation, HU ^a	55.2±8.0	60.2±2.8	51.1±4.2	32.3±7.2

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).

CT, computed tomography; HU, Hounsfield unit; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; Ab, antibody.

^aMeasured in unenhanced CT.

RESULTS

Cohort characteristics

The characteristics of the study participants are presented in Table 1. Overall, the participants had a mean BMI of 24.0 ± 3.1 kg/m². The mean age was 44.3 ± 8.8 years, and 69.2% of the study participants were men. Of the total participants, 43.0% (773 of 1,798 participants) had at least mild hepatic steatosis with a mean liver attenuation of ≤ 57 HU [14,16], and 5.8% (104 of 1,798 participants) had a mean liver attenuation of ≤ 40 HU, which is consistent with moderate to severe hepatic steatosis [10,15,16]. As the severity of hepatic steatosis increased, the values of metabolic parameters, including FPG, HbA1c, BMI, and triglyceride, increased, while high-density lipoprotein cho-

lesterol decreased. A sex difference was also shown with more men being affected by hepatic steatosis than women.

Relationship between steatosis and incident diabetes

Table 2, Fig. 1 show the risk of incident diabetes according to the categorized mean liver attenuation. During the median follow-up period of nearly 5 years (interquartile range, 4.2 to 5.3), 108 of 1,798 participants (6.0%) progressed to diabetes. The incidence of diabetes was 17.3% in the moderate to severe hepatic steatosis group (a mean liver attenuation of ≤ 40 HU) and 9.0% in the mild steatosis group (a mean liver attenuation of 40 to 57 HU), while it was 2.9% in participants without hepatic steatosis (a mean liver attenuation of > 57 HU). In a multivariate adjustment model, participants in the moderate to severe steatosis

Table 2. Hazard Ratio for Incident Diabetes by Liver Attenuation Groups

Variable	Liver attenuation, HU			Continuous liver attenuation, /SD decrease
	> 57	57–40	≤ 40	
No. of participants	1,025	669	104	
No. of participants who developed DM (%)	30 (2.9)	60 (9.0)	18 (17.3)	
Person-years of follow-up	4,793	3,027	425	
Incident cases of DM per 1,000 person-years	6.3	19.8	42.4	
Adjusted HR (95% CI) ^a				
Unadjusted	1	3.21 (2.07–4.99)	7.04 (3.92–12.64)	1.67 (1.49–1.88)
Age and sex	1	2.98 (1.91–4.65)	6.26 (3.44–11.40)	1.66 (1.46–1.88)
Age, sex, BMI, FPG, TG, and HDL-C	1	2.30 (1.42–3.73)	3.19 (1.63–6.23)	1.39 (1.19–1.62)
Multivariate ^b	1	2.33 (1.42–3.80)	3.24 (1.64–6.42)	1.40 (1.20–1.63)

HU, Hounsfield unit; SD, standard deviation; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; BMI, body mass index; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

^aEstimated by Cox proportional hazard analysis; ^bAdjusted for age, sex, BMI, FPG, triglyceride, HDL-C, alcohol consumption, presence of hepatitis B surface antigen and hepatitis C virus antibody.

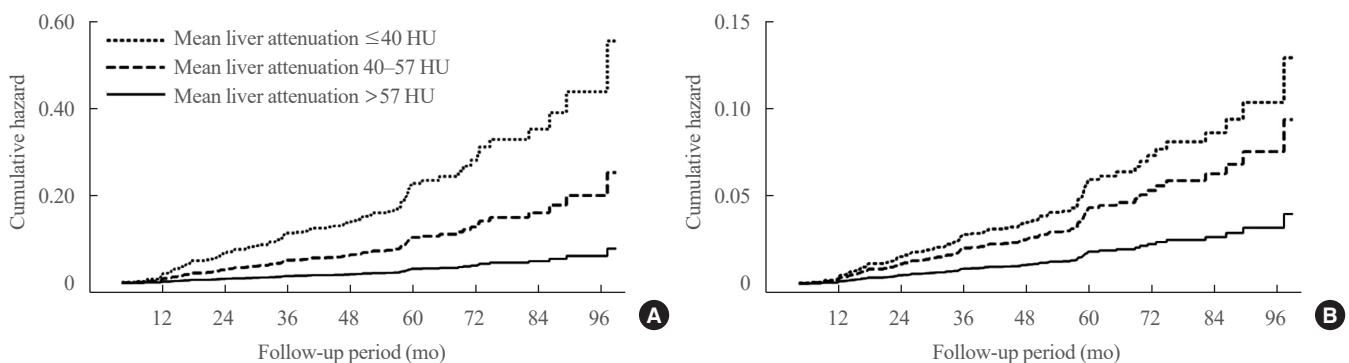


Fig. 1. Cumulative hazard for incident diabetes by liver attenuation groups. (A) Unadjusted. (B) Adjusted for age, sex, body mass index, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, alcohol consumption, presence of hepatitis B surface antigen, and hepatitis C virus antibody. HU, Hounsfield unit.

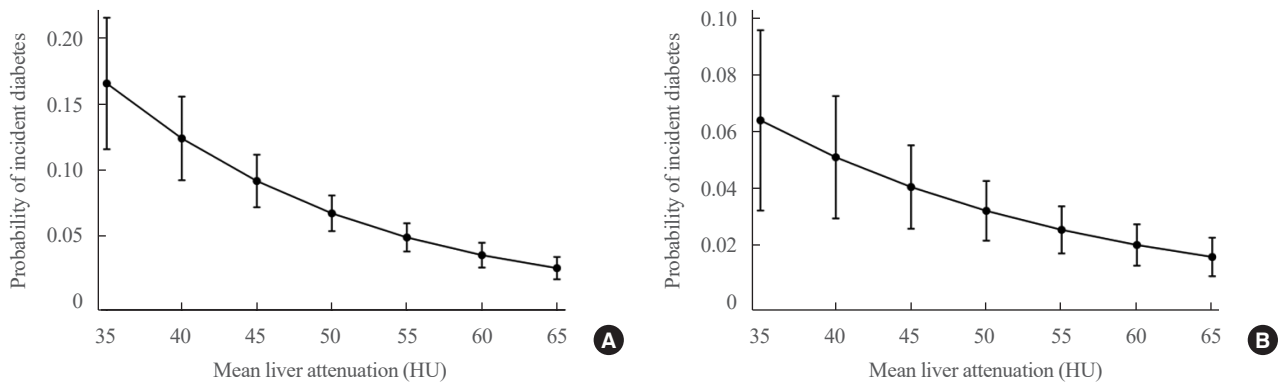


Fig. 2. Probability of incident diabetes by the mean liver attenuation on unenhanced computed tomography. (A) Unadjusted. (B) Adjusted for age, sex, body mass index, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, alcohol consumption, presence of hepatitis B surface antigen, and hepatitis C virus antibody. HU, Hounsfield unit.

group had a HR of 3.24 (95% confidence interval [CI], 1.64 to 6.42) for the development of diabetes, and those in the mild steatosis group had a HR of 2.33 (95% CI, 1.42 to 3.80) when compared with participants without hepatic steatosis. One standard deviation (SD) decrease in mean CT attenuation values of the liver was associated with a 40% increase in the development of diabetes (multivariate adjusted HR per SD decrement, 1.40; 95% CI, 1.2 to 1.63). The probability of incident diabetes increased with decreasing mean CT liver attenuation (Fig. 2).

DISCUSSION

In this asymptomatic cohort, we found that 43.0% of 1,798 Korean adults were affected by hepatic steatosis, and 5.8% (104 individuals) had moderate or greater hepatic steatosis. The risk of incident diabetes increased among individuals with hepatic steatosis, and most importantly, greater severity of steatosis was associated with a higher risk of incident diabetes.

In the present study, we used a liver attenuation value of 57 HU measured by unenhanced CT as a threshold indicative of at least mild hepatic steatosis [14], and the prevalence of hepatic steatosis was 43.0%. This value exceeds the global prevalence of NAFLD based on ultrasound, which has previously been reported to be between 20% and 35% of the adult population [19]. However, direct comparison is difficult, given the different sensitivities of CT and ultrasound in identifying steatosis [20]. Moreover, the prevalence of fatty liver depended on the specific diagnostic CT attenuation criteria, and these criteria also varied in their sensitivity for detecting mild hepatic steatosis [21]. Therefore, for other CT attenuation criteria that include milder severity of steatosis [21], using a liver attenuation of \leq (spleen

attenuation+5 HU) and liver-to-spleen ratio of ≤ 1.1 lowered the prevalence to 30.1% and 29.3%, respectively. Meanwhile, in our study, the prevalence of moderate to severe steatosis was 5.8% when 40-HU threshold was applied. This was similar to the prevalence reported in other studies that used same criterion of 40-HU threshold [21,22], although the study population had different background characteristics. A liver attenuation value of ≤ 40 HU represents the most accurate criterion for moderate to severe disease [10,21].

We previously demonstrated that sustained presence of hepatic steatosis detected by ultrasound had an independent effect on incident diabetes [23]. The presence of fatty liver had a differential association with incident diabetes based on its duration. In the present study, fatty liver had a graded association with the risk of incident diabetes based on the severity of steatosis. The risk of incident diabetes increased with increasing severity of hepatic steatosis. Our results suggest that not only the persistence of fatty liver but also the severity of steatosis was independently associated with an increased risk of diabetes. Recently, hepatic steatosis has also been reported to have a quantitative association with liver fibrosis, showing higher probability of significant liver fibrosis with increasing severity of hepatic steatosis [24]. Evidence from liver biopsy cohort studies revealed that in patients with fatty liver disease, the risk of incident diabetes was higher when significant liver fibrosis was present [5]. Identifying the severity of hepatic steatosis could play a more important role in assessing the risk of developing diabetes than just detection of fatty liver.

Insulin resistance is not independent of hepatic steatosis and can be exacerbated by bidirectional communication through metabolic inflammation [25]. Intrahepatic fat leads to activation

of immune response represented by hepatic c-Jun N-terminal kinase and nuclear factor κ B signaling cascades [25,26]. Chronic metabolic inflammation induced by intrahepatic fat promotes skeletal muscle, adipose tissue, and pancreatic dysfunction through liver-derived inflammatory mediators, including cytokines, acute-phase protein, and hepatokines [25,27,28]. All of these contribute to the development of type 2 diabetes by causing hepatic and peripheral insulin resistance, leading to derangements in glucose and lipid metabolism [4,25]. Peripheral insulin resistance also exacerbates hepatic steatosis by increasing lipolysis of adipocytes and circulating free fatty acids [27]. These pathophysiological mechanisms helped to interpret our findings that hepatic steatosis is a preferential risk factor for the development of type 2 diabetes.

Greater severity of steatosis was reported to be associated with higher risk of significant fibrosis [24,29]. In our study, more severe hepatic steatosis was associated with an increased risk of developing diabetes. Individuals with clinically significant fibrosis, especially those with type 2 diabetes, have a greater risk of cirrhosis, cardiovascular disease, and all-cause mortality [30]. These findings suggest that patients with moderate to severe hepatic steatosis are at higher risk for hepatic and extra-hepatic outcomes. The goal of screening is not to identify steatosis itself, but rather to identify patients in these high-risk groups [30]. Unenhanced CT is highly specific for identifying patients with moderate to severe hepatic steatosis [16,21,31]. CT images provide an objective measurement of liver fat content, and this noninvasive imaging modality has been increasingly used for the evaluation of fatty liver disease in many studies over the past two decades [16]. In our study, we used an abdominal CT to quantify the severity of hepatic steatosis.

Our study has several strengths and limitations. We categorized all the participants into three groups (non-steatosis, mild, and moderate to severe steatosis groups) using the baseline liver attenuation value on non-contrast CT images. Although it is a very accurate test for detecting moderate to severe hepatic steatosis, unenhanced CT is less accurate in the assessment of mild steatosis [16,21]. We did not exclude participants with significant alcohol consumption or positive serologic markers for hepatitis B or C infection. Excessive alcohol consumption and chronic infection with viral hepatitis can cause hepatic steatosis [32]. Given the definition of NAFLD [13], this may be a limitation of our study. However, we do not believe that this biased our results because we found similar results even after adjusting for alcohol consumption and the presence of viral hepatitis B or C infection. Recently, a new nomenclature, metabolic-associat-

ed fatty liver disease, was proposed to replace the term NAFLD, thereby highlighting the association between fatty liver disease and metabolic dysregulation, regardless of alcohol consumption or the presence of other liver diseases [33]. We did not consider physical activity and dietary data in our analysis, which might affect the results. Lastly, the lack of 2-hour post-load glucose tests might have underestimated the incidence of diabetes. This study is significant in that it uses longitudinal data to verify the association between the severity of hepatic steatosis and incident diabetes. Although observational studies do not allow for proving of causality, longitudinal studies better establish the correct sequence of events, identify changes over time, and provide insight into cause-and-effect relationships.

In conclusion, we found a positive association between the severity of hepatic steatosis and risk of incident diabetes. Greater severity of steatosis was associated with a higher risk of incident diabetes. Our findings suggest that quantitative measurement of hepatic steatosis is clinically important for assessing the risk of developing diabetes in patients with fatty liver.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.M.H., J.C.B. Acquisition, analysis, or interpretation of data: J.H.C., H.I.K., S.S., Y.J.L., J.W.L., K.M.K., J.C.B. Drafting the work or revising: J.M.H., J.H.C., J.C.B. Final approval of the manuscript: J.C.B.

ORCID

Ji Min Han <https://orcid.org/0000-0002-7881-9732>

Jung Hwan Cho <https://orcid.org/0000-0001-8578-2117>

Ji Cheol Bae <https://orcid.org/0000-0002-4763-5797>

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