# Visceral Fat Thickness Predicts Fatty Liver in Koreans with Type 2 Diabetes Mellitus

Our aim was to study whether visceral adiposity is a predictor of diabetic fatty liver in Korean type 2 diabetes mellitus. In this study, abdominal ultrasonography was used to assess the presence of fatty liver in 1,898 patients with type 2 diabetes. We measured visceral fat thickness by high-resolutional ultrasonography and insulin resistance by Kitt. Half of the cohort had a fatty liver (50.2%). High visceral fat thickness had the highest odds ratio for developing fatty liver in both sexes (odds ratio [S.D]: 3.14 [2.24-4.69], $p<0.00$ in male, 2.84 [2.04-3.93], $p<0.00$ in female). In addition, visceral fat thickness of 42.45 and 37.7 mm in men and women, respectively, were chosen as the discriminating value to predict the presence of fatty liver with a sensitivity of 71% and 73% and a specificity of 70% and 70% in men and women, respectively. The area under the receiver-operating characteristics curve was 0.759 in men and 0.764 in women. Therefore we could conclude that the degree of visceral adiposity predicts the presence of fatty liver type 2 diabetes mellitus, whether centrally obese or not, suggesting that hepatic fat accumulation in a diabetic fatty liver may be influenced by visceral fat accumulation regardless of waist circumference.

Key Words : *Visceral Fat Thickness; Fatty Liver; Type 2 Diabetes Mellitus*

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## INTRODUCTION

In Korea, as in western countries, the current number of people with obesity is the highest ever recorded (1). As a result, the escalating health risks due to obesity are not only a great problem in the western world, but also in the Korean society (1). Many studies have demonstrated that obesity is a strong risk factor for fatty liver (2, 3). However, the use of the term obesity is too broad. While overall obesity is clearly associated with fatty liver, body fat distribution appears to play a more important role in the pathogenesis of fatty liver. In particular, central obesity may be a key determinant in the pathogenesis of fatty liver, via both a strong association with insulin resistance and possibly as a source of free fatty acids (4) and has also been positively correlated with liver fat (5, 6) and hepatic insulin resistance in both men and women (7). Furthermore, in central obesity, especially accumulation of visceral fat is a more important risk factor for metabolic syndrome than subcutaneous fat, owing to its steatogenesis and the production of various cytokines (8, 9). Other studies have indicated that serum triglycerides, free fatty acid, leptin,

and tumor necrosis factor (TNF)-$\alpha$ from adipocytes in the visceral fat participate in the development of metabolic syndrome, including insulin resistance (10, 11). However, few studies have suggested a relationship between fatty liver and severity of visceral fat accumulation, especially in type 2 diabetic patients in Asia. From these results, we can conclude that accumulation of visceral fat may play a significant role in the severity of fatty liver disease. The aim of the present study was, therefore, to evaluate whether visceral adiposity is a predictor of diabetic fatty liver in Korean type 2 diabetes mellitus.

## MATERIALS AND METHODS

### Subjects

From January 2003 to June 2006, 4,793 patients were evaluated for type 2 diabetes at the Huh clinic. The exclusion criteria were as the follows: 1) alcohol intake of 140 g/week or more, 2) a positive serologic finding for hepatitis B or C virus,

3) the presence of auto-antibodies indicative of autoimmune hepatitis, 4) a history of another known liver disease, 5) malignancy, and 6) a medication history of insulin, corticosteroids, estrogens, methotrexate, tetracycline hydrochloride, amiodarone or tamoxifen citrate, or antiobesity drugs in the previous 6 months.

Finally, 1,898 patients with type 2 diabetes mellitus were enrolled in the study. The study protocol was approved by the Yonsei Medical University College of Medicine ethnical committee, and informed consent was obtained from each participant. All participants were interviewed to obtain their history of hypertension, myocardial infarction, cerebrovascular accident, and previous medication including insulin and alcohol consumption. The differentiation of each oral hypoglycemic agents was not carried out and the levels of diet and physical activity were not evaluated in this study. Their height, weight, waist and hip ratio, waist circumference were measured to the nearest half-centimeter or half-kilogram. The waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest and the hip circumference at the maximal protrusion of the greater trochanter.

The laboratory evaluation included the fasting blood glucose, fasting serum insulin, fasting c-peptide, HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The low-density lipoprotein cholesterol (LDL-C) was calculated using the equation by Friedewald et al. (12). The short insulin tolerance test was performed between 8 AM and 9 AM after an overnight fast. The patients were instructed not to take their morning insulin. An arterialized superficial hand vein was used for blood sampling and for insulin injection. The patients rested in the supine position for at least 30 min before the test. The test was then started with an intravenous bolus dose (0.1 U/kg) of ultra-rapid human insulin. Blood samples for blood glucose determination were taken before and then 6 and 15 min after administration of the insulin, with close observation of hypoglycemic events. Linear regression was used to estimate the slope of decline in log transformed blood glucose concentration. Blood glucose values from 4 to 16 min were used for the analysis. Kitt was calculated from the formula $69.3/t_{1/2}$ (13, 14). The blood pressure was measured using a standard mercury sphygmomanometer after the subject had been seated for at least 10 min. The percentage of whole blood fat was measured by means of the bioelectrical impedance analysis method (Inbody 2.0, Biospace Co. Ltd. Seoul, Korea). The diagnosis of fatty liver was based on the results of abdominal ultrasonography which was done by a well trained technician. All ultrasonographic images were stored in the image server. One gastroenterologist reviewed the images and made the diagnosis of fatty liver without reference to any of the participants' other individual data for the 4 known criteria (hepato-renal echo contrast, liver brightness, deep attenua-

tion, and vascular blurring). The participants were required to have a diagnosis of nonalcoholic fatty liver. Another ultrasonography was performed to measure visceral fat thickness using a high-resolution ultrasonographic system (SA 9900; Medison, Seoul, Korea) as described by Suzuki et al., Armellini et al., and Kim et al. (15-17). The subjects were examined in the supine position and all frozen images were collected immediately after inspiration to avoid the effect of respiration. Visceral fat thickness was defined as the distance between the anterior wall of the aorta and the internal face of the rectoabdominal muscle perpendicular to the aorta. Transverse scanning was performed by using a 3.5 MHz probe to measure visceral fat thickness at 1 cm above the umbilicus.

### Definition of metabolic variables

To define risk factors for fatty liver in both sexes, we determined the odds ratio of developing fatty liver in type 2 diabetic patients with high visceral fat thickness, hypertriglyceridemia, low HDL-C, obesity, central obesity, insulin resistance, and fasting hyperglycemia compared to patients without these conditions. Men and women with waist circumference values of 90 and 80 cm or more, respectively, were considered to have central obesity and obesity was defined as a BMI of 25 kg/m$^2$ or more, according to the World Health Organization perspective on the western pacific region for Asians (18). The presence of insulin resistance was defined as a kitt of 2.5%/min or less. Hypertriglyceridemia and low HDL-C level were defined according to the Adult treatment Panel III of the National Cholesterol Education Program guidelines (Triglyceride level >1.7 mM/L HDL-C level <1.0 mM/L in men or 1.3 mM/L in women) (19). A high visceral fat thickness was defined according to Kim et al. (VFT >47.6 mm in men or >35.5 mm in women) (17).

### Statistical analysis

Statistical analyses were performed using SPSS software (Version 11.5; SPSS Inc, Chicago, IL, U.S.A.) and were carried out separately in men and women because of the difference in basal clinical characteristics between two sexes. The intergoup comparisons were performed using an independent t-test. Logistic regression, which had been adjusted for age, was used to evaluate risk factors of fatty liver in male and female type 2 diabetes mellitus patients. To assess the cutoff point of visceral fat thickness for fatty liver, a receiver-operating characteristics (ROC) curve was performed to determine the sensitivity and specificity using visceral fat thickness as a predictor of fatty liver. A $p<0.05$ was considered significant.

## RESULTS

The prevalence of fatty liver was 50.2% in all the subjects

and slightly higher in males. The characteristics of the subjects according to sex are shown in Table 1. In males, there were significant differences between the subjects with and without fatty liver in terms of age, weight, BMI, waist circumference, waist hip ratio, percentage of body fat, blood pressure, serum insulin, c-peptide, Kitt, total cholesterol, HDL-C, triglyceride, AST, ALT, and visceral fat thickness. In females, a comparison between subjects with and without fatty liver showed a tendency similar to that in the male group except that serum insulin showed no difference and HbA1c and LDL-C were higher in fatty liver subjects (Table 1). According to multiple logistic regression analysis, high visceral fat thickness,

hypertriglyceridemia, central obesity, insulin resistance, and low HDL-C were independently associated with fatty liver in male type 2 diabetes patients, whereas in female patients, high visceral fat thickness, central obesity, insulin resistance, and hypertriglyceridemia were associated with fatty liver (Table 2). The odds ratio of high visceral fat thickness for fatty liver showed the highest values as 3.14 (CI: 2.24-4.39) and 2.84 (CI: 2.04-3.93) in males and females, respectively (Table 2).

As shown in Fig. 1, the area under the ROC curve for VFT as a predictor of the presence of fatty liver was 0.759 (95% CI: 0.734-0.794; $p<0.001$) in the men and 0.764 (95% CI:

Table 1. Patient characteristics according to sex

| N=1,898 | Male (n=944) | | | Female (n=954) | | |
|---|---|---|---|---|---|---|
| | Non fatty liver (n=452) | Fatty liver (n=492) | p | Non fatty liver (n=493) | Fatty liver (n=461) | p |
| Age (yr) | 55.4±11.2 | 53.7±10.6 | 0.01 | 56.8±10.2 | 58.3±9.3 | 0.02 |
| Height (cm) | 168.7±5.8 | 169.4±6.1 | 0.06 | 155.9±5.4 | 156.3±5.5 | 0.26 |
| Weight (kg) | 65.2±11.1 | 73.8±13.7 | 0.00 | 54.9±8.7 | 63.3±10.4 | 0.00 |
| BMI (kg/m²) | 22.8±4.4 | 25.6±4.6 | 0.00 | 22.7±3.6 | 25.6±4.3 | 0.00 |
| Waist circumference (cm) | 80.6±12.4 | 88.4±11.9 | 0.00 | 75.0±10.8 | 83.9±8.5 | 0.00 |
| Visceral fat thickness (mm) | 39.9±15.8 | 56.18±17.2 | 0.00 | 33.3±17.2 | 48.3±16.7 | 0.00 |
| % of body fat (%) | 20.6±5.4 | 24.9±5.4 | 0.00 | 28.7±5.8 | 33.4±6.1 | 0.00 |
| Systolic blood pressure (mmHg) | 132.8±20.7 | 135.7±17.5 | 0.01 | 134.9±20.7 | 142.0±18.9 | 0.00 |
| Diastolic blood pressure (mmHg) | 87.1±12.8 | 90.6±11.2 | 0.00 | 84.5±10.9 | 88.3±10.1 | 0.00 |
| S-insulin (pM/L) | 55.9±1.06 | 89.6±274.8 | 0.01 | 89.6±276.2 | 124.1±445.6 | 0.15 |
| C-peptide ($\mu$g/L) | 1.7±1.0 | 2.3±0.9 | 0.00 | 1.5±0.8 | 2.2±1.0 | 0.00 |
| Fasting blood glucose (mM/L) | 7.51±3.49 | 7.48±2.72 | 0.87 | 7.44±3.4 | 7.46±2.62 | 0.91 |
| HbA1c (%) | 8.1±2.4 | 8.2±1.8 | 0.43 | 8.0±2.0 | 8.3±1.7 | 0.03 |
| Kitt (%/min) | 2.2±1.0 | 1.8±0.9 | 0.00 | 2.2±0.9 | 1.7±0.8 | 0.00 |
| Total cholesterol (mM/L) | 4.65±1.14 | 4.97±1.10 | 0.00 | 4.99±1.16 | 5.26±1.1 | 0.00 |
| HDL-C (mM/L) | 1.31±0.39 | 1.16±0.31 | 0.00 | 1.32±0.46 | 1.33±0.35 | 0.00 |
| Triglyceride (mM/L) | 1.4±1.17 | 2.13±1.58 | 0.00 | 1.39±0.75 | 1.91±1.02 | 0.00 |
| LDL-C (mM/L) | 2.68±0.89 | 2.74±1.04 | 0.30 | 2.84±0.93 | 3.01±1.00 | 0.00 |
| AST (ukat/L) | 0.43±0.17 | 0.55±0.33 | 0.00 | 0.43±0.18 | 0.55±0.31 | 0.00 |
| ALT (ukat/L) | 0.41±0.22 | 0.62±0.47 | 0.00 | 0.38±0.25 | 0.52±0.30 | 0.00 |

Data are expressed as mean±SD.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density liporotein cholesterol.

Table 2. Odds ratio of the fatty liver in type 2 diabetes male and female subjects

| Disorder | Male group | | Female group | |
|---|---|---|---|---|
| | OR (95%CI) | p | OR (95%CI) | p |
| High VFT | 3.14 (2.24-4.39)* | 0.00 | 2.84 (2.04-3.93)* | 0.00 |
| Hypertriglyceridemia | 2.40 (1.73-3.32)* | 0.00 | 1.71 (1.22-2.40)* | 0.00 |
| Low HDL-C level | 1.48 (1.05-3.29)* | 0.02 | 1.05 (0.76-1.47) | 0.75 |
| Obesity | 1.64 (1.13-2.38)* | 0.01 | 2.16 (1.47-3.18)* | 0.00 |
| Central obesity | 1.96 (1.28-2.98)* | 0.00 | 2.23 (1.51-3.29)* | 0.00 |
| Insulin resistance | 1.60 (1.13-2.26)* | 0.00 | 1.73 (1.21-2.50)* | 0.00 |
| Fasting hyperglycemia | 1.18 (0.76-1.84) | 0.47 | 0.96 (0.625-1.48) | 0.86 |
| High HbA1c | 1.03 (0.71-1.49) | 0.86 | 1.45 (0.99-2.13) | 0.06 |
| Age | 0.98 (0.97-1.19) | 0.12 | 0.99 (0.98-1.01) | 0.79 |

Data are expressed as odds ratios (95% confidence intervals). Significant values appear in bold type. * $p<0.05$.
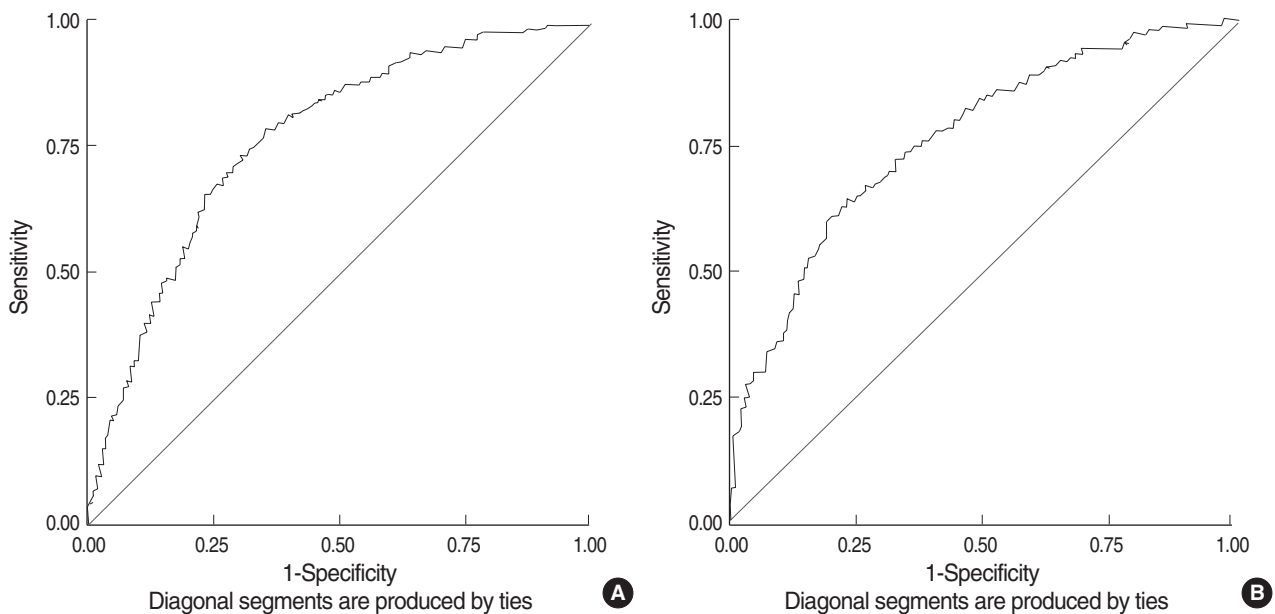VFT, visceral fat thick; HDL-C, high-density lipoprotein cholesterol.

**Fig. 1.** Receiver-operating characteristic (ROC) analysis of visceral fat thickness as a predictor of the presence of fatty liver in men (**A**) and women (**B**). Visceral fat thickness of 42.4 and 37.7 mm in men and women, respectively, were chosen as the discriminating value to predict the presence of fatty liver with a sensitivity of 71% and 73% and a specificity of 70% and 70% in men and women, respectively. The area under the ROC curve (AUC) was 0.759 in men and 0.764 in women.

0.728-0.789) in the women. A VFT of 42.45 mm and 37.7 mm in men and women, respectively, was found to be the discriminating cutoff point for fatty liver with sensitivity of 71% and 73% and a specificity of 70% and 70% in men and women, respectively.

## DISCUSSION

This study shows a high prevalence of fatty liver in Korean type 2 diabetes patients, and this is the first large study to show the important role of visceral fat thickness for the development of fatty liver in Korean type 2 diabetes patients. Also, this is the first large study to determine the cutoff point of visceral fat thickness for fatty liver in type 2 diabetes patients.

The prevalence of fatty liver varies from 10 to 20% in the general population (20) and increases to 50-75% in subjects with type 2 diabetes mellitus (21). We have estimated that approximately 50.2% of patients had a fatty liver in our study. This result is similar to the findings from other studies (22, 23).

Our study confirmed the previous finding that Asian patients with fatty liver have metabolic disorders that are similar to those of their western counterparts (24). Patients with fatty liver showed a higher prevalence of metabolic components such as obesity, hypertension, and dyslipidemia with a high rate of insulin resistance in our study. South Asian people including South Koreans are reported to be more centrally obese for the same degree of weight gain when compared to East Asian people, but the former are more insulin resistant (25). This is also true for cases of non-alcoholic steatohepatitis

(NASH) in seemingly lean (but actually centrally obese) South Asians. Among Pacific Islanders, the converse appears to hold true; when compared to Caucasians, insulin resistance is lower for any given body mass index. These data refer to the general population, but since our data were derived mainly from type 2 diabetes patients, the results are somewhat different. Compared to cases of fatty liver in the general population from South Asia, fatty liver patients with type 2 diabetes mellitus had a higher rate of obesity, insulin resistance, and a central obesity of 44.9% and 68.1% in females and males, respectively. This suggests that South Asians with type 2 diabetes mellitus do not follow the general rule of being lean but centrally obese (26); however, they do show characteristics similar to those of western people with a fatty liver.

According to previous studies on Asian people, fatty liver is more prominent in men (24, 26, 27). However, in our study, the male-to-female ratio was almost equivalent. This might also represent the difference between the prevalence of fatty liver in the general population and that in type 2 diabetes mellitus patients. Conclusively, when South Asian patients have a fatty liver and type 2 diabetes mellitus, they show the same trends as western people.

Patients with a fatty liver showed an increased visceral fat thickness over those without fatty liver, independently of waist circumference. In contrast to male patients with a fatty liver who were not centrally obese, female patients with a fatty liver had an increased waist circumference, exceeding 80 cm, the range for central obesity. This means that regardless of waist circumference, fatty liver patients always have visceral fat thickness. The different result in male and female group might be

due to the different actions of the sex hormones such as testosterone and estrogen. It appears that the effects of sex steroids on visceral fat deposition vary in men and women, perhaps owing to the effects of progestins (28). The biochemical or molecular basis for the regional differences in sex steroid effects on adipose metabolism is not well elucidated. However, estrogen appears to produce a greater stimulation of preadipocyte proliferation in subcutaneous than in omental fat (29, 30), but testosterone decreases subcutaneous fat and increases visceral fat (28, 31). This suggests that no matter whether patients are centrally obese or not, they might have a high amount of visceral fat, and this can be a major risk factor for fatty liver in male type 2 diabetes patients.

In terms of lipid profiles, the presence of fatty livers was associated with elevated total cholesterol, triglyceride, and reduced serum HDL-C in both sexes, but there was no consistent correlation with LDL-C levels in either sex. This might be explained by diabetic dyslipidemia and its role in atherogenesis, which would affect the LDL particle size rather than the LDL-C level. Levels of fasting blood glucose and HbA1c were increased in patients with fatty liver but not significantly. In type 1 diabetes, hepatic steatosis is related to inadequate serum levels of insulin and hence to poor diabetic control. In type 2 diabetes, however, it is primarily related to concurrent obesity rather than the duration of diabetes or the adequacy of control (21). Our study was mainly conducted in type 2 diabetes patients, and this is why our data showed no significant difference in FBG and HbA1c levels between the patients with and without fatty liver. Patients with hepatic steatosis usually have elevated transaminase levels (32), and our data were consistent with this finding. This can explain the elevated c-peptide and s-insulin levels in both male and female patients with fatty liver.

The relationship between obesity and fatty liver is well known (2, 3). However, it has been proposed that the waist circumference, which reflects central obesity, is more related to fatty liver than BMI is (33, 34). In multiple regression analysis, adjusted for age, insulin resistance, and dyslipidemia, the visceral fat thickness of all metabolic indices showed the strongest predictive value for fatty liver (OR, 3.14 [CI: 2.24-4.39] and 2.84 [CI: 2.24-4.39] in males and females, respectively). This study indicates that fatty liver is implicated, in centrally non-obese male subjects with a waist circumference <90 cm but with high visceral fat accumulation. Previous studies on the relationship between visceral fat accumulation and fatty liver exist, but only a few included type 2 diabetes patients (22, 35).

In addition, this study suggested that a VFT of 42.5 mm and 37.7 mm in men and women, respectively, was a cutoff for predicting the presence of fatty liver with a high specificity and sensitivity in patients with type 2 diabetes mellitus. Therefore, the ultrasonographic measurement of VFT might be a good and noninvasive method for predicting the presence of fatty liver in type 2 diabetes patients.

Our study was limited by the fact that ultrasonography cannot distinguish simple fatty liver from steatohepatitis, which can only be detected by a liver biopsy. Further studies are required to assess the relationship between the pathological evaluation for the grading of a fatty liver and steatoheaptitis and visceral fat accumulation. In addition, ultrasonography is not a method normally used to quantify the amount of fat, but may be used as an alternative method of assessing visceral adiposity. According to Kim et al. (17), the intraobservational reproducibility of the ultrasonographic estimation was 1.5-2.0% for the visceral fat thickness and the reproducibility between the 2 operators was 1.8-2.8%. So we should keep in mind that ultrasonography has such limitations in measuring visceral fat thickness.

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