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Original Article

The influence of waist circumference on insulin resistance and nonalcoholic fatty liver disease in apparently healthy Korean adults

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Background/Aims: Waist circumference (WC) is a risk factor for metabolic syndrome and is related to insulin resistance (IR) and nonalcoholic fatty liver disease (NAFLD). The purpose of this study was to determine the association between WC and IR and NAFLD in apparently healthy Korean adults.

Methods: The volunteers included in this cross-sectional study comprised 9,159 adults (5,052 men, 4,107 women) who participated in a comprehensive health checkup program. IR was evaluated by the homeostasis model assessment of IR (HOMA-IR) and was considered to be present when the HOMA-IR score was >2. NAFLD was evaluated by ultrasound examination. Elevated alanine aminotransferase (ALT) was defined as >40 IU/L in men and >35 IU/L in women. Logistic regression was performed to determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) for NAFLD, IR, and ALT according to categorized levels of WC.

Results: NAFLD was found in 2,553 (27.9%) of the participants (82.6% men, 17.4% women), while IR and elevated ALT were found in 17.2% (68.1% men, 31.9% women) and 10% (83% men, 17% women), respectively. After adjusting for confounding factors, the prevalence of NAFLD, IR, and elevated ALT was significantly associated with increases in WC quartile: highest quartile for NAFLD in men, OR=15.539, 95% CI=12.687-19.033; highest quartile for NAFLD in women, OR=48.732, 95% CI=23.918-99.288 (P<0.001); and highest quartile for IR in men, OR=17.576, 95% CI=13.283-23.255; highest quartile for IR in women, OR=11.078, 95% CI=7.813-15.708 (P<0.001); highest quartile for elevated ALT in men, OR=7.952, 95% CI=6.046-10.459; and highest quartile for elevated ALT in women, OR=8.487, 95% CI=4.679-15.395 (P<0.001).

Conclusions: WC contributes to IR and NAFLD in apparently healthy Korean adults, and thus may be an important factor in the development of IR and NAFLD. **(Clin Mol Hepatol 2013;19:140-147)**

Keywords: Waist circumference; Insulin resistance; Nonalcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the most commonly encountered chronic liver disease, encompasses a wide spectrum of liver damage, ranging from simple steatosis to nonalcoholic steatohepatitis, advanced fibrosis, and hepatic cancer.[1-3] The incidence of NAFLD is increasing worldwide due largely to changes in lifestyle and increases in obesity and type 2 diabetes mellitus

Abbreviations:

ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; FBS, fasting plasm glucose; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; NAFLD, non alcoholic fatty liver disease; NASH, non alcoholic steatohepatitis; ORs. Odds ratio; WC, waist circumference

*All authors had access to the data and played a role in writing the manuscript. Deok Yun Ju and Young Gil Choe should be considered co-first authors.

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(T2DM).[4,5] NAFLD is associated with many factors, including obesity, T2DM, dyslipidemia, insulin resistance (IR), metabolic syndrome, and cardiovascular disease.[4,6-8] For this reason, NAFLD is regarded as a hepatic component of metabolic syndrome.[9] Waist circumference (WC) is one of the diagnostic criteria proposed by the National Cholesterol Education Program (NECP), and has been identified as a valuable predictor of cardiovascular risk. Recent studies have reported a relation on the risk of IR and NAFLD with increasing WC.[10-12] However, few studies have been performed on the risk of IR and NAFLD with increasing WC in South Korea. The purpose of this study was to examine the association between WC and IR and NAFLD in apparently healthy Korean adults.

MATERIALS AND METHODS

Participants

A cross sectional analysis was conducted among healthy Korean adults. Initial data was obtained from 27,033 participants in a healthy checkup program at Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea in 2009. We excluded participants with a history of alcohol consumption in excess of 20 g/day (n=2,294), chronic liver diseases such as serologic proven viral hepatitis B (n=1,087) and C (n=73), abnormal ultrasonographic findings of liver cirrhosis or malignancy, or past history of dyslipidemia or cardiovascular disease (n=195). We also excluded individuals with known DM, fasting plasma glucose (FBS) level ≥126 mg/dL or HbA1c ≥6.5% (n=784), metabolic syndrome according to the International Diabetes Federation definition (n=6,386), missing data (n=5,429), and smokers (n=6,870). After applying these exclusion criteria, 9,159 (5,052 men and 4,107 women) participants were eligible for this study.

Measurements

WC was measured with a flexible tape under fasting conditions, at the level of the umbilicus in a standing position. Height and body weight measurements were taken barefoot while light clothing with automated instruments (FA-94H, Fanics, Korea). Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Medical history and lifestyle factors such as alcohol consumption, smoking, and history of DM, dyslipidemia, or cardiovascular disease, were assessed in 2009 using a standard questionnaire. Blood samples were collected from the antecubital vein after overnight fasting. FBS, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Enzymatic colorimetric assay was used to measure TC and TG. The homogeneous enzymatic colorimetric test and a selective inhibition method were used to measure LDL-C and HDL-C, respectively. The fasting glucose level was measured by the hexokinase method and serum insulin concentration was measured using an immunoradiometric assay (INS-IRMA; Biosource, Nivelles, Belgium). The coefficients of variation were intra-assay 2.1-4.5% on fasting glucose and intra-assay 4.7-12.2% on serum insulin, respectively. As a marker of insulin resistance, the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR=(fasting insulin [μIU/mL]×fasting serum glucose [mmol/l]/22.5).[13] IR was considered to be present when the HOMA-IR score was >2. HBsAg and HBsAb were measured by chemiluminescent micro-particle immunoassay (Architect i2000SR; Abbott Laboratories, Abbott Park, IL, USA). HCV Ab was measured by polymerase chain reaction (COBAS Amplicor HCV assay; Roche, Basel, Switzerland). The immunoturbidimetric assay used a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) to measure the HbA1c level (reference value range of 4.4-6.4%). Abdominal ultrasonography (ASPEN; Acuson, PA, USA) with a 3.5 MHz probe was performed in all participants by one of three experienced radiologists, and fatty liver was diagnosed based on known standard criteria, including hepatorenal echo contrast, liver brightness, and vascular blurring.[14] The term NAFLD is used to describe a condition of fat accumulation in the liver in the absence of excessive alcohol consumption (less than 20 g per day) and any other specific causes of hepatic steatosis.[15] Non-alcoholic steatohepatitis (NASH) is defined as NAFLD that associated with a elevated ALT level.

Statistical analysis

Results are expressed as number of participants with percentage (%) or mean value with standard deviation. Comparisons of the NAFLD and non-NAFLD groups were performed with the t-test and Pearson's χ^2-test. We estimated the odds ratio (OR [95% CI]) for NAFLD development as a function of WC and BMI using a multivariate logistic regression model. SPSS version 20.0 (IBM Inc., Armonk, NY, USA) was used for all analyses. *P*-values less than

0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to identify the sensitivity and specificity of WC and BMI cut-off points for the detection of NAFLD and IR. Optimal cut-off points were selected at the point where sum of sensitivity and specificity were high.

RESULTS

Among the 9,159 participants, 2,553 (27.9% [82.6% men, 17.4% women]) had NAFLD, 1,576 (17.2% [68.1% men, 31.9% women]) had IR, and 915 (10% [83% men, 17% women]) had elevated ALT. Participants with NAFLD were older and significantly more obese (as assessed by WC and BMI) than were participants without NAFLD. WC, systolic blood pressure (BP), diastolic BP, ALT, insulin, FBS, HbA1c, HOMA-IR, TC, and LDL-C levels were significantly elevated in the NAFLD group. HDL-C levels were significantly lower in the NAFLD group (P<0.001) (Table 1).

Waist circumference and NAFLD

As the WC quartile increased, the risk for NAFLD increased, with ORs of 3.472, 6.619, 15.539 in men and 5.704, 12.549, 48.732 in women when compared with the lowest quartile. Also, as the BMI category increased, the risk for NAFLD increased, with ORs of 3.477, 7.917, 25.507 in men and 4.463, 11.911, 39.476 in women when compared with the lowest category (BMI<23.0). Increased WC and BMI is strongly associated with NAFLD (P<0.001) (Table 2).

Waist circumference and insulin resistance (HOMA-IR)

As WC quartile increased, the risk for IR increased, with ORs of 2.615, 6.058, 17.576 in men and 1.930, 3.412, 11.078 in women when compared with the lowest quartile. Also, as BMI category increased, the risk for IR increased, with ORs of 3.036, 7.298, 22.580 in men and 3.272, 6.297, 22.748 in women when compared with the lowest category (BMI<23.0). Increased WC and BMI is strongly associated with IR (P<0.001) (Table 3).

Waist circumference and elevated ALT

As WC quartile increased, the risk for elevated ALT increased, with ORs of 1.941, 3.348, 7.952 in men and 1.449, 2.357, 8.487 in women when compared with the lowest quartile. Also, as BMI

Table 1. Clinical characteristics of study participants according to the presence of NAFLD

Total (n=9,159)	Non-NAFLD (n=6,606)	NAFLD (n=2,553)	*P*-value
Age (yrs)*	41.64±4.88	42.49±5.13	<0.001
BMI (kg/m^2)*	22.38±2.53	25.63±2.61	<0.001
Waist circumference (cm)*	79.23±6.93	88.08±6.86	<0.001
Systolic BP (mmHg)*	113.18±11.85	118.89±11.86	<0.001
Diastolic BP (mmHg)*	72.63±9.14	77.20±9.23	<0.001
AST (IU/L)*	20.66±9.86	25.59±9.93	<0.001
ALT (IU/L)*	18.93±12.19	34.55±21.69	<0.001
Insulin (μIU/mL)*	4.83±2.49	7.94±4.29	<0.001
FBS (mg/dL)*	95.48±7.42	100.48±8.08	<0.001
HbAlc (%)*	5.60±0.27	5.69±0.29	<0.001
HOMA-IR*	1.15±0.63	1.99±1.15	<0.001
Total cholesterol (mg/dL)*	191.06±31.84	208.06±33.20	<0.001
HDL cholesterol (mg/dL)*	59.14±13.07	50.06±9.93	<0.001
LDL cholesterol (mg/dL)*	105.68±27.12	123.33±28.62	<0.001
Triglyceride (mg/dL)*	120.23±80.63	125.49±80.96	0.005

*Data are mean±standard deviation.
P-values are from *t*-tests.
BMI, body mass index; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbAlc, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

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Table 2. The risk of developing NAFLD according to WC and BMI category

	Men			Women		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
WC						
1st quartile	1			1		
2nd quartile	3.472	2.844-4.237	<0.001	5.704	2.671-12.183	<0.001
3rd quartile	6.619	5.434-8.064	<0.001	12.549	6.057-26.003	<0.001
4th quartile	15.539	12.687-19.033	<0.001	48.732	23.918-99.288	<0.001
BMI						
<23.0	1					
23.0-24.99	3.477	2.942-4.110	<0.001	4.463	3.380-5.894	<0.001
25.00-27.99	7.917	6.674-9.391	<0.001	11.911	8.930-15.888	<0.001
≥28	25.507	19.150-33.974	<0.001	39.476	26.638-58.502	<0.001

Note: adjusted for age.
WC in men: 1st quartile (≤80.2), 2nd quartile (80.3-84.6), 3rd quartile (84.7-89.1), 4th quartile (≥89.1).
WC in women: 1st quartile (≤73.1), 2nd quartile (73.2-77.1), 3rd quartile (77.2-82.0), 4th quartile (≥82.1).
NAFLD, nonalcoholic fatty liver disease; WC, waist circumference, BMI, body mass index.
Logistic regression analysis.

Table 3. The risk of developing IR according to WC and BMI category

	Men			Women		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
WC						
1st quartile	1			1		
2nd quartile	2.651	1.950-3.604	<0.001	1.930	1.298-2.870	<0.001
3rd quartile	6.058	4.539-8.085	<0.001	3.412	2.351-4.952	<0.001
4th quartile	17.576	13.283-23.255	<0.001	11.078	7.813-15.708	<0.001
BMI						
<23.0	1			1		
23.0-24.99	3.036	2.381-3.871	<0.001	3.272	2.562-4.179	<0.001
25.00-27.99	7.298	5.785-9.207	<0.001	6.297	4.798-8.266	<0.001
≥28	22.580	17.035-29.929	<0.001	22.748	15.647-33.071	<0.001

Note: adjusted for age.
WC in men: 1st quartile (≤80.2), 2nd quartile (80.3-84.6), 3rd quartile (84.7-89.1), 4th quartile (≥89.1).
WC in women: 1st quartile (≤73.1), 2nd quartile (73.2-77.1), 3rd quartile (77.2-82.0), 4th quartile (≥82.1).
NAFLD, nonalcoholic fatty liver disease; WC, waist circumference, BMI, body mass index; IR, insulin resistance.
Logistic regression analysis.

category increased, the risk for elevated ALT increased, with ORs of 2.038, 4.472, 11.181 in men and 2.565, 5.809, 17.528 in women when compared with the lowest category (BMI<23.0). Increased WC and BMI is strongly associated with elevated ALT (*P*<0.001) (Table 4).

Waist circumference and non-alcoholic steatohepatitis (NASH)

As WC quartile increased, the risk for NASH, with ORs of 3.630, 7.453, 18.060 in men and 2.059, 4.584, 34.057 in women when compared with the lowest quartile. Increased WC in men is strongly associated with NASH (*P*<0.001). Increased WC in wom-

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Table 4. The risk of elevated ALT levels according to WC and BMI category

	Men			Women		
	OR	95% CI	*P*	OR	95% CI	*P*-value
WC						
1st quartile	1			1		
2nd quartile	1.941	1.428-2.638	<0.001	1.449	0.706-2.977	0.312
3rd quartile	3.348	2.505-4.475	<0.001	2.357	1.213-4.581	0.011
4th quartile	7.952	6.646-10.459	<0.001	8.487	4.679-15.395	<0.001
BMI						
<23.0	1			1		
23.0-24.99	2.038	1.572-2.641	<0.001	2.565	1.642-4.006	<0.001
25.00-27.99	4.472	3.506-5.703	<0.001	5.809	3.737-9.030	<0.001
≥28	11.181	8.414-14.857	<0.001	17.528	10.847-28.324	<0.001

Note: adjusted for age.
WC in men: 1st quartile (≤80.2), 2nd quartile (80.3-84.6), 3rd quartile (84.7-89.1), 4th quartile (≥89.1).
WC in women: 1st quartile (≤73.1), 2nd quartile (73.2-77.1), 3rd quartile (77.2-82.0), 4th quartile (≥82.1).
NAFLD, nonalcoholic fatty liver disease; WC, waist circumference, BMI, body mass index; ALT, alanine aminotransferase.
Logistic regression analysis.

Table 5. The risk of developing NASH according to WC category

	Men			Women		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
WC						
1st quartile	1					
2nd quartile	3.630	2.289-5.756	<0.001	2.059	0.376-11.269	0.405
3rd quartile	7.453	7.453-11.545	<0.001	4.584	0.988-21.267	0.052
4th quartile	18.060	11.829-27.574	<0.001	34.057	8.311-139.559	<0.001

Note: adjusted for age.
WC in men: 1st quartile (≤80.2), 2nd quartile (80.3-84.6), 3rd quartile (84.7-89.1), 4th quartile (≥89.1).
WC in women: 1st quartile (≤73.1), 2nd quartile (73.2-77.1), 3rd quartile (77.2-82.0), 4th quartile (≥82.1).
NASH, non-alcoholic steatohepatitis; WC, waist circumference, BMI, body mass index.
Logistic regression analysis.

en has an association with developing NASH (Table 5).

DISCUSSION

We assessed the association between WC and BMI and IR and NAFLD in apparently healthy Koreans. In this study, 27.9% of healthy participants were affected by NAFLD. The previous study have shown the prevalence of NAFLD was 18.6% and BMI, diabetes mellitus, hypertriglyceridemia, ALT level were independently associated with the presence of NAFLD in Koreans.[16] NAFLD has become an important public health problem because of its high prevalence, potential progression to severe liver disease, and association with serious cardio-metabolic abnormalities, including T2DM, metabolic syndrome, and coronary heart disease.[8,17,18] Mortality is significantly increased among individuals with NAFLD compared with the general population of the same age and sex, and is predicted by the presence of impaired fasting glucose/diabetes, cirrhosis, and older age.[19] ALT seems an appropriate marker of fatty liver disease, and ALT enzyme activity and NAFLD are associated with cardiovascular risk. Treatment of NAFLD should be aimed at reducing hepatic fat content and the concomitant cardiovascular disease risk.[20] Obesity is the condition most often associated with NAFLD. Obesity is associated with a spectrum of liver

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Table 6. The AUC of BMI and WC in NAFLD and IR

	Men		Women	
	AUC	95% CI	AUC	95% CI
WC				
NAFLD	0.759	0.746-0.773	0.821	0.801-0.840
IR	0.771	0.756-0.787	0.737	0.713-0.761
BMI				
NAFLD	0.760	0.747-0.773	0.830	0.811-0.850
IR	0.763	0.747-0.778	0.740	0.715-0.765

ROC curve analysis.
Note: adjusted for age.
AUC, area under curve; NAFLD, nonalcoholic fatty liver disease; WC, waist circumference; BMI, body mass index; IR, insulin resistance.

abnormalities known as NAFLD that is characterized by an increase in intrahepatic triglyceride (IHTG) content (i.e., steatosis) with or without inflammation and fibrosis (i.e., steatohepatitis).[21] Abdominal obesity is strongly associated with cardiovascular disease risk, other diseases and mortality.[22,23] Central obesity seems to be an important risk factor for NAFLD, even in those with a normal BMI, and may be a key link with IR.[3,24] Central obesity is a correlate of visceral adiposity and is more closely linked to IR, the central event in NASH, than is generalized obesity.[25] In patients with NAFLD liver necro-inflammation, fibrosis increased significantly with visceral fat in a dose-dependent manner. Visceral fat remained an independent predictor of liver inflammation and fibrosis even when measures of IR, hepatic steatosis, adipokines, and age were considered.[26] WC is a convenient measure of abdominal obesity.[27] and has a simple predictable relationship with intra-abdominal fat volume or area, which is likely to relate to the prediction of health risks.[28] BMI and WC have been considered as predictors of NAFLD severity and as independent predictors of steatosis.[29,30] Measurement of WC may be a preliminary method for surveys of people at higher risk of lifestyle-related disorders in Japanese men, especially among those with moderate BMI.[31] Previous studies have shown an association between obesity and liver disease.[32-34] Other studies have reported WC increases in NAFLD.[8,12] The major finding of our study is that increased WC and BMI were associated with a significantly increased risk of IR and NAFLD. The area under the curve (AUC) of BMI and WC in NAFLD, were 0.760, 0.759 in men, 0.830, 0.821 in women. And in IR AUC of BMI and WC were 0.763, 0.771 in men, 0.740, 0.737 in women (Table 6). BMI and WC have a predictive value for NAFLD and IR, but the AUC are alike, WC has no superiority in comparison with BMI to predict NAFLD. Based on the best optimum sensitivity and specificity rates, the best cutoff point of WC and BMI in prediction for NAFLD were 84.945 cm and 24.465 kg/m^2 in men, 80.395 cm and 22.715 kg/m^2 in women. In prediction for IR were 85.980 cm and 24.495 kg/m^2 in men, 80.295 cm and 22.715 kg/m^2 in women. There are several limitations of this study. First, three radiologist performed ultrasonography. Even though all of three radiologist were very experienced, they could be affected by interobserver variation. Second, although we excluded subjects with diabetes and metabolic syndrome, the prevalence of NAFLD was high as compared with previous study.[15] It may be due to the missing data and probable selection bias because all participants were not receive the ultrasonography. Third, NAFLD and NASH were diagnosed by ultrasonography rather than liver biopsy pathology. Despite these limitations, the present study is a meaningful investigation of the relationship between WC and NAFLD in non-diabetic subjects independent of obesity and other metabolic components. In conclusion, WC and BMI contribute to IR and NAFLD in apparently healthy Koreans, and so these factors may be important in the development of IR and NAFLD. These observations reinforce the importance of using both BMI and WC in clinical practice, as they may be helpful in evaluating the risk of NAFLD and IR. Further studies on WC, IR, and NAFLD are required to confirm these findings.

Conflicts of Interest

The authors have no conflicts to disclose.

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