Gamma-glutamyltransferase, waist circumference, visceral fat and risk for prevalence of type 2 Diabetes

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Jong Koo Kim

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ABSTRACT

Background

Serum γ-glutamytransferase (GGT) and obesity have been regarded as risk factors for type 2 diabetes. Some observational studies have shown that the association of obesity with the risk of type 2 diabetes according to serum GGT is either weakened or strengthened. However, the evidence of the interaction between GGT and obesity on the risk of diabetes is insufficient, and the association between visceral adiposity and diabetes according to serum GGT has not been examined.

Purpose

We examined the association between various parameters of obesity and the risk of prevalence of diabetes in accordance with serum GGT and analyzed the interaction between visceral adiposity and GGT on the risk of prevalence of diabetes in cross-sectional study..

Methods

There were 2,948 participants, aged 40 to 70 years from Korean Rural Genomic Cohort (KRGC). The participants received at least one medical examination and completed a questionnaire during 2005-2006. We examined the risk of prevalence of diabetes according to quartiles of waist circumference (WC), visceral fat area (VFA) and serum GGT, respectively. We determined the combined effect of variables and the interaction between WC or VFA and GGT on the risk of diabetes.

Results

Adjusted odds ratios (ORs) for prevalence of diabetes showed an increased response to successive quartiles of WC, VFA, and GGT. Area under the curves for WC, VFA and GGT associated with prevalence of diabetes were similar, respectively. Adjusted ORs for the strata defined by pairs of variables were increased (ORs = 2.01, 2.68, 3.88 for GGT and VFA; ORs = 2.24, 2.82, 4.17 for GGT and WC). The risk of WC or VFA on prevalence of diabetes was not associated within the lower quartiles of GGT. However, risk of prevalence of diabetes was increased according to quartiles of GGT in all categories of WC or VFA. The interaction between WC or VFA and GGT on the risk of prevalence of diabetes was not statistically significant (p value=0.22 and 0.34).

Conclusion

Our findings revealed a combined effect of WC or VFA and serum GGT on the risk of prevalence of diabetes. These results indicate that serum GGT may be a more influential factor than abdominal obesity or visceral fat on the risk of prevalence of diabetes.

INTRODUCTION

Traditionally, serum γ-glutamytransferase (GGT) has been regarded as a biomarker of alcohol consumption or liver disease (Brenner et al, 1997). However, different epidemiological studies have shown an association between serum GGT activity and many cardiovascular risk factors or metabolic components, even when serum GGT level is within the reference range (Nilssen et al, 1990; Brenneret al, 1997). In addition, prospective observational studies have shown that serum GGT activity predicts development of cardiovascular disease (CVD) (Wannamethee et al, 1995; Ruttmann et al, 2005), hypertension (Miura et al, 1998; Lee et al, 2003), stroke (Jousilahti et al, 2000), and type 2 diabetes (Perry et al, 1998; Lee et al, 2003; Lee et al, 2004).

Although serum GGT is used as a biomarker for hepatic damage, cellular GGT is a membrane binding enzyme responsible for the extracelluar catabolism of glutathione to synthesize intracellular glutathione (Pompella et al, 2004). Thus, GGT plays an important role in antioxidant systems with the primary function of maintaining intracellular concentration of glutathione (Forman et al, 1997). GGT levels correlate positively with C-reactive protein (CRP), a marker of inflammation, and F2-isoprostanes, a marker of oxidative stress (Lee et al, 2003). GGT levels also correlate inversely with antioxidant levels, such as serum carotenoids and tocopherols (Lee et al, 2004).

Obesity is a common disorder in many industrialized countries (Conway et al, 2004). Obesity is thought to be an important risk factor for type 2 diabetes (Mensah et al, 2004). The obese population with abdominal obesity is more frequently associated with the development of CVD, hypertension, and diabetes compared to obese people with non-abdominal obesity.

Some prospective studies have shown that the association of obesity with risk of type 2 diabetes may be weak in people with low normal serum GGT (Lee et al, 2003; Lee et al, 2004). Recently, in a study designed to investigate the possible interaction between GGT and obesity on the risk of type 2 diabetes, the association between obesity and prevalence of diabetes became clear with increasing GGT. In this study, the authors suggested that obesity itself may not be a sufficient risk factor for type 2 diabetes (Lim et al, 2007). Despite of these findings, the evidence of the interaction between GGT and obesity in predicting type 2 diabetes is not sufficient. Moreover, in comparison with obesity, it is known that visceral

fat distribution is more strongly associated with a risk for diabetes, hypertension, and metabolic syndrome. However, the study concerning the association between visceral adiposity and type 2 diabetes according to serum GGT activity has not been performed.

Therefore, to identify the relation among serum GGT, abdominal obesity and type 2 diabetes and to examine the interaction between these factors, we investigated that the association of abdominal obesity with type 2 diabetes according to different GGT activities. We examined visceral fat area (VFA) to estimate visceral adiposity and to more accurately assess risk of abdominal obesity for diabetes. In addition, we also analyzed that the interaction between VFA and serum GGT on the risk of type 2 diabetes.

METHOD

Study Population

The Korean Rural Genomic Cohort (KRGC) is a prospective cohort that was designed to assess risk factors for mortality, morbidity, incidence of various chronic diseases such as diabetes mellitus, hypertension and cardiovascular disease. The KRGC study was also designed to ascertain genomic characteristics for metabolic syndrome, atherosclerosis and different cancers in Korean people.

The KRGC includes 10,111 Koreans and is composed of participants who were 40 to 70 year old healthy prople, living in 5 rural areas (Won-ju, Pyung-chang, Keum-san, Na-ju, and Kang-reung). The data were collected in 2005 and 2006. Of these geographical areas, we chose 5,178 participants from 2 areas (3,181 in Won-ju and 1,997 in Pyung-chang). The participants received at least one medical examination and completed a questionnaire during that period. The current analysis was limited to 3,241 participants whose body compositions were analyzed by bioelectrical impedance analysis (BIA). The 293 participants who had reported a history of any liver disease such as acute or chronic hepatitis, fatty liver and liver cirrhosis were excluded. Additionally, participants with missing data on any covariate information were also excluded from this study. Finally, 2,948 participants (1,168 men and 1,780 women) were included in the final analyses. (Figure 1.)

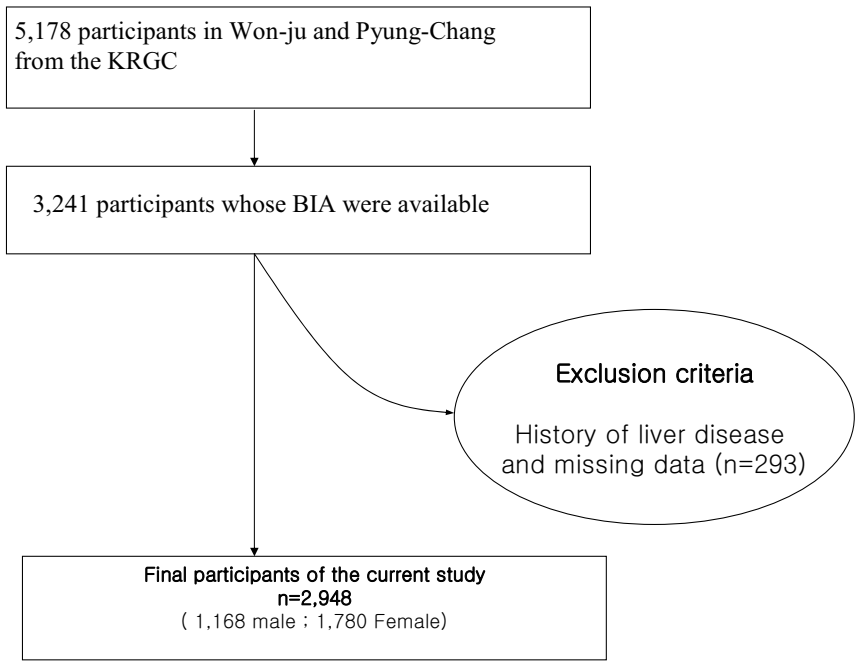


Figure 1. The selection procedure of the study population

Data Collection

The medical examinations were performed according to a standard procedure and conducted by trained medical staffs. Participants were questioned about their health behaviors including history of smoking, alcohol consumption, and exercise status. Participants were also asked if they were currently being treated for any diseases. If so, they were asked for the date of diagnosis and a list of medications being taken. The completed questionnaires were reviewed by a trained staff and then entered into a database. The data were also checked again during the analysis. Smoking history was categorized as "non-smoker", "ex-smoker" and "current smoker". Alcohol consumption was categorized as "non-drinker", "ex-drinker" and "current drinker". Exercise status was determined by a description of regular sweating. Body mass index (BMI, kg/m^2) was calculated as the ratio of weight (kilograms) divided by height squared ($meters^2$). Waist circumference (WC) was measured at the mid-point between the lower border of the rib cage and the iliac crest.

After a 12-h overnight fast, blood samples were taken from the antecubital vein of the participants. Various biochemical markers, including fasting plasma glucose, total cholesterol, triglyceride, high density lipoprotein (HDL) –cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT) (ADVIA 1650, Bayer, USA), and fasting insulin (Insulin RIA Kit, Biosource, Belgium) were measured. Diabetes was defined when a subject had a past history of the disorder, a medication history of diabetes or a fasting plasma glucose level $\geq$126mg/dL.

Medical data collection of the study was processed after obtaining consent from participants. The study was approved by Institutional Review Boards of Yonsei University Wonju College of Medicine.

VFA measurement

Bioelectrical impedance analysis is a widely used method for estimating body composition. This method is relatively simple, safe, noninvasive and convenient for the patient, and has been used in diverse settings, including private clinician's office, health promotion center, and hospital (NIH, 1996). Proper detector electrode placement is essential for accurate and reproducible BIA measurement. For this study,

the electrodes were positioned on both hands, just proximal to the metacarpal phalangeal joint line, and on both feet, without socks, just proximal to the metatarsal phalangeal joint line. Participants were in the standing position. Body composition such as body fat and VFA were analyzed automatically by BIA (Jeus 9.9, JAWON Medical, Korea). A preliminary study was done to assess validity and reliability of VFA measured by BIA. In that study of 50 people intra-abdominal VFA was measured using a CT scan at the level of the umbilicus (approximately the level of L4 and L5) in accordance with a method previously reported (Van der Kooy et al, 1993). The Hounsfield units of adipose tissue areas were in the range of -250 to -50. The results bshowed that correlation between VFA quantified by CT and VFA analyzed by BIA was comparable ($r=0.94$, p value <0.01).

Statistical Analysis

Chi-square test and one-way analysis of variance were used to analyze statistical differences among characteristics of the study participants according to GGT levels. Categorization of GGT levels into quartiles was based on the distribution of GGT levels among the study participants aged 40 to 70 years. Therefore, in the total population, GGT levels (IU/L) were categorized as follows: Q1 <13, Q2 13-18.9, Q3 19-32.9, and Q4 ≥33. According to gender, GGT levels were categorized as follows in men: Q1 <20, Q2 20-30.9, Q3 31-56.9, and Q4 ≥57, in women: Q1 <11, Q2 11-14.9, Q3 15-21.9, and Q4 ≥22.

Multiple logistic regression was performed to examine the association between WC, VFA, or serum GGT and prevalence of diabetes after adjusting for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol. Area under the curves of GGT, VFA and WC associated with an increase in the prevalence of diabetes were calculated using the receiver operating characteristics (ROC) curve. We used multiple logistic analysis to determine the interactive association between BMI, or WC and VFA as the variables for estimating abdominal obesity and visceral adiposity, and prevalent diabetes after adjusting for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.

All analyses were conducted using SAS statistical software, version 8.1 (SAS Institute Inc, Cary, NC). All statistical tests were two-sided, and statistical significance was determined at p value<0.05. (Figure

All statistical tests were two-sided, and statistical significance was determined at p value<0.05. (Figure 2.)

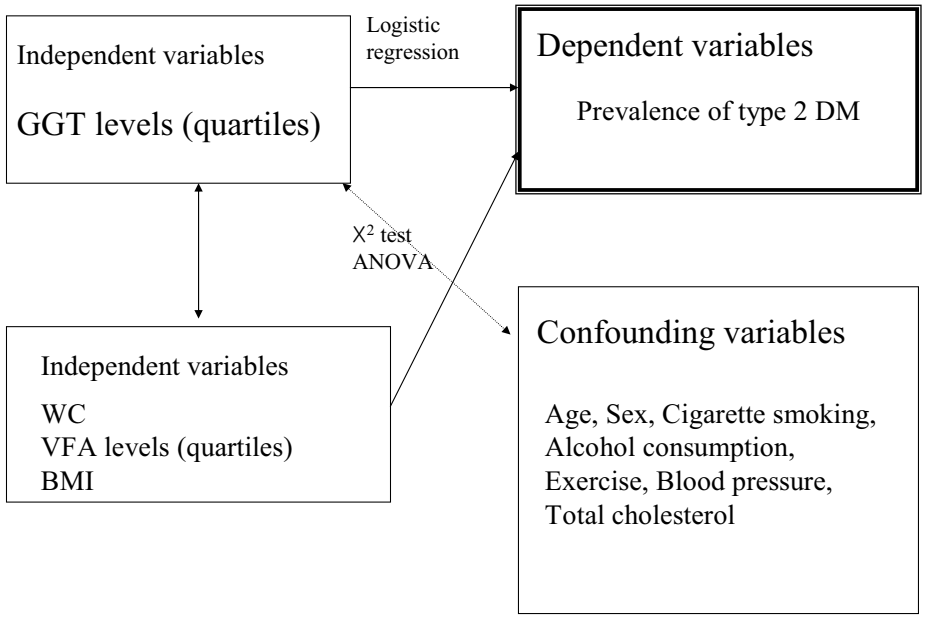


Figure 2. The framework of the study

RESULTS

The general characteristics of the study population according to quartiles of serum GGT for each gender are shown in Tables 1, 2 and 3. The mean BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, TG, AST, ALT, fasting plasma glucose, and VFA increased with higher serum GGT activity. Higher serum GGT activity for both genders was found according to the percentages as current smokers and current drinkers. The percentages of non-smoker and non-drinker had inverse relation with serum GGT inactivity inversely associated with serum GGT activity. Exercise status was not significantly associated with serum GGT activity.

Table 1. General characteristics of participants

Characteristics	Male (n=1168)	Female (n=1780)
Age (years)	56.5±8.3	54.1±8.4
Waist circumference (cm)	86.4±7.9	80.9±8.8
Body Mass Index (kg/㎡)	24.4±3.4	24.6±3.4
Cigarette smoking (n,%)		
Non smoker	396(33.9)	1737(97.7)
Ex smoker	319(27.3)	10(0.6)
Current smoker	452(38.7)	31(1.7)
Alcohol consumption (n,%)		
No drinker	297(25.4)	1345(75.8)
Ex drinker	82(7.0)	14(0.8)
Current drinker	789(67.6)	415(23.4)
Exercise (n,%)		
Yes	370(31.8)	553(31.2)
No	793(68.2)	1222(68.8)
Systolic Blood Pressure (mm/Hg)	131.8±17.3	128.4±17.7
Diastolic Blood Pressure (mm/Hg)	85.0±15.8	81.5±11.7
Total Cholesterol (mg/dL)	195.7±34.6	200.9±37.7
Triglyceride (mg/dL)	167.7±122.9	129.5±79.0
HDL-Cholesterol (mg/dL)	44.6±11.2	47.8±11.1
Fasting Plasma Glucose (mg/dL)	99.9±23.7	93.9±18.4
AST (IU/L)	30.2±16.6	24.5±8.7
ALT (IU/L)	28.3±17.0	21.2±11.8
GGT (IU/L)	55.6±93.5	20.4±25.6
VFA (㎠)	123.4±30.3	84.3±33.7

Abbreviations: HDL, High-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; VFA, visceral fat area.

*Data are expressed as mean±SD unless otherwise indicated.

Table 2. Characteristics of the study population according to GGT levels in men

	Quartiles of GGT level (IU/L)				*P* value for trend
	< 20 (n=280)	20.0-30.9 (n=288)	31.0-56.9 (n=302)	≥57 (n=298)	
Age(years)	57.7(8.3)	57.2(8.2)	56.3(7.8)	55.1(8.5)	0.000
Waist circumference (cm)	83.2(7.6)	85.8(7.9)	88.1(7.6)	88.1(7.3)	0.000
Body Mass Index (kg/㎡)	23.3(3.1)	24.5(4.2)	25.0(2.9)	24.7(3.0)	0.000
Cigarette smoking (%)					0.000†
Non smoker	31.6	29.3	21.2	17.9	
Ex smoker	19.1	26.6	26.6	27.6	
Current smoker	20.8	19.2	29.4	30.5	
Alcohol consumption (%)					0.000†
No drinker	45.5	28.3	18.2	8.1	
Ex drinker	31.7	24.4	28.0	15.9	
Current drinker	15.1	23.3	28.5	33.1	
Exercise					0.363
Yes	23.7	23.6	25.7	27.0	
No	24.6	26.8	26.2	22.4	
Systolic Blood Pressure (mm/Hg)	128.5(15.9)	131.0(17.0)	133.1(17.5)	134.3(18.0)	0.000
Diastolic Blood Pressure (mm/Hg)	83.0(10.9)	83.2(10.6)	86.8(24.1)	86.6(12.2)	0.000
Total Cholesterol (mg/dL)	185.8(32.2)	196.3(31.7)	200.5(32.4)	199.5(39.7)	0.000
Triglyceride (mg/dL)	114.4(66.9)	146.9(106.6)	179.6(106.9)	225.9(161.1)	0.000
HDL- Cholesterol (mg/dL)	42.9(9.8)	44.6(10.5)	44.2(10.6)	46.8(13.4)	0.000
AST (IU/L)	24.3(5.9)	26.1(6.5)	29.1(8.5)	40.7(27.9)	0.000
ALT (IU/L)	20.1(6.7)	23.9(10.0)	29.0(13.2)	39.4(24.9)	0.000
Fasting Plasma Glucose (mg/dL)	97.4(24.3)	96.9(19.5)	101.8(25.8)	103.4(23.9)	0.000
VFA (c㎡)	112.3(29.6)	121.4(27.5)	131.8(32.3)	127.3(28.2)	0.000

Abbreviations: GGT, γ-glutamyltransferase; HDL, High-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransfease; VFA, visceral fat area.

*Data are expressed as mean (SD) unless otherwise indicated.

† *P* value

Table 3. Characteristics of the study population according to GGT levels in women

	Quartiles of GGT level (IU/L)				*P* value
	< 11	11.0-14.9	15.0-21.9	≥22	for trend
	(n=417)	(n=432)	(n=463)	(n=468)	
Age(years)	51.6(8.1)	53.9(8.5)	55.0(8.3)	55.5(8.1)	0.000
Waist circumference (cm)	77.3(7.7)	79.7(8.5)	81.9(8.6)	84.3(8.8)	0.000
Body Mass Index (kg/㎡)	23.5(2.8)	24.2(3.0)	24.9(3.2)	25.7(4.0)	0.000
Cigarette smoking (%)					0.000†
Non smoker	23.8	24.4	26.1	25.7	
Ex smoker	10.0	30.0	20.0	40.0	
Current smoker	9.7	16.1	22.6	51.6	
Alcohol consumption (%)					0.000†
No drinker	25.0	24.8	27.1	23.1	
Ex drinker	21.4	28.6	21.4	28.6	
Current drinker	18.3	22.4	22.9	36.4	
Exercise					0.355
Yes	22.3	24.4	26.9	26.4	
No	25.9	24.1	24.1	26.0	
Systolic Blood Pressure (mm/Hg)	124.7(16.3)	129.5(17.6)	130.1(17.8)	132.0(17.9)	0.000
Diastolic Blood Pressure (mm/Hg)	79.1(10.6)	80.4(12.3)	82.5(11.5)	83.6(11.7)	0.000
Total Cholesterol (mg/dL)	186.7(32.0)	197.2(33.2)	203.9(36.3)	214.1(42.5)	0.000
Triglyceride (mg/dL)	99.9(49.9)	113.4(53.7)	141.0(85.2)	159.4(98.3)	0.000
HDL- Cholesterol (mg/dL)	48.2(11.4)	47.9(10.8)	47.0(10.3)	48.3(11.6)	0.851
AST (IU/L)	22.0(5.1)	22.6(5.0)	23.6(5.5)	28.2(13.3)	0.000
ALT (IU/L)	16.2(5.9)	17.8(6.5)	20.7(7.6)	29.2(17.6)	0.000
Fasting Plasma Glucose (mg/dL)	89.1(11.7)	91.2(12.8)	94.3(17.7)	100.2(25.1)	0.000
VFA (㎠)	69.4(27.6)	79.1(30.0)	88.1(33.6)	98.8(35.6)	0.000

Abbreviations: GGT, γ-glutamyltransferase; HDL, High-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; VFA, visceral fat area.

*Data are expressed as mean (SD) unless otherwise indicated.

†*P* value

Risk of waist circumference, visceral fat area, and γ-glutamyltransferase on prevalence of diabetes

The multivariate adjusted odds ratios (95% CI) of prevalence of diabetes in each quartile of WC were 1.83(1.19-28.2), 2.30(1.50-3.52), 3.44(2.27-5.21), when compared with the reference category. The corresponding adjusted odds ratio (95% CI) of prevalence of diabetes across VFA quartiles were 1.00, 1.16(0.77-1.74), 1.92(1.28-3.37), 2.23(1.48-3.37). The corresponding adjusted odds ratio (95% CI) of prevalence of diabetes according to GGT quartiles were 1.00, 1.25(0.82-1.92), 2.23(1.50-3.32), 3.81(2.50-5.79), respectively (Table 4).

Table 4 also shows the risk of prevalence of diabetes according to WC, VFA, and GGT after stratification by alcohol consumption. When non-drinker was defined as a non-drinker or ex-drinker, it was found that for the non-drinking group and current drinking group, the adjusted odds ratio showed an increased response to successive quartiles of WC, VFA, and GGT.

In Figure 1, area under the curve (AUC) for GGT using the receiver-operating characteristics (ROC) curve was 0.65 (p <0.001). Using the same method, the AUC for WC and VFA were 0.65 (p <0.001) and 0.63 (p <0.001), respectively.

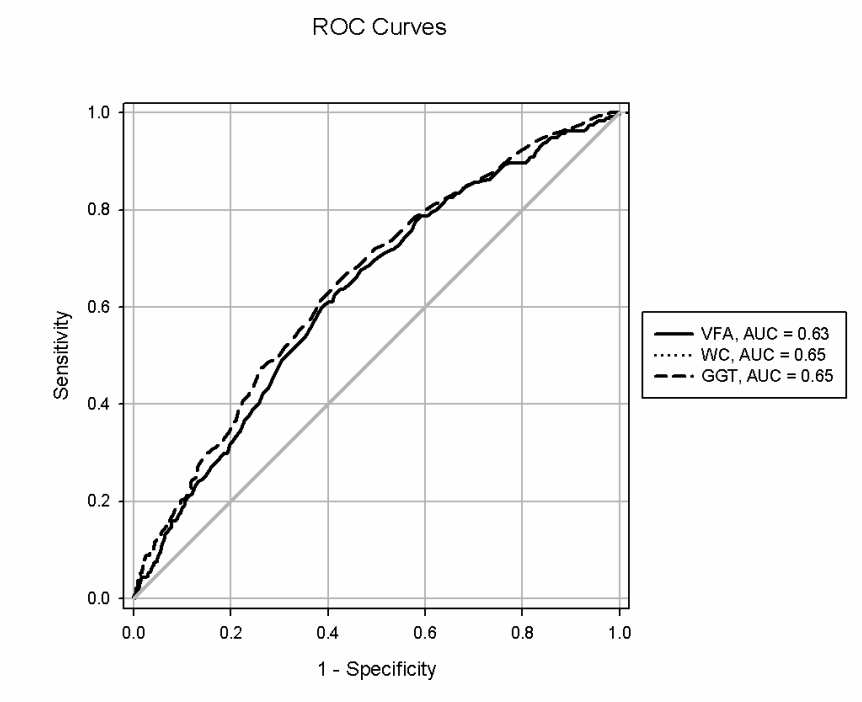
Table 4. Adjusted odds ratio (ORs) and 95% CI for prevalence of diabetes by Category of WC, VFA or GGT according to alcohol consumption.

	OR(95.5% CI)		
	Total	Non-Drinker	Current Drinker
Waist circumference, cm			
< 77	1.0	1.0	1.0
77-82.9	1.83(1.19-28.2)	2.20(1.26-3.85)	1.30(0.6-2.51)
83-88.9	2.30(1.50-3.52)	2.61(1.48-4.61)	1.84(0.97-3.50)
≥89	3.44(2.27-5.21)	3.94(2.26-6.86)	2.72(1.45-5.10)
Visceral fat area, cm^2			
< 71	1.0	1.0	1.0
71-99.9	1.16(0.77-1.74)	1.09(0.68-1.77)	1.23(0.56-2.69)
100.0-121.9	1.92(1.28-3.37)	2.29(1.41-3.73)	1.62(0.76-3.43)
≥122	2.23(1.48-3.37)	1.96(1.16-3.30)	2.34(1.10-4.99)
γ-glutamyltransferase, IU/L			
< 13.0	1.0	1.0	1.0
13-18.9	1.25(0.82-1.92)	1.33(0.82-2.15)	1.05(0.41-2.67)
19-32.9	2.23(1.50-3.32)	2.44(1.53-3.88)	1.92(0.86-4.38)
≥33	3.81(2.50-5.79)	3.23(1.86-5.57)	3.84(1.72-8.59)

*Adjusted for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.

† Non-drinker is defined as Non-drinker plus Ex-drinker.

Figure 1. ROC (receiver-operating characteristics) curve of VFA, WC and GGT associated with increase in the prevalence of type 2 diabetes.



Abbreviations: GGT, γ-glutamyltransferase; VFA, visceral fat area; WC, waist circumference; AUC, area under the curve.

Combined effect of waist circumference, visceral fat area, and γ-glutamyltransferase on prevalence of diabetes

We explored patterns of effect modification among WC, VFA and GGT using multiple logistic analyses. Table 5 shows adjusted odds ratio estimated for the strata defined by pairs of three variables: GGT, VFA, and WC. For GGT and VFA, the pattern of odds ratio estimates suggested a possibly additive effect. The interaction between GGT and WC was also possibly additive.

Table 5. Adjusted odds ratio (ORs) and 95% CI of prevalent diabetes

Variable1	Variable2	No	OR (95% CI)
GGT, IU/L	VFA, cm^2		
< 19	< 100	48	1.0
< 19	≥100	50	2.01(1.30-3.11)
≥19	< 100	61	2.68(1.78-4.05)
≥19	≥100	190	3.88(2.63-5.74)
GGT, IU/L	WC, cm		
< 19	< 83	41	1.0
< 19	≥83	57	2.24(1.46-3.44)
≥19	< 83	64	2.82(1.84-4.32)
≥19	≥83	187	4.17(2.83-6.15)

Abbreviations: GGT, γ-glutamyltransferase; VFA, visceral fat area; WC, waist circumference.

*Adjusted for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.

Interaction among waist circumference, visceral fat area, BMI and serum GGT on the risk for prevalence of diabetes

Fig 2 shows multivariate adjusted odds ratio (ORs) and 95% CI for prevalence of diabetes by category of WC and quartiles of serum GGT. Within the lowest quartile of GGT, WC was not associated with prevalence of diabetes, in contrast to the higher quartiles of serum GGT, risk for prevalence of diabetes increased for successive quartiles of WC. But, the interaction between WC and serum GGT on the risk for prevalence of diabetes was not significant. In Fig 3, adjusted odds ratio (ORs) and 95% CI of prevalent diabetes by category of VFA and quartiles of serum GGT are presented similarly to Fig 2. Such as the association between WC and risk of prevalent diabetes, ORs of VFA on the risk of prevalence of diabetes were not increased within the lower quartiles of GGT. However, independent of quartiles of VFA, risk for prevalence of diabetes was increased according to quartiles of serum GGT. The associations among BMI, serum GGT, and prevalence of diabetes were similar to Fig 2 and 3 (Fig 4). The interactions of VFA and BMI to serum GGT were not significant, either.

Figure2. Interaction between WC and serum GGT on the risk for prevalence of type 2 diabetes among men and women. Adjusted for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.

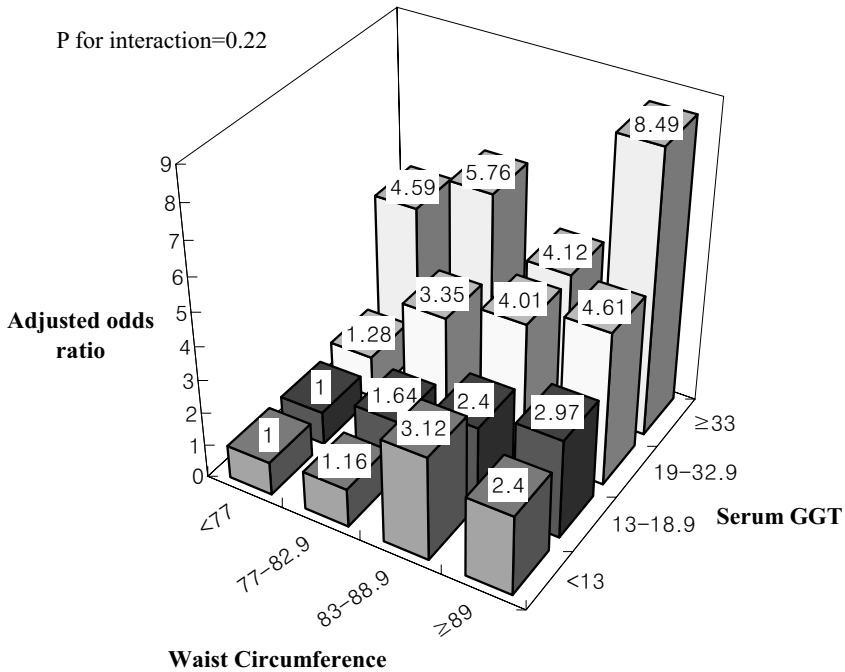


Figure 3. Interaction between VFA and serum GGT on the risk for prevalence of type 2 diabetes among men and women. Adjusted for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.

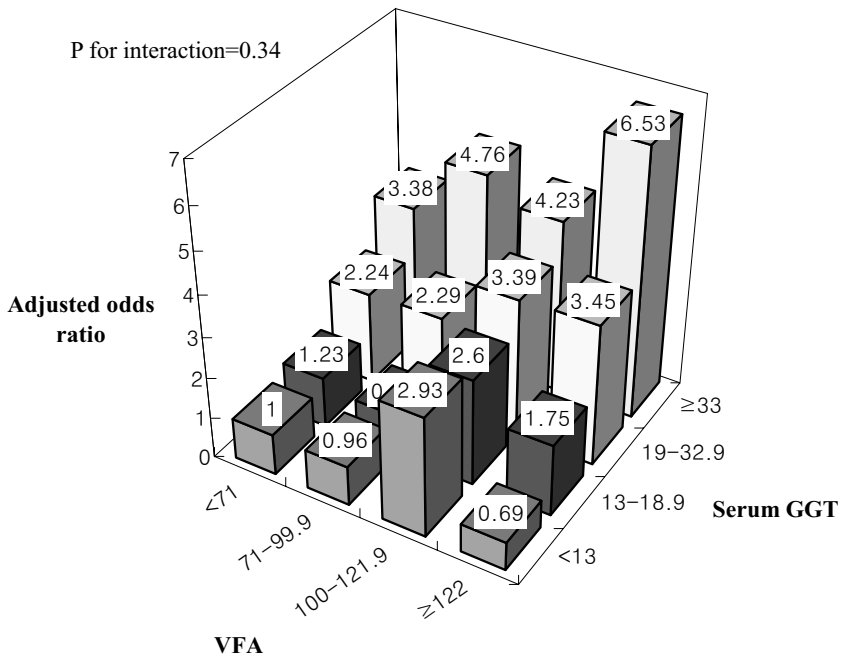
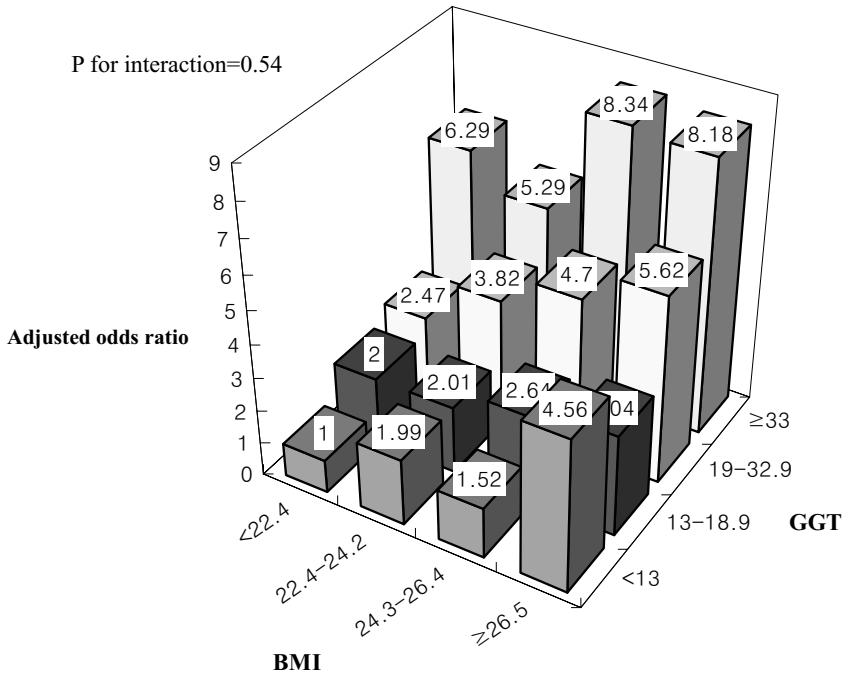


Figure 4. Interaction between BMI and serum GGT on the risk for prevalence of type 2 diabetes among men and women. Adjusted for age, sex, cigarette smoking, alcohol consumption, exercise, systolic blood pressure, and total cholesterol.



DISCUSSION

In this cross-sectional study, we found that higher levels of WC and VFA were directly associated with an increased risk of type 2 diabetes. Serum GGT activity was also positively associated with the prevalence of diabetes. However, the association between various parameters of abdominal obesity and the prevalence of diabetes was not clear after stratification by serum GGT. On the contrary, as WC or VFA increased, the association between serum GGT and prevalence of diabetes was strengthened. No interaction among these three risk factors was observed statistically.

In previous prospective cohort studies, the association of BMI with incidence of diabetes was stronger among participants with high normal GGT compared to those with low normal GGT (Lee et al, 2003; Lee et al, 2004). In a recent cross-sectional study, the association of obesity with the prevalence for type 2 diabetes found that serum GGT activity was also increased in participants with high normal range of GGT, but not with low normal serum GGT activity (Lim et al, 2007). However, in our study, after stratified by quartiles of serum GGT, the association between BMI and the prevalence of type 2 diabetes was not significant in all categories of serum GGT. Yet, the association between GGT and prevalent diabetes was presented in each group of BMI after stratified by quartiles of BMI.

Despite of the well-known complications of obesity (Bray et al, 1985), some very obese patients do not have fairly normal metabolic risk factors despite of their significant obesity. On the other hand, some moderately overweight patients are characterized by a metabolic cluster of diabetogenic and atherogenic abnormalities. Thus, recently, many studies have demonstrated that the distribution of visceral adipose tissue was correlated with metabolic risk factors such as reduced HDL particle size (Pascot et al, 2001), glucose tolerance and plasma insulin (Pouliot et al, 1992), plasma lipoprotein levels and hyperinsulinemia (Tchernof et al, 1996), and elevated C-reactive protein (Lemieux et al, 2001) that predictive of an increased risk for the development of type 2 diabetes and cardiovascular disease. Therefore, in particular, the association of WC or VFA with the prevalence of diabetes according to serum GGT was analyzed in this study.

An increase of serum GGT activity is conventionally known as a marker of alcohol abuse and /or liver damage (Teschke et al, 1977). However, other studies involving several ethnic groups have reported that

serum concentration of GGT, even within its normal range, is an independent risk factor for the development of diabetes (Perry et al, 1998; Lee et al, 2003, Lee et al, 2003, Nakanishi et al, 2004). Perry et al. (Perry et al, 1998) speculated that visceral adipose tissue could play a role in the association of GGT with type 2 diabetes. The same authors also interpreted GGT as a marker of hepatic steatosis and hepatic insulin resistance associated with diabetic pathogenesis (Perry et al, 1998). Recently, Iwasaki et al. reported serum level of GGT was associated with visceral adiposity independent of hepatic fat content (Iwasaki et al, 2008). Our data presented a trend in which neither WC nor VFA were not associated with prevalence of diabetes after stratification by serum GGT not only within the low normal range of GGT but also at higher levels of GGT. In contrast to this finding, serum GGT was positively associated with prevalence of diabetes in each group of quartiles of WC or VFA.

This interaction between WC or VFA and serum GGT on the risk of prevalence of diabetes was not statistically significant (p for interaction=0.22, 0.34) and different from the interaction between BMI and GGT on type 2 diabetes found in a previous study (Lim et al, 2007). In spite of that, this finding suggests that serum GGT may be more influential on the risk of diabetes than abdominal obesity or visceral adiposity. That is visceral fat can be considered as a risk factor for diabetes, and it is strengthened when it is combined with other risk factors such as increased GGT.

The mechanisms associated with the interaction of serum GGT and visceral fat on risk for diabetes remain unclear. Some experimental studies have reported that GGT plays a pivotal role in maintenance of antioxidant defense (Takanashi et al, 1997; Karp et al, 2001). Increase of GGT activity is a response to oxidative stress, facilitating reutilization of glutathione. Another study indicated that GGT was involved directly in the generation of reactive oxygen species (ROS) in the presence of Fe^{3+} (Drozdz et al, 1998). Serum GGT was positively associated with F2-isoprotanes and C-reactive protein (Lee et al, 2003) and inversely associated with serum antioxidant level (Lee et al, 2004).

In recent studies, some investigators reported a dose-response relation between serum concentrations of persistent organic pollutants (POPs), which are a kind of endocrine disruptor, and prevalence of diabetes (Lee et al, 2006). The same authors demonstrated that the association between obesity and diabetes became clearer when serum concentrations of POPs were increased, and also presented the positive association of POPs with serum GGT. They explained that POPs was associated with serum GGT because GGT is a marker of glutathione conjugation and synthesis and hypothesized that POPs stored in

fat tissue might be more important than obesity itself to explain the pathogenesis of type 2 diabetes (Lee et al, 2008).

This association between serum concentrations of POPs and obesity and the interaction between POPs and obesity on the risk of type 2 diabetes at least partially may explain the results of present study.

Our study has several limitations to take into consideration. First, it was a cross-sectional design, suggesting that caution should be used in causal interpretations. However, because similar findings were shown in previous observational studies, even though the independent variables were different, these results supports the conclusion that serum GGT has a stronger impact on the risk of diabetes than visceral fat or WC.

Second, VFA, as an indicator of visceral adipose tissue, was measured by BIA. Though BIA measurement has many practical advantages (eg. inexpensive, simple technique, noninvasive, available), the validity and reliability of BIA is not as excellent as those of CT scans to estimate visceral adipose tissue. Therefore, to overcome this disadvantage, we compared the results of VFA analyzed by BIA to those of VFA measured by CT scan. Although the study size was small, in this preliminary study, the results of BIA well correlated with those of CT scans. We also used the interaction between WC and serum GGT on the prevalence of diabetes to compare to that of VFA.

In summary, our findings revealed a combined effect of WC or VFA and serum GGT on the risk of prevalence of diabetes. These results indicate that serum GGT may be a more influential factor than abdominal obesity or visceral fat on the risk of prevalence of diabetes. Accordingly, in clinical settings, the association between WC or VFA, even though it is measured by BIA, and serum GGT may be practical to evaluate the risk of diabetes.

REFERENCES

Bioelectrical impedance analysis in body composition measurement: National Institute of Health Technology Assessment Conference Statement December 12-14, 1994. Am J Clin Nutr 1996; 64: 524S-32S.

Bray GA. Complications of obesity. Ann Intern Med 1985; 103: 1052-62.

Brenner H, Rothenbacher D, Arndt V, Schuberth S, Fraisse E, Fliedner TM. Distribution, determinants, and prognostic value of gamma-glutamytransferase for all-cause mortality in a cohort of construction workers from southern Germany. Prev Med 1997; 26: 305-10.

Conway B, Rene A. Obesity as a disease: no lightweight matter. Obes Rev 2004; 5: 145-51.

Drozdz R, Parmentier C, Hachad H, Leory P, Siest G, Wellman M. Gamma-glutamyltransferase dependent generation of reactive oxygen species from a glutathione/transferrin system. Free Radic Biol Med 1998; 25: 786-92.

Forman HJ, Liu R-M, Tian L. Glutathione cycling in oxidative stress. Lung Biol Health Dis 1997; 105: 99-121.

Iwasaki T, Yoneda M, Kawasaki S, Fujita K, Terauchi Y. Hepatic fat content-independent association of the serum level of gamma-glutamytransferase with visceral adiposity, but not subcutaneous adiposity. Diabetes Res Clin Pract 2008; 79; e13-e14.

Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamytransferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000; 31: 1851-5.

Karp DR, Shimooku K, Lipsky PE. Expression of gamma-glutamyl transpeptidase protects ramos B cells from oxidation-induced cell death. J Biol Chem 2001; 276: 3798-804.

Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamytransferase and diabetes- a 4 year follow-up study. Diabetologia 2003; 46: 359-64.

Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. Gamma-glutamytransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003; 49: 1358-66.

Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Yuomilehto J. Gamma-glutamytransferase, obesity,

and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. J Clin Endocrinol Metab 2004; 89: 5410-4.

Lee DH, Gross MD, Jacobs DR Jr. Association of serum carotenoids and tocopherols with gamma-glutamytransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) Study. Clin Chem 2004; 50: 582-8.

Lee DH, Lee IK, Song KE, Steffes M, Toscano W, Baker BA, et al. A strong dose-responese relation between serum concentrations of Persistent Organic Pollutants and diabetes: result from the National Health and Examination Survey. Diabetes Care 2006; 29: 1638-44.

Lee DH, Steffes MW, Jacobs DR Jr. Can persistent organic pollutants explain the association between serum γ-glutamytransferase and type 2 diabetes? Diabetologia 2008; 51: 402-7.

Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein : another component of the atherothrombic profile of abdominal obesity. Arterioscler Thromb Vasc Biol 2001; 21: 961-7.

Lim JS, Lee DH, Park JY, Jin SH, Jacobs DR Jr. A stroing interaction between serum γ-glutamytransferase and obesity on the risk of prevalent type 2 diabetes: results from the Third National Health and Nutrition Examination Survey. Clin Chem 2007; 53: 1092-8.

Mensah GA, Mokdad AH, Ford E, Marayan KM, Giles WH, Vinicor F, et al. Obesity, metabolic syndrome, and type 2 diabetes: emerging epidemics and their cardiovascular implications. Cardiol Clin 2004; 22: 485-504.

Miura K, Nakagawa H, Nakamura H, Tabata M, Nagase H, Yoshida M, et al. Serum gamma-glutamytransferase level in predicting hypertension among male drinkers. J Hum Hypertens 1994; 8: 445-9.

Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamytransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 2004; 6: 1427-32.

Nilssen O, Forde OH, Brenn T. The Tromso Study: distribution and population determinants of gamma-glutamytransferase. Am J Epidemiol 1990; 132: 318-26.

Pascot A, Lemieux I, Prud'homme D, Tremblay A, Nadeau A, Couillard C, et al. Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. J Lipid Res 2001; 42: 2007-14.

Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamytransferase and risk of NIDDM. Diabetes Care 1998; 21: 732-7.

Pompella A, Emdin M, Passino C, Paolicchi A. The significance of γ-glutamytransferase in cardiovascular diseases. Clin Chem Lab Med 2004; 42: 1085-91.

Pouliot MC, Despres JP, Nadeau A, Moorjani S, Prud'homme D, Lupien Pj, et al. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes. 1992; 41: 826-34.

Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H. Vorarlberg Health Monitoring and Promotion Program Study Group: gamma- glutamytransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005; 112: 2130-7.

Takahashi Y, Oakes SM, Williams MC, Takahashi S, Miura T, Joyce-Brady M. Nitrogen dioxide exposure activates gamma-glutamytransferase gene expression in rat lung. Toxicol Appl Pharmacol 1997; 143: 388-96.

Tchernof A, Lamarche B, Prud'homme D, Nadeau A, Moorjani S, Labrie F, et al. The dense LDL phenotype. Association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. Diabetes Care 1996; 19: 629-37.

Teschke R, Brand A, Strohmeyer G. Induction of hepatic microsomal gamma-glutamytransferase activity following chronic alcohol consumption. Biochem Biophys Res commun 1977; 75: 718-24.

Van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. Int J Obes 1993; 17: 187-196.

Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamytransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol 1995; 142: 699-708.

국문 요약

연구배경

혈청 γ-glutamyltransferase (GGT) 와 비만은 2형 당뇨병의 위험요인으로 간주된다. GGT에 따라 비만과 2형 당뇨병의 관련성이 약화되거나 강화된다는 연구들이 있었으나 당뇨병에 대한 GGT와 비만의 상호작용에 대한 근거는 부족하며 GGT에 따른 내장지방도와 당뇨병과의 관련성에 대한 연구는 없다.

연구목적

저자들은 단면 연구를 통해 GGT에 따른 허리둘레, 내장지방면적과 당뇨병의 유병율 사이의 관련성을 알아보고, 당뇨병 유병율에 대한 내장지방도와 GGT의 교호작용을 알아보고자 한다.

연구방법

한국 농촌지역 유전체 코호트 (Korean Rural Genomic Cohort : KRGC) 중에서 40-70세 사이의 2,948명 을 대상으로 GGT와 허리둘레, 내장지방도의 당뇨병에 대한 비차비를 구하고 두 변수의 결합 효과를 구하였다. 각 변수를 4구간으로 구분한 후 당뇨병 유병율에 대한 GGT와 내장지방도, GGT와 허리둘레의 비차비와 교호작용 여부를 분석하였다.

연구결과

당뇨병 유병율에 대한 허리둘레, 내장지방면적, GGT의 비차비는 구간의 증가에 따라 증가하였다. 허리둘레, 내장지방면적, GGT의 당뇨병에 대한 구간 아래 면적은 비슷하였고, 각 변수를 짝을 지어 본 결합효과의 보정 비차비는 증가하였다 (GGT와 내장지방면적의