

• RAPID COMMUNICATION •

Serum insulin, insulin resistance, β -cell dysfunction, and gallstone disease among type 2 diabetics in Chinese population: A community-based study in Kinmen, Taiwan

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RESULTS: We studied 440 type 2 diabetics who attended sonography check-ups. After excluding eight insulin-treated diabetics, the prevalence of GSD among the remaining 432 was 13.9% (26/187) among males and 14.7% (36/245) among females. After adjustment for other GSD-associated risk factors in addition to age and obesity, GSD risk increased among females with levels of serum insulin [4th vs 1st quartile odds ratios (OR) = 4.46 (95%CI: 1.71-11.66)] and HOMA IR [4th vs 1st quartile OR = 4.46 (95%CI: 1.71-11.66)]. Better HOMA β -cell function was significantly related to decreased risk of GSD [4th vs 1st quartile OR = 0.16 (95%CI: 0.03-1.70)]. Among males, age and central obesity were the most significant risk factors for GSD. No association of GSD with serum insulin, HOMA IR, and HOMA β -cell was observed among males.

CONCLUSION: Serum insulin, insulin resistance, and β -cell dysfunction are risk factors for GSD in females, but not males with type 2 diabetes.

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Key words: Type 2 diabetes; Gallstone disease; Insulin resistance; β -cell dysfunction; Community-based study

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Abstract

AIM: To explore the association of serum insulin, insulin resistance, and β -cell dysfunction with gallstone disease (GSD) in type 2 diabetics.

METHODS: We used a community-based study conducted between 1991 and 1993 in Kinmen, Taiwan to identify type 2 diabetics. A screening program for GSD was performed in 2001 by a panel of specialists who employed real-time ultrasound sonography to examine the abdominal region after the patient had fasted for at least 8 h. Screening was conducted in 2001 on 848 patients diagnosed with type 2 diabetes. The HOMA method was used to compare the profile differences for insulin resistance (HOMA IR) and β -cell dysfunction (HOMA β -cell).

INTRODUCTION

Clinically, type 2 diabetes with concomitant gallstone disease (GSD) increases the incidence of acute cholecystitis and has a higher probability for progression to septicemia. It is generally believed that subjects with diabetes secrete more lithogenic bile than non-diabetics; i.e., diabetes and GSD might be viewed as closely linked diseases^[1]. Indeed, several community-based epidemiologic studies have demonstrated that not only diabetics have an increase in GSD-related morbidity^[2-4], but also, our previous report showed that the prevalence of overall GSD among type 2 diabetics was higher as compared with

other general Chinese populations when using the same methods of GSD assessment^[5]. In order to reduce health-care expenditures caused by GSD, organized preventive strategies are recommended.

Insulin resistance syndrome, initially described by Reaven^[6], is a cluster of risk factors for coronary artery disease. This pathological condition is characterized by an inadequate physiological response of peripheral tissues to circulating insulin, and results in metabolic and hemodynamic disturbances^[7]. Hyperinsulinemia has also characteristically been found in subjects with type 2 diabetes as a result of insulin resistance, which is considered to be of primary importance in the pathogenesis of diabetes. In addition, impairment of β -cell function, which becomes most evident during insulin resistance due to increased demands for insulin, is also well known now as a major factor influencing the progression from normal glucose tolerance, through impaired glucose tolerance to frank type 2 diabetes^[8,9]. Results of the epidemiological studies have shown that increased insulin resistance and decreased insulin secretion are strongly related to the risk of developing type 2 diabetes^[10-12].

The insulin-related factors responsible for the development of GSD remain to be clarified. Although it has been suggested that serum insulin affects the development of this co-disease in the general population^[13,14], few community-based studies have been conducted to explore the direct effect of serum insulin, insulin resistance, and β -cell dysfunction to GSD among the diabetics. Additionally, other factors, including diabetic duration and glucose toxicity, have been proposed to affect the development of GSD in type 2 diabetics^[3]. Using the community-based study in Kinmen, Taiwan, we aimed to determine whether serum insulin, insulin resistance, and β -cell dysfunction, were independently related to GSD among type 2 diabetics.

MATERIALS AND METHODS

Organization of community-based gallstone disease screening for type 2 diabetes

We used baseline data from a community-based screening for type 2 diabetes targeted to subjects aged 30 years or more in Kinmen, Taiwan, between January 1991 and December 1993. The details of the study design and execution have been described in detail elsewhere^[15]. The identification of type 2 diabetes was based on the WHO definition in 1985^[16]: subjects with fasting plasma glucose (FPG) ≥ 7.8 mmol/L (≥ 140 mg/dL) or 2 h postload ≥ 11.1 mmol/L (≥ 200 mg/dL) were defined as individuals with type 2 diabetes. Subjects with a history of type 2 diabetes and who received medication were defined as known cases. However, in the GSD screening done in 2001, the patients that fulfilled the criteria of the revised WHO criteria (revised in 1999) were enrolled. Patients with FPG ≥ 7.0 and < 7.8 mmol/L in 1991 to 1993 were also recruited^[17]. A total of 1 123 type 2 diabetics aged 30 and above were identified based on the population survey carried out by the Yang-Ming Crusade in Kinmen. After

excluding those who migrated or died, the remaining 858 type 2 diabetics formed a cohort who were eligible for abdominal ultrasound sonography. These 858 subjects were invited by telephone calls or invitation letters in 2001 to be screened for GSD. Informed consent was obtained from all participants before the survey^[5].

Information concerning biochemical markers and diagnosis of gallstone disease

The details of the data collection have also been described in detail elsewhere^[5]. In brief, baseline information including demographic and biochemical variables was collected in the period 1991-93. Face to face interviews were conducted by the Yang-Ming Crusade, a volunteer organization of well-trained medical students of National Yang-Ming University. Fasting blood samples were drawn by public health nurses. Overnight fasting serum and plasma samples (preserved with EDTA and NaF) were collected and kept frozen (-20°C) until analysis. FPG concentrations were determined using the hexokinase-glucose-6-phosphate dehydrogenase method with a glucose (HK) reagent Idt (Gilford, Oberlin, OH, USA). Higher systolic blood pressure (SBP) was defined as SBP ≥ 140 mmHg, and higher diastolic blood pressure (DBP) was defined as DBP ≥ 90 mmHg. Obesity was defined by a body mass index (BMI) ≥ 25 kg/m², an abnormal total cholesterol was defined as ≥ 5.17 mmol/L (≥ 200 mg/dL), a raised triglyceride as ≥ 2.24 mmol/L (≥ 200 mg/dL), a raised blood urea nitrogen (BUN) as ≥ 7.14 mmol/L (≥ 20 mg/dL), a high level of uric acid was defined for males as ≥ 0.42 mmol/L (≥ 7 mg/dL) and for females as ≥ 0.36 mmol/L (≥ 6 mg/dL), and central obesity as a waist circumference ≥ 90 cm in males or ≥ 80 cm in females^[18].

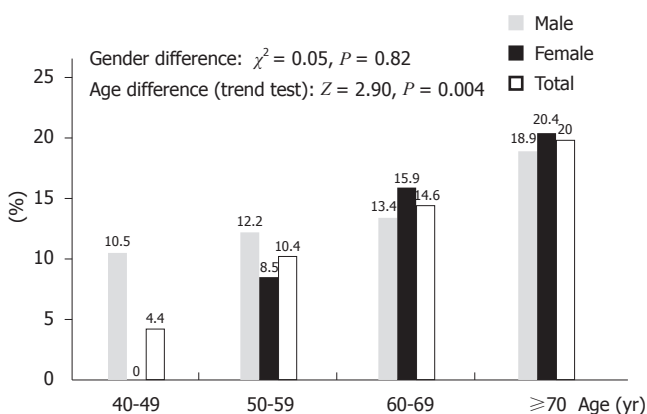
The follow-up screening regime for GSD was performed in 2001. GSD was diagnosed by a panel of specialists using real-time ultrasound sonography to examine the abdominal region, after fasting for at least 8 h, for the presence of "movable hyperechoic material with acoustic shadow". Cases of GSD were classified as follows: single gallbladder stone; multiple gallbladder stones; and cholecystectomy, excluding gallbladder polyps. Cases were identified as any type of GSD among type 2 diabetics. Furthermore, in order to ensure consistency of GSD diagnosis among the specialists, the Kappa statistic was used to assess the agreement of interobserver reliability among study specialists. A pilot study was performed with 50 randomly selected type 2 diabetics who were not study subjects. For interobserver reliability, the Kappa value for diagnosis of GSD was 0.77 (95%CI: 0.50-0.96).

Assessment of insulin resistance and β -cell dysfunction

The HOMA method was used to compare differences in the profiles for insulin resistance (HOMA IR) and for β -cell dysfunction (HOMA β -cell) in subjects with and without GSD^[19]. The HOMA model assumes that the control of FPG and fasting insulin (FI) is governed by a self-contained feedback loop between the pancreas, liver, and insulin-sensitive and insulin-insensitive glucose

Table 1 Crude and age-adjusted odds ratios of baseline-associated factors of GSD among type 2 diabetics in Kinmen

	GSD (yes vs no)							
	Male				Female			
	Crude OR (95%CI)		Age-adjusted OR (95%CI)		Crude OR (95%CI)		Age-adjusted OR (95%CI)	
Age (≥ 65 vs < 65 yr)	3.14	(1.32-7.47) ^a	-	-	2.25	(1.04-4.90) ^a	-	-
Type 2 diabetes (known vs new cases)	0.90	(0.34-2.39)	0.87	(0.32-2.34)	1.44	(0.68-3.02)	1.46	(0.68-3.13)
FPG (≥ 11.1 vs < 11.1 mmol/L)	2.12	(0.70-6.37)	1.95	(0.64-5.94)	1.24	(0.50-3.07)	1.49	(0.59-3.79)
SBP (≥ 140 vs < 140 mmHg)	1.70	(0.73-3.97)	1.50	(0.63-3.56)	2.59	(1.23-5.46) ^a	1.99	(0.92-4.31)
DBP (≥ 90 vs < 90 mmHg)	1.44	(0.62-3.35)	1.57	(0.67-3.73)	1.12	(0.52-2.42)	1.21	(0.55-2.67)
Obesity (yes vs no)	2.04	(0.85-4.88)	2.00	(0.83-4.83)	2.97	(1.30-6.83) ^a	2.88	(1.24-6.70) ^a
Central obesity (yes vs no)	2.76	(1.13-6.77) ^a	2.36	(1.01-5.97)	1.85	(0.68-5.02)	1.47	(0.53-4.09)
Cholesterol (≥ 5.17 vs < 5.17 mmol/L)	1.02	(0.19-1.91)	0.88	(0.18-1.09)	0.92	(0.45-1.88)	0.85	(0.41-1.77)
Triglyceride (≥ 2.24 vs < 2.24 mmol/L)	1.92	(0.12-2.36)	1.61	(0.13-2.84)	1.43	(0.20-2.46)	1.35	(0.15-1.96)
BUN (≥ 7.14 vs < 7.14 mmol/L)	0.44	(0.16-1.25)	0.38	(0.13-1.09)	1.65	(0.75-3.61)	1.30	(0.58-2.93)
Uric acid (high vs normal)	0.30	(0.09-1.06)	0.29	(0.08-1.03)	1.61	(0.77-3.38)	1.12	(0.51-2.48)
AST (≥ 40 vs < 40 U/L)	1.05	(0.08-5.72)	0.60	(0.07-5.31)	3.68	(1.01-9.32) ^a	3.93	(1.04-10.89) ^a
ALT (≥ 40 vs < 40 U/L)	1.09	(0.19-4.33)	1.09	(0.21-5.61)	2.00	(0.67-6.02)	2.20	(0.71-6.85)
Serum insulin (2 nd vs 1 st quartile)	0.29	(0.06-1.33)	0.30	(0.06-1.39)	1.39	(0.44-4.40)	1.68	(0.52-5.45)
(μ U/mL) (3 rd vs 1 st quartile)	0.61	(0.19-2.00)	0.56	(0.17-1.86)	2.05	(0.71-5.88)	2.20	(0.75-6.45)
(4 th vs 1 st quartile)	0.61	(0.18-2.03)	0.65	(0.20-2.17)	5.38	(2.14-13.48) ^a	5.32	(2.08-13.64) ^a
Log HOMA IR (2 nd vs 1 st quartile)	0.61	(0.19-2.00)	0.60	(0.18-1.99)	1.17	(0.38-3.57)	1.65	(0.52-5.29)
(3 rd vs 1 st quartile)	0.58	(0.06-1.29)	0.49	(0.06-1.36)	2.60	(1.02-6.64) ^a	2.66	(1.02-6.94) ^a
(4 th vs 1 st quartile)	0.63	(0.19-2.08)	0.60	(0.18-2.01)	2.60	(1.01-6.66) ^a	2.59	(1.01-6.76) ^a
Log HOMA β -cell (2 nd vs 1 st quartile)	1.16	(0.35-3.80)	1.27	(0.38-4.25)	0.35	(0.08-1.55)	0.45	(0.10-2.03)
(3 rd vs 1 st quartile)	0.52	(0.11-2.43)	0.51	(0.11-2.39)	0.16	(0.02-1.23)	0.17	(0.02-1.35)
(4 th vs 1 st quartile)	0.25	(0.03-2.97)	0.22	(0.03-1.73)	0.17	(0.02-1.28)	0.16	(0.02-1.21)

^a $P < 0.05$.**Figure 1** Sex and age-specific prevalence of gallstone diseases among type 2 diabetics in Kinmen.

metabolizing tissues^[19]. The formulas were developed and validated against the hyperinsulinemic-euglycemic clamp for insulin resistance and the hyperglycemic clamp for insulin secretion^[19]. The details are as follows:

$$\text{Insulin resistance (HOMA IR)} = \frac{\text{FI} \times \text{FPG}}{22.5}$$

$$\beta\text{-cell function (HOMA } \beta\text{-cell)} = \frac{20 - \text{FI}}{\text{FPG} - 3.5}$$

Because the HOMA model is not applicable to type 2 diabetics treated with insulin, eight insulin-treated subjects were excluded from the HOMA analysis. In addition, due to skewed distributions, the values of the HOMA model were subjected to log transformation in further analysis and re-transformed for tabulations.

Statistical analysis

Statistical analysis was performed using SAS version 9.0

(SAS Institute Inc., Cary, NC, USA). In the univariate analysis, crude and adjusted OR (adjustment for sex and age) were estimated and 95% confidence intervals (CI) were used. Multiple logistic regression was used to investigate whether insulin resistance and β -cell dysfunction were independently associated with GSD after adjustment for confounding factors. A P value < 0.05 was considered statistically significant. In addition, HOMA IR, and HOMA β -cell scores were divided into quartiles after log transformation.

RESULTS

In our earlier study in 2001, 440 of 858 type 2 diabetic subjects (51.3%) had received real-time ultrasound sonography of the abdomen^[5]. Using this cohort in the present study, and after excluding eight type 2 diabetics who had been treated with insulin, we determined the distribution of GSD among the remaining 432 participants. Figure 1 shows the sex- and age-specific prevalence of all types of GSD among type 2 diabetics. The sex-specific prevalence values [male: 13.9% (26/187); female: 14.7% (36/245)] were not significantly different ($\chi^2 = 0.05$, $P = 0.82$). The prevalence of all types of GSD was significantly increased with age [Z (trend) = 2.90, $P = 0.004$]. Among the subjects aged 40-59 years, males had a higher prevalence of GSD than females. Conversely, among subjects aged 60 and above, females had a higher prevalence of GSD than males.

Table 1 presents the crude and age-adjusted OR for the association between certain relevant baseline-associated risk factors and GSD. Among males, baseline factors that were significantly related to GSD included age (≥ 65 vs < 65 years, crude OR = 3.14, 95%CI: 1.32-7.47) and central obesity (yes vs no, age-adjusted OR = 2.36, 95%CI:

Table 2 Multiple logistic regression of association between baseline serum insulin, insulin resistance, β -cell dysfunction and GSD among type 2 diabetics in Kinmen

Variables	GSD (yes <i>vs</i> no)					
	Male			Female		
	OR	(95%CI)	<i>P</i> for trend test	OR	(95%CI)	<i>P</i> for trend test
Model I						
Age (≥ 65 <i>vs</i> <65 years)	1.04	(1.00-1.09)	-	1.05	(1.02-1.09)	-
Obesity (yes <i>vs</i> no)	-	-	-	2.35	(1.04-5.62)	-
Central obesity(yes <i>vs</i> no)	2.66	(1.01-6.99)	-	-	-	-
Serum insulin (μ U/mL)						
2 nd <i>vs</i> 1 st quartile	0.39	(0.08-1.99)	0.51	1.47	(0.44-4.87)	<0.0001
3 rd <i>vs</i> 1 st quartile	0.52	(0.14-1.95)		2.01	(0.68-5.96)	
4 th <i>vs</i> 1 st quartile	0.56	(0.16-2.04)		4.46	(1.71-11.66)	
Model II						
Age (≥ 65 <i>vs</i> <65 years)	1.04	(1.02-1.09)	-	1.06	(1.02-1.10)	-
Obesity (yes <i>vs</i> no)	-	-	-	2.25	(1.02-5.52)	-
Central obesity(yes <i>vs</i> no)	2.68	(1.03-6.97)	-	-	-	-
Log HOMA IR						
2 nd <i>vs</i> 1 st quartile	0.79	(0.22-2.78)	0.18	1.63	(0.49-5.43)	0.02
3 rd <i>vs</i> 1 st quartile	0.53	(0.07-1.51)		1.63	(0.55-4.82)	
4 th <i>vs</i> 1 st quartile	0.68	(0.20-2.36)		2.81	(1.03-7.91)	
Model III						
Age (≥ 65 <i>vs</i> <65 years)	1.05	(1.00-1.10)	-	1.05	(1.01-1.09)	-
Obesity (yes <i>vs</i> no)	-	-	-	2.58	(1.09-6.13)	-
Central obesity(yes <i>vs</i> no)	2.82	(1.03-7.69)	-	-	-	-
Log HOMA β -cell						
2 nd <i>vs</i> 1 st quartile	0.94	(0.60-9.97)	0.14	0.45	(0.10-2.09)	0.01
3 rd <i>vs</i> 1 st quartile	0.78	(0.15-4.09)		0.17	(0.02-1.31)	
4 th <i>vs</i> 1 quartile	0.32	(0.04-2.89)		0.16	(0.03-1.70)	

Other independent variables controlled in model included age, type of cases, SBP, DBP, cholesterol, triglyceride, BUN, uric acid, AST, and ALT.

1.01-5.97). According to univariate analysis in which the highest quartile was compared with the lowest, the female diabetics with GSD (compared to those without GSD) were older (≥ 65 vs < 65 years, crude OR = 2.25, 95%CI: 1.04-4.90), were more obese (yes vs no, age-adjusted OR = 2.88, 95%CI: 1.24-6.70), had higher AST values (≥ 40 vs < 40 U/L, age-adjusted OR = 3.93, 95%CI: 1.04-10.89), had greater serum insulin values (4th vs 1st quartile, age-adjusted OR = 5.32, 95%CI: 2.08-13.64) and had higher log HOMA IR values (4th vs 1st quartile, age-adjusted OR = 2.59, 95%CI: 1.01-6.76).

Associations between baseline serum insulin, insulin resistance, β -cell dysfunction, and GSD in each gender after adjustment for confounding factors were examined using a multiple logistic regression model. Fasting insulin was correlated with HOMA IR and HOMA β -cell dysfunction. These correlations were shown to be independent through the use of separate models. Furthermore, because the level of significance was very similar for raw (non-transformed) and log transformed data, in order to interpret the results more easily, the results for serum insulin were calculated for raw values. As shown in Table 2, older age was significantly associated with GSD in both males and females. Among males, there was a statistically significant association of GSD with central obesity, but no association of GSD with serum insulin, log HOMA IR, or log HOMA β -cell. Among females, not only obesity, but also serum insulin ($P < 0.0001$ for trend test) and log HOMA IR ($P = 0.02$ for trend test) were significantly related to GSD (after adjustment

for confounding variables). The association of GSD with serum insulin (4th vs 1st quartile, OR = 4.46, 95%CI: 1.71-11.66) and log HOMA IR (4th vs 1st quartile, OR = 2.81, 95%CI: 1.03-7.91) was revealed when the highest quartile was compared with the lowest. Although an association between log HOMA β -cell dysfunction and GSD was not found in the multivariate model, the test for trend was still strongly significant ($P = 0.01$).

DISCUSSION

Consistent with other epidemiologic studies^[3,5], our study also revealed that age is a significant risk factor for GSD among type 2 diabetics (after adjustment for confounding factors). Larger amounts of cholesterol secreted by the liver and a decrease in the catabolism of cholesterol to bile acid were observed in the elderly population^[20]. Long-term exposure, such as longer duration of type 2 diabetes, also might account for the increased risk of developing GSD among the elderly population^[21]. In addition, the present study also showed the interaction between sex and age to prevalence of GSD. Further epidemiological and etiological investigations are clearly needed in order to clarify the pathophysiological mechanisms of interactive effects between sex, age, and GSD among type 2 diabetics.

Obesity might raise the saturation of bile by increasing biliary secretion of cholesterol, with the latter probably depending on a higher synthesis of cholesterol in obese subjects^[5,22]. Our data demonstrated a significant association between obesity and GSD among females.

As in other studies, both univariate and multivariate analyses showed significantly higher BMI among females when compared to controls^[23,24]. However, among males, the present study failed to find a positive association between higher BMI and GSD, whereas central obesity was significantly associated with GSD. These results are consistent with those of other population-based studies^[25,26]. It has been suggested that BMI might not be as good an indicator of obesity among males as among females^[27]. Some studies have also suggested that failing to find a relationship between BMI and GSD among males reveals a tendency for a positive association with other indices of obesity, such as slimming treatment and skinfold thickness^[27,28]. Another possible reason is that loss of muscle bulk might be associated with GSD among males, i.e., males with GSD had gained less weight during adult life than non-GSD males despite having more abdominal fat, suggesting that they had lost more lean body mass^[26]. Because central obesity was shown to be an important predictor of type 2 diabetes and various metabolic abnormalities, further study is needed to determine the contribution to and pathophysiological mechanisms of the formation of GSD in type 2 diabetics.

The results of this community-based study provide further support for an association between hyperinsulinemia and insulin resistance with GSD among females. Female diabetics with GSD had significantly higher baseline serum insulin, higher HOMA IR and lower HOMA β -cell function in comparison to controls without GSD pathology. This relationship persisted even after controlling the most common confounding factor of the association, such as central obesity, which was related to GSD and serum insulin^[3]. Males showed no significant differences from controls regarding insulin resistance or its surrogates, lending support to a proposed interaction of these factors and sex with regard to lithogenesis. Previous clinical case-control studies and epidemiologic studies also showed similar results in the general population and in the diabetic population^[3,13,29]. The mechanism underlying the interaction between insulin and gallstone formation is undetermined, though it has been speculated that decreased GSD motility and increased cholesterol saturation of bile are involved^[29]. Gallstone motility had been demonstrated to be impaired in diabetics, favoring cholesterol gallstone crystal formation and growth^[30]. Insulin may inhibit basal and cholecystokinin-stimulated gallbladder motility^[31]. Another possible reason for the lack of an association between serum insulin and GSD among males is abdominal adiposity, which probably explains the hyperinsulinemia as the association of serum insulin with the disappearance of GSD. In addition, the fact that the HOMA model was used to estimate insulin resistance could be viewed as showing an interaction between serum insulin and FPG. The higher insulin levels mean the greater insulin resistance. Insulin resistance related to GSD with response to the duration of type 2 diabetes would also increase the risk of prevalent GSD^[3].

Among females, a positive relationship between serum C-peptide and GSD was obtained in previous studies^[13]. Measurement of C-peptide under standardized conditions

provides a sensitive, well accepted and clinically validated assessment of β -cell function^[32]. The intravenous glucose tolerance test (IVGTT) is widely used to test pancreatic β -cell function. Plasma C-peptide concentration is measured and used to infer insulin secretion since it is secreted in equimolar amounts with insulin, and its extraction by the liver is negligible^[33]. In the present study, HOMA β -cell dysfunction was strongly related to GSD among females but not among males, implying that insulin secretion might act differently in relation to GSD formation in males and females, even among those with type 2 diabetes.

The present study took advantage of several important and valuable methods. First, most previous studies were hospital-based, and Berkson's bias (selection bias) was inevitable. A community-based study design, such as the one we used, could diminish this kind of selection bias. Second, potential information bias was reduced because GSD screening for type 2 diabetics in 2001 was collected without the knowledge by the specialists of results of the baseline biochemical factors in 1991-1993. Third, we used ultrasound examination instead of clinical history of GSD as used in the previous study^[3]. Because of this, we should have improved diagnostic accuracy and diminished underestimation and misclassification of GSD. Nevertheless, associated biochemical markers of GSD were obtained retrospectively, and the causal relationship between serum insulin, insulin resistance, β -cell dysfunction and GSD could not be clarified in our study. Baseline characteristics pertinent to the risk of type 2 diabetes for attendants were not significantly different from those for non-attendants except for age, which means that the 51.3% who participated may also be representative of those refusing to join our study (after adjustment for age)^[5]. But the relatively lower response rate still might be caused by decreased statistical power. In addition, due to the complications and expense associated with the clamp technique (which prohibited its use in our community-based epidemiologic studies that had substantial sample sizes), the measurements of insulin resistance and β -cell dysfunction were based on an indirect method (the HOMA model). However, previous studies confirmed that the HOMA method and clamp-measured insulin resistance were highly correlated, implying that we could also obtain unbiased results using less sophisticated methods^[34,35].

In conclusion, the present study shows that there are gender differences with regard to the relationships between serum insulin, insulin resistance, β -cell dysfunction and GSD among type 2 diabetics (after adjustment for confounding factors). These observations suggest that factors related to type 2 diabetes might need to be considered separately in male and female diabetic patients in the pathogenic mechanism of increased risk of GSD.

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