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World J Gastroenterol 2006 July 28; 12(28): 4536-4540
World Journal of Gastroenterology ISSN 1007-9327

CLINICAL RESEARCH

A population-based follow-up study on gallstone disease among type 2 diabetics in Kinmen, Taiwan

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Received: 2006-01-24 Accepted: 2006-02-18

Abstract

AIM: To assess the incidence of and risk factors for gallstone disease (GSD) among type 2 diabetics in Kinmen, Taiwan.

METHODS: A screening program for GSD was performed by two specialists who employed real-time abdominal ultrasound to examine the abdominal region after patients had fasted for at least eight hours. Screening, which was conducted in 2001, involved 848 patients diagnosed with type 2 diabetes. After exclusion of 63 subjects with prevalent GSD, 377 participants without GSD were invited in 2002 for a second round of screening. A total of 281 (74.5%) subjects were re-examined.

RESULTS: Among the 281 type 2 diabetics who had no GSD at the first screening, 10 had developed GSD by 2002. The incidence was 3.56% per year (95% CI: 1.78% per year-6.24% per year). Using a Cox regression model, age (RR = 1.07, 95% CI: 1.00-1.14), waist circumference (RR = 1.12, 95% CI: 1.01-1.29), and ALT (RR = 1.13, 95%CI: 1.01-1.26) appeared to be significantly correlated with development of GSD.

CONCLUSION: Older age is a known risk factor for the development of GSD. Our study shows that greater waist circumference and elevated ALT levels are also associated with the development of GSD among type 2 diabetics in Kinmen.

Key words: Type 2 diabetes; Gallstone disease; Incidence density; Population-based study

Tung TH, Ho HM, Shin HC, Chou P, Liu JH, Chen VTK, Chan DC, Liu CM. A population-based follow-up study on gallstone disease among type 2 diabetics in Kinmen, Taiwan. *World J Gastroenterol* 2006; 12(28): 4536-4540

http://www.wjgnet.com/1007-9327/12/4536.asp

INTRODUCTION

Gallstone disease (GSD), a digestive disorder with multifactorial origins, is very common worldwide. Within the past few years ultrasonographic studies have provided estimates of GSD prevalence and of predisposing factors in various populations[1-5]. Although some controversy exists regarding the association between diabetes and GSD, population-based epidemiologic studies have demonstrated that diabetic subjects have an increased morbidity of GSD[6-8]. Moreover, our previous report showed that the prevalence of overall GSD among type 2 diabetics is higher than in other general Chinese populations when using the same methods for GSD assessment[5].

Previous study had explored the prevalence of GSD and associated factor among type 2 diabetics[5], and cross-sectional studies provided useful information of disease prevalence, however, they did not present the incidence or new cases in the study population. One must re-examine the population after a period of time in order to determine incidence and causal relationships between risk factors and

disease. From a preventive medicine viewpoint, primary prevention of GSD should focus on risk factors responsible for the occurrence of GSD. To explore the incidence of and risk factors for GSD is essential to prevent its development and the cholecystectomy caused by this complication, which is often insidious in nature. Therefore, it is necessary to conduct a population-based study which estimates GSD incidence. This is in part due to the fact that more than half of subjects with GSD are unaware of their condition and diagnosed cases seem to represent a selected group based on clinical studies[8]. Recently, however, a few population-based prospective studies have described the incidence and temporal relationship between the development of GSD and various risk factors among type 2 diabetics in Taiwan. The present study was conducted to explore the incidence and risk factors of GSD among type 2 diabetics in Kinmen, Taiwan based on a one-year follow-up period using real time abdominal ultrasound.

MATERIALS AND METHODS

Organization of gallstone disease screening for type 2 diabetics

Figure 1 shows the procedures for GSD screening between 2001 and 2002. Data used in this study were derived from a population-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 full elsewhere[9]. The identification of type 2 diabetes was based on the WHO definition in 1985[10], namely, subjects with a fasting plasma glucose (FPG) $\geqslant$ 140 mg/dL or a 2 h postload glucose $\geqslant$ 200 mg/dL. Subjects with a history of type 2 diabetes and who had received medication were defined as known cases. However, in the GSD screening done in 2001, even patients who fulfilled the criteria of the revised WHO 1999 were enrolled. That is, additional patients with FPG $\geqslant$ 126 mg/dL and <140 mg/dL in 1991 to 1993 were also recruited[11]. A total of 1123 type 2 diabetics aged 30 and over were identified based on face-to-face interviews carried out by the Yang-Ming Crusade, a volunteer organization of well-trained medical students of National Yang-Ming University. After exclusion of those who migrated or died, the remaining 858 type 2 diabetics formed a cohort to receive first round abdominal ultrasound in 2001. A total of 440 (51.3%) subjects were examined in first screening for GSD. Sixty-three out of 440 type 2 diabetics were diagnosed with GSD. The overall prevalence of GSD was 14.4%, including single stone 8.0% (n = 35), multiple stones 3.2% (n = 14), and cholecystectomy 3.2% (n = 14) [5]. The 377 diabetics without GSD screened in 2001 were then invited by telephone calls or invitation letters in 2002 to receive a second round of abdominal examinations. Informed consent was obtained from all participants before the GSD screening[5].

Data collection and diagnosis of gallstone disease

In the present study, 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℃) until analysis for measurements of biochemistry markers. FPG concentrations were determined using the hexokinase-glucose-6-phosphate dehydrogenase method with a glucose (HK) reagent ldt (Gilford, Cberlin, OH). The BMI, waist circumference, uric acid, and HbA_{1c} data were also collected during the GSD screening in 2001. The duration of type 2 diabetes in patients who were previously diagnosed with the disease was confirmed by the questionnaire. In addition, the screening protocol for GSD was performed in 2001 and 2002. GSD was diagnosed by two specialists using real-time abdominal ultrasound to examine the abdominal region after participants had fasted for at least 8 h. GSD was identified based on 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.

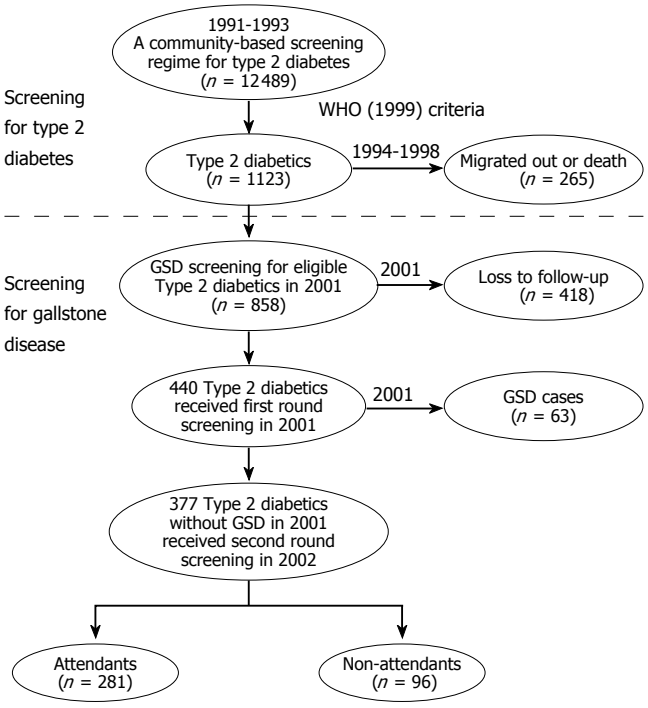

Figure 1 The procedure of screening for gallstone disease among type 2 diabetics during 2001-2002 in Kinmen.

Inter-observer reliability in ultrasound sonography

In order to set up a consistent diagnosis of GSD among two specialists, the Kappa statistic was used to assess inter-observer reliability among study specialists. A pilot study was performed with a randomly selected cohort (n = 50) of type 2 diabetics other than the study subjects. Our pilot study on inter-observer reliability showed a Kappa value for diagnosis of GSD of 0.77 (95%CI: 0.50-0.96).

Statistical analysis

Statistical analysis was performed using SAS software. The incidence of GSD was determined per year based on the ratio of the observed number of cases to the total number of patient-years at risk. Ninety-five percent confidence intervals (95% CI) for incidence were calculated using the Poisson distribution. In the univariate analysis, a t-test was

Table 1 Attendance rate of gallstone disease screening among type 2 diabetics in Kinmen

Variable	Eligible population	Screened population	Attendance rate
	n	*n*	(%)
Sex			
Male	167	121	72.5
Female	210	160	76.2
Age (yr)			
40-49	43	33	76.7
50-59	87	56	64.4
60-69	134	111	82.8
70+	113	81	71.7
Total	377	281	74.5

Table 2 Sex- and age-specific incidence of gallstone disease among type 2 diabetics in Kinmen

Variable	Incidence of any gallstone disease		
	No. of no GSD at first screening	New cases	Incidence density (% per year) (95%CI)
Sex			
Male	121	2	1.65 (0.03-5.10)
Female	160	8	5 (2.29-9.31)
P-value			0.12
Age (yr)			
40-49	33	0	0 (-)
50-59	56	2	3.57 (0.06-11.03)
60-69	111	4	3.6 (1.12-8.37)
70+	81	4	4.94 (1.53-11.47)
P-value			0.04
Total	281	10	3.56 (1.78-6.24)

Table 3 Univariate analysis of risk factors for the development of gallstone disease among type 2 diabetics in Kinmen

Variables	Development of gallstone disease			
	Yes	No	*P* value for *t* test	Definitions of disease condition
	Mean ± SD	Mean ± SD		
Age (yr)	69.90 ± 8.79	63.11 ± 10.72	0.04	-
Duration of diabetes (yr)	9.60 ± 0.84	9.44 ± 1.59	0.59	-
Fasting plasma glucose (mg/dL)	148.50 ± 18.45	144.94 ± 39.35	0.58	⩾ 126 mg/dL
HbA1c (%)	8.19 ± 0.93	8.33 ± 2.05	0.69	⩾ 7%
Systolic blood pressure (mmHg)	152.49 ± 13.91	145.08 ± 16.35	0.16	⩾ 140 mmHg
Diastolic blood pressure (mmHg)	89.55 ± 9.40	86.74 ± 9.52	0.36	⩾ 90 mmHg
Body mass index (Kg/m^2)	26.57 ± 1.07	25.36 ± 2.87	0.01	⩾ 27 kg/m^2
Waist circumference (cm)	89.74 ± 7.95	85.23 ± 7.52	0.000	⩾ 90 cm for males or ⩾ 80 cm for females
Total cholesterol (mg/dL)	220.09 ± 20.57	210.99 ± 26.82	0.000	⩾ 200 mg/dL
Triglyceride (mg/dL)	178.50 ± 38.95	144.28 ± 66.72	0.11	⩾ 200 mg/dL
AST (U/L)	25.40 ± 6.95	22.40 ± 8.15	0.01	⩾ 40 U/L
ALT (U/L)	31.36 ± 9.34	22.39 ± 10.28	0.01	⩾ 40 U/L
Uric acid (mg/dL)	6.07 ± 1.20	5.94 ± 1.29	0.76	⩾ 7 mg/dL for males or ⩾ 6 mg/dL for females

applied for continuous variables. Multiple Cox regression was used to investigate the independence of factors associated with development of GSD. $P < 0.05$ was considered statistically significant. The results are presented as mean ± SD.

RESULTS

Of 377 type 2 diabetics without GSD in 2001, 281 subjects attended the second round of abdominal ultrasound examinations in 2002. The overall attendance rate was thus about 74.5%. Subjects were considered as censored cases if the outcomes were not available. Table 1 shows that females had higher attendance rates than males (76.2% versus 72.5%), and old people (50-59 and over 70 year of age) had a slightly lower attendance rate than other age groups.

Table 2 presents gender-specific and age-specific one-year incidences of GSD. Overall incidence of GSD was 3.56% per year (95%CI: 1.78% per year-6.24% per year). This incidence shows a clear trend with age ($P = 0.04$) with values increasing monotonically: from 0% per year at age 40-49 years to 3.57% per year at age 50-59 years, 3.60% per year at age 60-69 years to 4.94% per year at older ages. There was no consistent pattern by age group. Females had a slightly higher incidence (5.00% per year versus 1.65% per year, $P = 0.12$) than males, although the gender difference was not statistically significant.

Table 3 shows the risk factors for the development of GSD in type 2 diabetics by univariate analysis. The risk factors that were significantly related to the development of GSD included age (*t*, T = 1.98, $P = 0.04$), BMI (T = 3.18, $P = 0.01$), waist circumference (T = 8.16, $P = 0.0001$), total cholesterol (T = 4.94, $P = 0.0001$), AST (T = 2.83, $P = 0.01$), and ALT (T = 2.69, $P = 0.01$).

To assess the independence of the contributions of these factors to the development of GSD, the significant variables from univariate analysis for GSD were further examined using a Cox regression model including age, BMI, waist circumference, total cholesterol, AST, and ALT. As Table 4 shows, age (RR = 1.07, 95%CI: 1.00-1.14), waist circumference (RR = 1.12, 95%CI: 1.01-1.29), and ALT (RR = 1.13, 95%CI: 1.01-1.26) appeared to be independently correlated with development of GSD.

DISCUSSION

Incidence and risk factors for the development of gallstone disease

Abdominal ultrasound for GSD screening is viewed as a robust method. Previous clinical studies have shown reliable positive (0.99-1.00) and negative (0.90-0.96) predictive

Table 4 Cox regression model of risk factors associated with the development of gallstone disease among type 2 diabetics in Kinmen

Variables	Development of gallstone disease (yes *vs* no)	
	Relative risk	(95% CI)
Sex (female *vs* male)	2.60	0.52-13.11
Age (yr)	1.07	1.00-1.14
Body mass index (Kg/m^2)	1.03	0.57-1.34
Waist circumference (cm)	1.12	1.01-1.29
Total cholesterol (mg/dL)	1.01	0.98-1.03
AST (U/L)	0.91	0.77-1.07
ALT (U/L)	1.13	1.01-1.26

values of ultrasonographic diagnosis[12]. In the present study, the annual incidence of overall GSD was higher than that in other general population-based studies[12-15], implying that type 2 diabetes might be a positive risk factor for GSD development. Possible pathogenic reasons are that type 2 diabetes combined with GSD might induce acute cholecystitis more often and have a higher probability of progression to septicemia than does gallbladder dysfunction in non-diabetic patients[16], and late-onset diabetic patients have a higher lithogenic bile index than non-diabetics after adjustment for sex and age[17]. In addition, hyperglycemia in diabetic subjects might exert effects on gallbladder motility[18].

An association between GSD and use of exogenous estrogens was confirmed[19]. The lithogenic effects of estrogen are mediated in part by an increase in bile cholesterol saturation[19]. However, previous studies showed that cholesterol GSD is common in Western populations whereas pigment GSD is major components in Taiwan[1]. Unlike result for cholesterol GSD, our results did not show a causal relationship between female sex and development of pigment GSD. The different findings for Orientals from those shown for Occidentals suggest that cholesterol GSD has not yet become a major GSD component in Taiwanese diabetic populations.

Using both univariate analysis and a multiple Cox regression model, our study also demonstrated that age is a significant risk factor for the development of GSD. This result is not concordant with results from other studies that had longer screening intervals[8,13,15]. Larger amounts of cholesterol secreted by the liver and decreases in the catabolism of cholesterol to bile acid were observed in the elderly[20]. Although the long-term exposure to many other risk factors in the elderly might account for their increased chance of developing GSD[5], age still remained a major factor leading to GSD development, irrespective of locality, standard of living, or after adjustment for other demographic and clinical characteristics in the multivariate analysis.

Several population-based studies demonstrated that liver cirrhosis represents a strong risk factor for GSD[21,22]. The annual incidence of GSD in patients with cirrhosis appears to be about eight times higher than in the general population[21]. Alanine aminotransferase (ALT) has, for some time, been viewed as a sensitive indicator of liver-cell injury[23]. Currently, the determination of serum ALT levels constitutes the most-frequently applied test for the identification of patients suffering from liver disease. This parameter also acts as a surrogate marker for disease severity and/or as an index of hepatic activity[24]. Our results showing that elevated ALT levels constitute higher risk of GSD development suggest that appropriate integrated diagnosis and therapy in the early stage of liver dysfunction might eventually enable us to prevent incident GSD. Instead of being a sign of more serious liver disease like liver cirrhosis, further studies should be conducted to explore the possibility of whether elevated ALT levels is an indicator for GSD because it indicates a fatty liver (and thus a high BMI), and early stage of chronic liver disease.

Obesity could raise the saturation of bile by increasing biliary secretion of cholesterol, the latter probably depending on a higher synthesis of cholesterol in obese subjects[25]. Being overweight at baseline was strongly associated with the incidence of GSD which was also suggested in epidemiologic studies[13]. In this follow-up study, we found that a higher waist circumference rather than a higher BMI was significantly and positively associated with GSD development. Thus abdominal obesity might be more important than BMI for identifying diabetics at high risk of GSD. One possible reason is that due to a high correlation between BMI and waist circumference (r = 0.64), waist circumference might explain the effect of BMI on GSD development in type 2 diabetic subjects. Another possible reason is that a large waist circumference might be an unambiguous indicator of excess body fat, except in the presence of abdominal tumors or ascites, and might be a better estimate of overall body fat than is BMI. In addition, from the biological perspective, BMI becomes primarily a surrogate of lean body mass when BMI and height-adjusted waist circumference are included in the same model, because the variation in BMI attributable to adiposity is essentially controlled by the height-adjusted waist circumference variable[14]. Nevertheless, further epidemiological and etiologic investigations are needed to explore the pathophysiological mechanism underlying gender-related differences in waist circumference and GSD among diabetics.

Methodological considerations

Although using a follow-up study design can clarify the temporal relationship of potential risk factors and the development of GSD, there are some limitations in the present study. First, the characteristics pertinent to the risk of type 2 diabetes for study subjects were not significantly different from non-respondents (except for age), indicating that subjects who did not return for follow-up might have more severe GSD. Also, we assumed that all the new GSD cases occurred in 2002. Since additional GSD cases could occur in subsequent years, the incidence of GSD may be underestimated. Second, all the patients had diabetes in the study population, therefore, an evaluation of the extent of GSD incidence in subjects without diabetes was difficult. Third, we did not attempt to estimate the incidence

of gallstone formation but rather the incidence of newly screened GSD. Our analysis only focused on clinically relevant GSD. Fourth, due to a shorter follow-up period, we did not have a large enough sample size to estimate the "true" effects between potential risk factors and the incidence of GSD. Further long-term studies should be conducted to explore the morbidity of GSD and plausible biological mechanisms underlying its development.

In conclusion, our reports show that the incidence of GSD is 3.56% per year. Significant risk factors for the development of GSD include not only older age, but also, higher waist circumference and elevated ALT levels among type 2 diabetics.

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S- Editor Wang J **L- Editor** Zhu LH **E- Editor** Ma WH