

Enigmatic Ectopic Fat: Prevalence of Nonalcoholic Fatty Pancreas Disease and Its Associated Factors in a Chinese Population

Chih-Yuan Wang, MD, PhD;* Horng-Yih Ou, MD, PhD;* Ming-Fong Chen, MD, PhD; Tien-Chun Chang, MD, PhD; Chih-Jen Chang, MD

Background—Fatty infiltration of the pancreas is an enigmatic manifestation of ectopic fat deposition in obesity. Studies have shown that pancreatic lipid accumulation interferes with insulin secretion in humans. However, the prevalence of fatty pancreas and its associated factors in the general population remain unclear. The aim of this study was to investigate the prevalence of fatty pancreas and its association with diabetes, nonalcoholic fatty liver disease (NAFLD), and cardiometabolic risk factors in a Chinese population.

Methods and Results—This was a cross-sectional study. A total of 8097 subjects with or without fatty pancreas (n=1297 and 6800, respectively) were recruited. Each subject was assessed by using abdominal sonography to diagnose NAFLD and fatty pancreas. Clinical and metabolic parameters were compared between groups, and their associations with fatty pancreas were examined. The prevalence of fatty pancreas was 16%. The fatty pancreas group had a significantly greater proportion of subjects with diabetes (12.6% versus 5.2%) and NAFLD (67.2% versus 35.1%) than did the non-fatty pancreas group ($P<0.001$). In the logistic regression analysis, age ($P<0.001$), general or central obesity ($P<0.001$), diabetes ($P<0.001$), and NAFLD ($P<0.001$) were independently associated with fatty pancreas after adjustment for sex, lipid profile, alanine transaminase/aspartate transaminase ratio, hypertension, smoking, alcohol drinking, and exercise.

Conclusions—The prevalence of fatty pancreas is high in the general population. Both diabetes and NAFLD are important associated factors of fatty pancreas, independent of age, sex, adiposity, and other cardiometabolic risk factors. (*J Am Heart Assoc.* 2014;3:e000297 doi: 10.1161/JAHA.113.000297)

Key Words: diabetes • nonalcoholic fatty liver disease • nonalcoholic fatty pancreas disease • obesity

Obesity is an increasing problem worldwide, with significant adverse health and economic effects.¹ Although the rate of obesity seems to have plateaued in some countries, such as the United States, the incidence of related conditions, such as diabetes, cardiovascular diseases, and several forms of cancer, is likely to rise continuously over the next 2 decades.² Furthermore, several recent studies suggest that both in the general population and subjects with coronary

artery disease, indices of abdominal obesity are a better predictor of all-cause and cardiovascular mortality than is body mass index (BMI).^{3–5}

Central obesity per se is one of the clinical intermediate phenotypes of ectopic fat deposition.⁶ In susceptible human subjects, a positive energy balance and impaired lipid storage capacity of the subcutaneous fat to store excess energy result in excess visceral adiposity and increased accumulation of fat at undesired sites (ectopic fat deposition),⁷ such as the liver, skeletal muscle, heart, and even pancreatic β cells.⁸ Fatty infiltration of the liver in the absence of excess alcohol intake and other chronic conditions of the liver is termed nonalcoholic fatty liver disease (NAFLD). Several studies have shown that NAFLD is associated with insulin resistance, type 2 diabetes, metabolic syndrome, atherosclerosis,^{9–11} and a greater risk of adverse cardiovascular events.¹² Therefore, NAFLD can be considered an early predictor of metabolic disorders, even in the normal-weight population,¹³ and early detection of NAFLD could have potential benefits in clinical practice.

Similar to the condition in the liver, excessive lipid deposition in the pancreas is referred to as pancreatic

Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taiwan (C.-Y.W., M.-F.C., T.-C.C.); Departments of Internal Medicine (H.-Y.O.) and Family Medicine (C.-J.C.), National Cheng-Kung University Hospital, College of Medicine, National Cheng-Kung University, Taiwan.

* Drs Wang and Ou contributed equally to the study.

Correspondence to: Chih-Jen Chang, MD, Department of Family Medicine, National Cheng Kung University Hospital, 138, Sheng Li Road, Taiwan, 70403. E-mail: em75210@email.ncku.edu.tw

Received July 19, 2013; accepted December 6, 2013.

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steatosis or nonalcoholic fatty pancreas disease (NAFPD).¹⁴ Long-term exposure to a high-fat diet in rats induces both interlobular and intralobular fat accumulation, inflammatory cell infiltration, and fibrosis in the pancreas, and thus damage to the normal pancreatic architecture and islets.¹⁵ Likewise, C57BL/6 mice fed a high-fat diet develop insulin resistance and features of both NAFLD and NAFPD.^{16,17}

In human studies, pancreatic fat content is closely associated with increasing BMI,¹⁸ insulin resistance,^{19,20} metabolic syndrome,^{18,19} and hepatic fat content.^{18,20–22} However, reports on the relationship between fatty pancreas and β -cell function are inconsistent. Some studies indicate that pancreatic lipid content is negatively associated with insulin secretion in nondiabetic subjects²³ or individuals with impaired fasting glucose (IFG)/impaired glucose tolerance (IGT),²⁴ while others suggest no relationship between β -cell function and pancreatic fat in subjects with IFG and/or IGT²⁵ or diabetes patients.²⁶ However, while there have been studies with a small number of selected subjects,^{18,19,22} there have been no large-scale studies to examine the prevalence and associated factors of fatty pancreas. Therefore, the aim of this study was to investigate the prevalence of fatty pancreas and its association with NAFLD and cardiometabolic risk factors in a Chinese population.

Subjects and Methods

This is a retrospective research in which all examinees who received a health checkup at the Health Management Center of National Taiwan University Hospital (NTUH) between January 2009 and December 2009 were screened. All authors declare that this research has followed all applicable institutional and government regulations concerning ethics and has been approved by the NTUH Institutional Review Board.

After an overnight 12-hour fast, all subjects received a blood test, including complete blood count, routine biochemistry, and fasting plasma glucose. Wearing light indoor clothes, each subject's body height (to the nearest 0.1 cm), weight (to the nearest 0.1 kg), and waist circumference (WC) (to the nearest 0.1 cm) were measured. The WC was performed at the end of normal expiration in duplicate on bare skin midway between the lower rib margin and the iliac crest. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Subjects with a BMI ≥ 25 kg/m² were defined as obese.²⁵ Central obesity was defined as WC ≥ 90 cm in men and ≥ 80 cm in women. Habitual physical exercise was categorized as "regular physical exercise" (vigorous exercise at least 3 times per week) and "no regular physical exercise." Cigarette smoking was categorized as "current smokers" (at least 1 pack per month, lasted for half a year) and "nonsmokers", and alcohol consumption as "drinkers" (at least one drink per week, lasted for half a year) and "nondrinkers."

For the blood pressure measurement, subjects were resting in a supine position in a quiet atmosphere, and measurements were obtained in a fasting state between 08:00 and 10:00 AM. Two blood pressure readings, separated by intervals of at least 5 minutes, were taken with an appropriate-sized cuff wrapped around the right upper arm using a DINAMAP vital signs monitor (model 1846SX; Critikon Inc). Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Blood glucose was measured by using a hexokinase method (Roche Diagnostic GmbH). Diabetes was defined according to the American Diabetes Association recommendation.²⁷ Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were determined in the central laboratory of the National Taiwan University Medical Center with an autoanalyzer (Hitachi 747E). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Low-HDL cholesterol was defined as HDL cholesterol level of < 40 mg/dL for men or < 50 mg/dL for women, and hypertriglyceridemia was defined as triglyceride level of ≥ 150 mg/dL.

Liver and pancreas sonographic examinations were carried out simultaneously by a single experienced radiologist with high-resolution ultrasonography (HPM2410A; Hewlett Packard) using a 3.5-MHz linear transducer. Both NAFLD and NAFPD were diagnosed by hepatologists in NTUH who were blind to all the medical information of the examinees. The NAFLD diagnostic criteria included the characteristic echo patterns of hepatorenal echo contrast, bright liver, deep (posterior beam) attenuation, and vascular blurring.²⁸ "Fatty pancreas" was diagnosed when there was an increase in echogenicity of the pancreatic body over that of the kidney. Because the pancreas could not be compared directly with the kidney in the same window, the examiner compared the differences between hepatic and renal echogenicity and between hepatic and pancreatic echogenicity to obtain an objective pancreatorenal echo contrast. Using this method, all subjects were classified into either the fatty pancreas or the non-fatty pancreas group. The mean interobserver percentage of agreement for ultrasound diagnosis of fatty pancreas was 72% ($\kappa=0.63$).

Subjects with the following conditions or diseases were excluded: (1) an age of < 18 or ≥ 80 years; (2) a BMI of ≥ 35 kg/m²; (3) alcohol consumption ≥ 20 g/d in the past year; (4) serum creatinine > 1.5 mg/dL; (5) any acute or chronic inflammatory disease as determined by a leukocyte count $> 10\,000$ /mm³ or clinical signs of infection; and (6) any other major diseases, including generalized inflammation or advanced malignant diseases contraindicating this study. All

authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

SPSS software (version 17.0; SPSS) was used for statistical analysis. All normally distributed continuous variables were expressed as mean±SD. Study subjects were divided into 2 groups based on the presence or absence of fatty pancreas, and their clinical characteristics were compared using Student *t* test (in continuous variables) or χ^2 tests (in categorical variables). The Kruskal–Wallis test was used in cases where the data was nonparametric. Logistic regression analysis adjusted for general obesity in model 1 and central obesity in model 2 was used to identify the clinical and metabolic factors

independently associated with fatty pancreas. A value of $P<0.05$ was considered statistically significant.

Results

In the final analysis, a total of 8097 subjects were included and classified into fatty pancreas (n=1297, 16%) and non-fatty pancreas (n=6800, 84%) groups. Table 1 shows the comparison of clinical characteristics between groups. There were significant differences in age, sex, WC, BMI, systolic/diastolic blood pressure, fasting plasma glucose, hemoglobin A_{1C}, alanine transaminase (ALT), aspartate transaminase (AST), ALT/AST ratio, creatinine, total cholesterol, triglycerides, HDL cholesterol, and LDL/HDL cholesterol ratio. The fatty pancreas group had a significantly greater proportion of

Table 1. Clinical and Laboratory Characteristics of Subjects

	Fatty Pancreas		P Value
	(+)	(-)	
N	1297	6800	—
Age, y	56±10	51±11	<0.001
Gender, male (%)	62	54	<0.001
Waist circumference, cm	91±8	84±8	<0.001
BMI, kg/m ²	25.8±3.0	23.5±3.0	<0.001
Systolic blood pressure, mm Hg	124±14	117±15	<0.001
Diastolic blood pressure, mm Hg	73±9	69±10	<0.001
Fasting plasma glucose, mg/dL	101±22	94±16	<0.001
Hemoglobin A _{1C} , %	5.8±0.8	5.6±0.6	<0.001
AST, U/L	26±10	24±10	<0.001
ALT, U/L	32±20	27±21	<0.001
ALT/AST ratio	1.2±0.4	1.1±0.4	<0.001
Creatinine, mg/dL	1.0±0.17	0.97±0.17	<0.001
Total cholesterol, mg/dL	208±35	203±34	<0.001
Triglycerides, mg/dL*	141±77	112±76	<0.001
Hypertriglyceridemia, %	36.2	20.2	<0.001
HDL, mg/dL	47±11	52±13	<0.001
Low-HDL, %	39.7	27.1	<0.001
LDL, mg/dL	122±32	115±31	<0.001
Hypertension, %	12.7	7.1	<0.001
Obesity, %	56.7	29.4	<0.001
Central obesity, %	68.7	42.2	<0.001
Regular physical exercise (≥3 times/wk), %	30.8	29.3	NS
Current smoking, %	11.1	10.8	NS
Current alcohol drinking, %	1.5	1.4	NS

Data expressed as mean±SD. Hemoglobin A_{1C} indicates glycosylated hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

*Kruskal–Wallis test.

subjects with diabetes (12.6% versus 5.2%) and NAFLD (67.2% versus 35.1%), compared with the non-fatty pancreas group ($P<0.001$; Figure), and similar results were found for hypertension (12.7% versus 7.1%), general obesity (56.7% versus 29.4%), central obesity (68.7% versus 42.2%), low-HDL cholesterol (39.2% versus 27.1%), and hypertriglyceridemia (36.2% versus 20.2%). There were no significant differences in the lifestyle factors, such as exercise, alcohol consumption, and smoking, between the 2 groups.

To investigate the effects of clinical variables on the risk of fatty pancreas, we performed logistic regression analysis. In nondiabetic individuals, age ($P<0.001$), general or central obesity ($P<0.001$), hypertriglyceridemia ($P=0.001$), fatty liver ($P<0.001$), and ALT/AST ratio ($P=0.002$) were independently associated factors of fatty pancreas (Table 2). In the whole group of subjects (Table 3), age ($P<0.001$), general obesity ($P<0.001$), diabetes ($P<0.001$), low-HDL cholesterol ($P<0.05$), hypertriglyceridemia ($P<0.001$), fatty liver ($P<0.001$), and ALT/AST ratio ($P=0.004$) were independently associated with fatty pancreas after adjustment for sex, hypertension, smoking, alcohol drinking, and exercise (model 1). The results were still the same when substituting general obesity with central obesity in the logistic regression analysis (model 2).

Furthermore, we evaluated the relationships between fatty pancreas and NAFLD and diabetes, with adjustment of cardiometabolic risk factors (Table 4). We found that age, hypertension, low-HDL cholesterol, hypertriglyceridemia, ALT/AST ratio, fatty pancreas, and NAFLD were significantly associated with diabetes. The ORs of diabetes for fatty pancreas and NAFLD were 1.593 (95% CI 1.300 to 1.953) and 2.235 (95% CI 1.783 to 2.801), respectively.

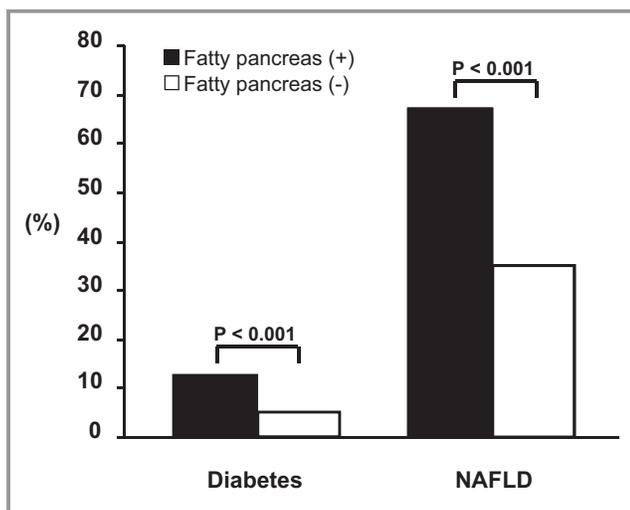


Figure. The prevalence of diabetes and nonalcoholic fatty liver disease (NAFLD) in subjects with or without fatty pancreas.

Discussion

To the best of our knowledge, this is the first study to investigate the prevalence of fatty pancreas, an enigmatic ectopic fat, and its risk factors in a large cohort. Our results explicitly indicate that NAFLD and diabetes were strongly associated with fatty pancreas after adjustment for age, sex, adiposity, ALT/AST ratio, and other cardiometabolic risk factors.

To date, there are only a few studies regarding pancreatic steatosis, and its pathophysiological mechanisms are largely unknown. It was Ogilvie who first coined the term “pancreatic lipomatosis” for “excessive storage of fat in pancreatic tissue.”²⁹ The term “lipomatosis” is now replaced by “steatosis.” Recently, van Greenen et al developed the first histopathological grading system, the “pancreatic lipomatosis score,” for the scoring of pancreatic steatosis.²¹ This grading system emphasizes the distribution of intralobular, interlobular, and total pancreatic fat. However, no dichotomous histopathological cutoff has been yet proposed to define “fatty pancreas.” In addition, there has been no study exploring the link between the pathological findings of fatty pancreas with those of imaging studies. One reason may be due to the difficulty of rapid autolysis encountered in autopsy specimens.³⁰ Furthermore, in contrast to the widely used liver biopsy for various diagnostic purposes, pancreatic biopsy has not been suggested and regularly performed in clinical practice.

Previous studies have shown that fatty pancreas is associated with BMI,^{18,22,24} visceral fat,¹⁹ and fatty liver.^{18,22,31} However, an association of NAFLD and fatty pancreas has never been demonstrated in large-cohort studies. Most of these studies had a small sample size ($n=120$ to 293), and the subjects are highly selective, either “scheduled for endoscopic ultrasound” for a diseased state^{18,22,31} or “visited the obesity clinic”¹⁹ for investigation, which limits the generalizability of their results. In contrast, our study recruited a general population admitted for a physical checkup. With a significantly larger number of subjects, we observed that the prevalence of fatty liver was 16%, which could be considered a reliable estimate for the general population. Furthermore, we found that both NAFLD and BMI or WC were independently associated with fatty pancreas.

From the viewpoint of ectopic fat deposition, it is conceivable that NAFLD and fatty pancreas are closely related. In an animal study, mice fed a high-fat diet develop obesity and insulin resistance accompanied by features of both NAFLD and NAFPD.¹⁶ However, a longer duration of high-fat diet feeding increased triglyceride content in the pancreas but not the liver, suggesting that the pancreas is particularly susceptible to ectopic fat deposition.³² Although

Table 2. Logistic Regression Analysis Showing Factors Independently Associated With Fatty Pancreas in Nondiabetic Individuals

	Model 1			Model 2		
	OR	95% CI	P Value	OR	95% CI	P Value
Age, y	1.050	1.042 to 1.057	<0.001	1.046	1.038 to 1.053	<0.001
Sex, male vs female	0.845	0.682 to 1.047	0.124	1.180	0.945 to 1.474	0.143
General obesity, yes vs no	1.908	1.641 to 2.219	<0.001	—	—	—
Central obesity, yes vs no	—	—	—	2.163	1.853 to 2.524	<0.001
Hypertension, yes vs no	1.026	0.821 to 1.282	0.823	1.069	0.856 to 1.335	0.558
Low-HDL, yes vs no	1.157	0.996 to 1.345	0.057	1.160	0.998 to 1.348	0.053
Hypertriglyceridemia, yes vs no	1.321	1.126 to 1.549	0.001	1.322	1.127 to 1.550	0.001
NAFLD, yes vs no	2.221	1.895 to 2.602	<0.001	2.197	1.878 to 2.569	<0.001
ALT/AST	1.385	1.128 to 1.701	0.002	1.382	1.125 to 1.698	0.002
Creatinine	1.174	0.658 to 2.095	0.588	1.294	0.724 to 2.312	0.384
Current smoking, yes vs no	1.049	0.836 to 1.315	0.681	1.014	0.808 to 1.273	0.902
Current alcohol drinking, yes vs no	1.203	0.961 to 1.506	0.106	1.170	0.933 to 1.466	0.174
Regular physical exercise, yes vs no	0.835	0.716 to 1.010	0.073	0.849	0.727 to 1.025	0.111

ALT indicates alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

two human studies using magnetic resonance spectroscopy or imaging failed to demonstrate the relationship between pancreatic and hepatic fat, their results are limited by the small number of study subjects (n=36 and 17).^{23,33} In contrast, one recent histopathological study examining the relationship between pancreas fat and liver fat suggested that a cutoff of >15% total pancreatic fat is significantly correlated with hepatic steatosis. Meanwhile, both interlobular and total

pancreatic fat were related to macrovesicular liver fat and NAFLD activity score, but the relationship disappeared after adjustment for BMI. This result implies the relationship between NAFLD and fatty pancreas is mediated by general obesity.²¹ However, we demonstrated in the present study that adjustment for general or central obesity did not affect the association between NAFLD and fatty pancreas. This discrepancy may be attributed to the differences in the study

Table 3. Logistic Regression Analysis Showing Factors Independently Associated With Fatty Pancreas in the Whole Subjects

	Model 1			Model 2		
	OR	95% CI	P Value	OR	95% CI	P Value
Age, y	1.048	1.041 to 1.055	<0.001	1.044	1.037 to 1.051	<0.001
Sex, male vs female	0.839	0.702 to 1.040	0.083	1.138	0.927 to 1.398	0.217
General obesity, yes vs no	1.864	1.618 to 2.146	<0.001	—	—	—
Central obesity, yes vs no	—	—	—	2.046	1.769 to 2.366	<0.001
Hypertension, yes vs no	0.993	0.811 to 1.216	0.944	1.036	0.847 to 1.268	0.731
Diabetes, yes vs no	1.465	1.194 to 1.797	<0.001	1.474	1.202 to 1.808	<0.001
Low-HDL, yes vs no	1.166	1.013 to 1.342	0.033	1.170	1.016 to 1.346	0.029
Hypertriglyceridemia, yes vs no	1.282	1.104 to 1.487	0.001	1.289	1.111 to 1.496	0.001
NAFLD, yes vs no	2.279	1.960 to 2.650	<0.001	2.279	1.963 to 2.644	<0.001
ALT/AST	1.339	1.104 to 1.625	0.003	1.337	1.102 to 1.622	0.003
Creatinine	1.332	0.780 to 2.274	0.293	1.443	0.845 to 2.465	0.179
Current smoking, yes vs no	0.995	0.804 to 1.232	0.965	0.964	0.778 to 1.195	0.740
Current alcohol drinking, yes vs no	1.183	0.958 to 1.461	0.119	1.159	0.937 to 1.433	0.174
Regular physical exercise, yes vs no	0.875	0.758 to 1.010	0.067	0.890	0.771 to 1.027	0.111

ALT indicates alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

Table 4. Logistic Regression Analysis for Factors Associated With Diabetes

	Diabetes		
	OR	95% CI	P Value
Age, y	1.087	1.076 to 1.099	<0.001
Creatinine	1.071	0.509 to 2.255	0.856
ALT/AST ratio	2.103	1.602 to 2.760	<0.001
Hypertension, yes vs no	1.413	1.098 to 1.819	0.007
Sex, female vs male	1.1282	0.957 to 1.718	0.096
NAFLD, yes vs no	2.235	1.783 to 2.801	<0.001
Fatty pancreas, yes vs no	1.593	1.300 to 1.953	<0.010
Low-HDL cholesterol, yes vs no	1.4567	1.201 to 1.792	<0.001
Hypertriglyceridemia, yes vs no	1.471	1.196 to 1.808	<0.001
Central obesity, yes vs no	1.216	0.982 to 1.506	0.073
Current smoking, yes vs no	1.281	0.947 to 1.733	0.108
Current alcohol drinking, yes vs no	0.954	0.696 to 1.309	0.772
Regular physical exercise, yes vs no	1.108	0.907 to 1.353	0.314

ALT indicates alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

design, the methods by which fatty infiltration of liver and pancreas were estimated, and the selection of study subjects, because our cohort was younger, had a larger sample size, and generally was healthier than that in the earlier study.

In contrast to NAFLD, the pathophysiological mechanisms and clinical relevance of fatty pancreas remain unclear. In the present study, we found that diabetes mellitus was independently associated with fatty pancreas, and vice versa. Subjects with fatty pancreas had an increased risk of diabetes (OR 1.593) compared with those without it. Many previous studies have indicated that fatty infiltration of the pancreas may contribute to a loss of β -cell mass and function,^{34,35} which possibly leads to the development of diabetes.³⁶ In obese Zucker diabetic fatty rats, the triacylglycerol content of islets in prediabetic rats increased significantly and preceded the development of diabetes.³⁷ However, in human studies, the data are inconsistent. One study finds that pancreatic fat, as measured by using magnetic resonance spectroscopy or magnetic resonance imaging, is negatively associated with glucose tolerance test–based measures of insulin secretion in nondiabetic subjects.²³ Moreover, the results of the regression analysis in Heni et al indicated that pancreatic fat is a stronger determinant of impaired insulin secretion than visceral fat in subjects with prediabetes.²⁴ In contrast to these studies, another study that used the gold standard hyperglycemic clamp found no relation between pancreatic fat content and β -cell function in subjects with impaired glucose metabolism.²⁵ Similarly, Tushuizen et al reported no association between pancreatic fat and β -cell dysfunction in diabetic patients.²³ This lack of association suggests that once

diabetes occurs, factors additional to pancreatic fat account for further declines in β -cell functioning.²³

In addition, whether diabetic patients have higher pancreatic fat content remains inconclusive. Using different techniques to assess the pancreatic fat content, Tushuizen et al²³ and Lingvay et al³⁸ found diabetic subjects had a significantly higher pancreatic fat content, defined by using magnetic resonance spectroscopy or magnetic resonance imaging, than nondiabetic ones, but Saisho et al, in their much larger cohort, observed no difference as measured with computed tomography.³⁹ In the present study, we showed that after controlling for age, sex, general or visceral obesity, NAFLD, and cardiometabolic risk factors, diabetes was significantly associated with fatty pancreas. This result is compatible with the notion that once diabetes develops, fatty replacement of damaged tissue may contribute to the extra-islet pancreatic fat.²² Alternatively, the increased levels of malonyl-coenzyme A caused by hyperglycemia may inhibit carnitine palmitoyltransferase-1, leading to a decrease in mitochondrial β -oxidation and further stimulation of intracellular triglyceride accumulation.⁴⁰ In addition, our finding that fatty pancreas was positively associated with age is compatible with the results of previous studies,^{39,41} and this may be due to the age-related decrease in pancreatic parenchymal volume and increased pancreatic fat content in the older subjects.^{39,41}

There are some limitations in this work, as follows. First, because this study used a cross-sectional design, it does not allow causal inference between fatty pancreas and diabetes or NAFLD, although the causal relationship is expected to link fatty pancreas with diabetes, not vice versa. Second, although fatty pancreas is associated with impaired insulin secretion

and insulin resistance, we did not measure the serum insulin level because it is not part of a routine health checkup, and we did not have the specimen for this measurement. Instead, we adjusted components of metabolic syndrome as a proxy for insulin resistance. Third, because the racial differences in the fatty pancreas have not yet been reported, more studies on this topic are needed. Fourth, we did not adjust for socioeconomic parameters, such as educational level or income, to investigate their possible effects on fatty pancreas because we did not have these data in our database. However, to the best of our knowledge, no previous studies have suggested any role for these socioeconomic variables in the prevalence of fatty pancreas. Finally, in this work, the diagnosis of fatty pancreas and NAFLD was made with sonography but not confirmed pathologically. Although magnetic resonance-based techniques are frequently used for measurement of pancreatic fat content, they are expensive and difficult to perform in clinical practice for a large-scale cohort.⁷ On the other hand, abdominal sonography is an established noninvasive and reproducible tool as a screening modality, which has been shown to be accurate and cost-effective in diagnosing fatty pancreas in previous cohort studies.^{7,19,42} The results of these earlier works support its use in the present study. More important, increased deposition of fat, which has infiltrated along the pancreatic septa, has been shown to be a major determining factor of pancreatic echogenicity in one study evaluating pancreatic echogenicity and its correlation with the morphologic appearance of the pancreas in computed tomography.²⁹ Therefore, it seems plausible to assume that the “fatty pancreas” found on ultrasonography is associated with increased fat deposition pathologically. Furthermore, the ultrasonography data were interpreted by hepatologists who were blind to the examinees’ past history or biochemical results, to reduce potential bias.

In conclusion, in this work we found a high prevalence of fatty pancreas via abdominal sonography in a large Chinese cohort drawn from the general population. Our results also show that both diabetes and NAFLD are important associated factors of fatty pancreas independent of age, sex, adiposity, and other cardiometabolic risk factors. Because obesity is one of the most important challenges to public health worldwide, there is a need for further studies to better understand ectopic pancreatic fat deposits.

Author Contributions

C.-Y. Wang designed and conducted the study, collected the data, analyzed and interpreted the data, drafted the manuscript, and contributed to the discussion. H.-Y. Ou analyzed the data, interpreted the data, drafted the manuscript, and contributed to the discussion. T.-C. Chang supervised the study and contributed

to the discussion. M.-F. Chen contributed to the study design, supervised the study, and reviewed/edited the manuscript. C.-J. Chang analyzed and interpreted the data, contributed to the discussion, and reviewed/edited the manuscript. All authors prepared and approved the manuscript for submission.

Disclosures

None.

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J Am Heart Assoc. 2014;3:e000297; originally published February 26, 2014;
doi: 10.1161/JAHA.113.000297

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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