

Combined Effect of Nonalcoholic Fatty Liver Disease and Impaired Fasting Glucose on the Development of Type 2 Diabetes

A 4-year retrospective longitudinal study

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OBJECTIVE—To evaluate whether there is a difference in the association between nonalcoholic fatty liver disease (NAFLD) and incident diabetes based on the presence of impaired fasting glucose.

RESEARCH DESIGN AND METHODS—A total of 7,849 individuals (5,409 men and 2,440 women) without diabetes, who underwent comprehensive health check-ups annually for 5 years, were categorized into four groups by the presence of impaired fasting glucose and NAFLD at baseline. The association between NAFLD and incident diabetes was evaluated separately in groups with normal and impaired fasting glucose.

RESULTS—For 4 years, the incidence of diabetes in the NAFLD group was 9.9% compared with 3.7% in the non-NAFLD group, with multivariable-adjusted hazard ratio of 1.33 (95% CI 1.07–1.66). However, this higher risk for diabetes only existed in the impaired fasting glucose group.

CONCLUSIONS—Our study suggests that NAFLD has an independent and additive effect on the development of diabetes under conditions of impaired insulin secretion.

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Nonalcoholic fatty liver disease (NAFLD) is reported to have an effect on incident diabetes (1–3). NAFLD coexists in a substantial percentage of patients with impaired fasting glucose (IFG) (4). This study was designed to ascertain whether there is a difference in the association between NAFLD and incident diabetes according to the presence of IFG.

RESEARCH DESIGN AND METHODS

Initial data were obtained from 10,950 individuals who participated in comprehensive health check-ups

annually for 5 years (between January 2005 and December 2009). Among these, 3,101 were excluded for alcohol intake >20 g/day, type 1 or type 2 diabetes, positive serologic markers for hepatitis B or C virus, liver cirrhosis, or missing data. All analyses were performed on 7,849 individuals (5,409 men and 2,440 women) who were aged ≥ 20 years (mean age, 44.5 years; Supplementary Table 1).

We categorized all participants into four groups according to the presence of IFG and NAFLD in the 2005 records. The hazard ratio (HR) of incipient diabetes associated with NAFLD was estimated

overall and separately in the normal fasting glucose (NFG) and IFG groups using Cox proportional hazards analysis. Also, we evaluated the combined effect of IFG and NAFLD on incident diabetes. Statistical analysis was performed using SPSS 17 software (SPSS, Chicago, IL).

Anthropometric and biochemical variables were measured as described previously (5). Lifestyle information was self-reported.

All subjects had an abdominal ultrasonogram (Logic Q700 MR, GE, Milwaukee, WI), and fatty liver was diagnosed based on known standard criteria, including hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring, using a 3.5 MHz probe (6). Several experienced radiologists performed the ultrasound examinations.

IFG was defined as fasting plasma glucose between 100 and 125 mg/dL (7). The development of diabetes was assessed from the annual records of all participants and defined as fasting plasma glucose ≥ 126 mg/dL or A1C $\geq 6.5\%$ (7). Also, subjects who had a history of diabetes or currently used insulin or oral antidiabetic drugs based on the self-report questionnaire at each visit were considered to have developed diabetes.

RESULTS

During the mean follow-up of nearly 4 years (47.4 ± 5.0 months), 435 of the 7,849 participants (5.5%) progressed to diabetes. The incidence of diabetes was 9.9% in the NAFLD group and 3.7% in the non-NAFLD group. In a multivariate model adjusted for age, sex, BMI, triglyceride, HDL cholesterol, smoking status, physical activity, alcohol intake, and coexisting IFG, subjects with NAFLD had an HR of 1.33 (95% CI 1.07–1.66) for the development of diabetes compared with the non-NAFLD groups (Supplementary Table 2). However, the significance of this association between NAFLD and incident diabetes was different based on whether IFG was present.

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Table 1—HRs of incident diabetes for the NAFLD and non-NAFLD groups according to the presence of IFG and combined effects of NAFLD with IFG on the development of diabetes

Variable	NFG (n = 5,800)		P	IFG (n = 2,049)		P
	Non-NAFLD	NAFLD		Non-NAFLD	NAFLD	
Subjects (N)	4,353	1,447		1,204	845	
Subjects who developed diabetes, n (%)	66 (1.5)	47 (3.2)		142 (11.8)	180 (21.3)	
Person-years of follow-up	17,363	5,773		4,646	3,155	
Incident case of diabetes per 100 person-years (n)	0.4	0.8		3.1	5.7	
Adjusted HR (95% CI)*						
Age and sex	1 (reference)	2.01 (1.35–2.98)	0.001	1 (reference)	1.86 (1.48–2.33)	<0.001
Age, sex, BMI, TG, HDL-C, and systolic BP	1 (reference)	1.37 (0.87–2.18)	0.167	1 (reference)	1.31 (1.02–1.69)	0.035
Multivariate†	1 (reference)	1.39 (0.88–2.23)	0.148	1 (reference)	1.30 (1.02–1.68)	0.037
Adjusted HR (95% CI)*						
Age and sex	1 (reference)	2.03 (1.39–2.97)		7.52 (5.60–10.09)	13.97 (10.43–18.71)	
Age, sex, BMI, TG, HDL-C, and systolic BP	1 (reference)	1.37 (0.92–2.04)		6.68 (4.95–9.00)	8.83 (6.41–12.16)	
Multivariate†	1 (reference)	1.39 (0.93–2.08)		6.79 (5.03–9.16)	8.95 (6.49–12.35)	

BP, blood pressure; HDL-C, HDL cholesterol; TG, triglycerides. *Estimated from Cox proportional hazards analysis. †The multivariate Cox regression model was adjusted for baseline age, sex, BMI, TG, HDL-C, systolic BP, concurrent presence of IFG, smoking status (never smoked, former smoker, or current smoker), physical activity (a minimum of 30 min at least 3 times per week or less), and alcohol consumption (current drinker or not).

Participants with NAFLD had a significantly higher HR for the development of diabetes only if IFG was present, reaching 1.30 (95% CI 1.02–1.68), whereas the HR was 1.39 (95% CI 0.88–2.23) in the NFG groups. After multivariable adjustment, those with IFG alone had an HR of 6.79 (95% CI 5.03–9.16) for the development of diabetes compared with NFG subjects without NAFLD, whereas those with NAFLD alone had an HR of 1.39 (95% CI 0.93–2.08). Among the subjects with IFG and NAFLD, we observed further increased risk of diabetes, with an HR of 8.95 (95% CI 6.49–12.35; Table 1 and Supplementary Fig. 1).

CONCLUSIONS—When we separately analyzed the association between NAFLD and incident diabetes based on the presence of IFG, an independent association was only shown in the subjects with IFG. Early in the natural history of type 2 diabetes, insulin resistance is well established, but glucose tolerance remains normal because of a compensatory increase in insulin secretion (8,9). Although animal studies showed that fat accumulation in the liver inhibited insulin signaling in hepatocytes, which decreased insulin activity to glycogen synthase and increased gluconeogenesis (10,11), the resulting elevation of insulin

concentration can overcome hepatic insulin resistance and cause a nearly normal suppression of hepatic glucose products (9), which could explain our inability to show an independent association between NAFLD and incident diabetes in the individuals with NFG. However, the presence of IFG indicates that β -cells already have impairment of insulin secretion and are unable to maintain a compensatory increase in insulin secretion (12). Our results differed according to the presence of IFG, suggesting that NAFLD has an independent effect on the development of diabetes under conditions of impaired insulin secretion.

The comparison of NAFLD with IFG helps us understand the relative importance of NAFLD in the development of diabetes. Although subjects with NAFLD alone were more obese and insulin resistant than those with IFG alone (Supplementary Table 3), the risk for incident diabetes was much higher in subjects with IFG alone than in those with NAFLD alone. However, the high risk of diabetes among subjects with IFG exaggerated by the presence of NAFLD, even after adjustment for BMI and other risk factors, indicates that IFG and NAFLD have an additive effect on the development of diabetes.

Several limitations to this study should be considered. The lack of a 2-h postload glucose test is a limitation because it might have resulted in inclusion of subjects with undiagnosed diabetes at baseline. The presence of impaired glucose tolerance was not considered, and this might also have an effect on the study results. Ultrasonography was used to diagnose fatty liver. Despite being considerably accurate, ultrasonography cannot identify fatty infiltration of the liver below the threshold of 30% (13). NAFLD is closely associated with abdominal obesity (14). However, our analysis was not adjusted for waist circumference reflecting abdominal obesity. Finally, we did not consider the use of other drugs for dyslipidemia in our analysis, and that might have influenced glucose levels (15).

This study suggests that NAFLD is an independent risk factor for diabetes. This independent association is shown particularly in individuals with IFG, indicating that NAFLD has an independent and additive effect on the development of diabetes under conditions of impaired insulin secretion.

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