Hypertriglyceridemia is an Independent Risk Factor for Development of Impaired Fasting Glucose and Diabetes Mellitus: a 9-year Longitudinal Study in Japanese

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Abstract

Objective Hypertriglyceridemia is often associated with impaired fasting glucose (IFG) and diabetes mellitus. But the contribution of hypertriglyceridemia to the development of IFG and diabetes mellitus remains unclear. We evaluated whether or not hypertriglyceridemia is a risk factor for the development of IFG and diabetes mellitus.

Methods From 1990 through 1999, 7,222 Japanese with normoglycemia at baseline were followed. Fasting plasma glucose levels were measured. IFG and diabetes mellitus were defined by ADA criteria.

Result The multivariate-adjusted relative risks for the development of IFG were 1.38 for hypertriglyceridemia ($p=0.001$), 1.30 for obesity ($p=0.003$), 1.29 for hypertension ($p=0.007$), 1.26 for family history of diabetes ($p=0.027$), and 1.02 for age ($p=0.035$). The multivariate-adjusted relative risks for the development of diabetes mellitus were 1.003 for triglyceride level ($p=0.013$), 1.30 for level of body mass index ($p=0.003$), and 2.38 for family history of diabetes ($p=0.001$).

Conclusion Hypertriglyceridemia is an independent risk factor for the development of IFG and diabetes mellitus in Japanese patients.

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Key words: hypertension, obesity

Introduction

Obesity, hypertension, diabetes mellitus, and hypertriglyceridemia are established coronary risk factors. Associations between obesity, hypertension, diabetes mellitus, and hypertriglyceridemia in coronary disease have been reported in many studies (1–4). Impaired fasting glucose defined by the 1997 American Diabetes Association criteria also has a high

mortality of ischemic heart disease (5–8). But the recent studies have been reported that impaired glucose tolerance as defined by the 1999 World Health Organization criteria is a risk factor for atherosclerosis, but impaired fasting glucose is not a risk factor (9, 10). However, impaired fasting glucose has a high incidence of the development of diabetes (11).

Although these risk factors are related to insulin resistance, the relationships between obesity, hypertension, impaired fasting glucose, diabetes, and hypertriglyceridemia are not clear (12–14). Obesity and insulin resistance are risk factors for the development of hypertension in several cross-sectional and longitudinal studies. Interestingly, hypertension, insulin resistance, and obesity are also risk factors for the development of diabetes mellitus (15–17).

A few studies state that hypertriglyceridemia is a risk factor for the development of impaired fasting glucose and diabetes mellitus (18–20). But there is also a study which showed that hypertriglyceridemia is not risk factor for the development of diabetes mellitus (21). Therefore, we investigated in a prospective study whether hypertriglyceridemia is a risk factor for the development of impaired fasting glucose and diabetes mellitus in the Japanese.

Subjects and Methods

Subjects

From January 1990 through December 1999, 14,766 Japanese were examined in the Health Examination Center of Kouseiren Takaoka Hospital, Takaoka City, Japan. Follow-up examinations over the 9-year period were carried out in 7,222 normoglycemic Japanese (3,306 men and 3,916 women) who were aged 18–85 years at their baseline. The participation rate was 48.9%. The average follow-up was 4.5 years.

Blood pressure measurement

Blood pressure was determined by a mercury sphygmomanometer in the sitting position. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pres-

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sure ≥ 90 mmHg. Also, hypertension was defined as a clinical diagnosis of hypertension with treatment.

Blood examinations

The subjects gave blood specimens during fasting for 12 hours. The levels of glucose and triglyceride were measured by the enzymatic assay. Impaired fasting glucose and diabetes mellitus were defined by the 1997 American Diabetes Association criteria (22). Impaired fasting glucose was defined as a fasting glucose level of 110–125 mg/dl. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dl or more. Also, diabetes mellitus was defined as being placed on treatment by a physician. Hypertriglyceridemia was defined as a triglyceride level of 150 mg/dl or more. Also, hypertriglyceridemia was defined as a clinical diagnosis of hypertriglyceridemia with treatment.

Obesity

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI level of 25.0 kg/m² or more.

Statistical methods

All statistical analyses were performed with SPSS version 10.1. Differences between hypertriglyceridemic and normotriglyceridemic subjects in baseline characteristics were analyzed using Student's *t* tests. Multivariate Cox regression models were applied to assess the risk factors for impaired fasting glucose and diabetes mellitus.

Results

Baseline examination

Table 1 shows the clinical data of subjects with hypertriglyceridemia and without hypertriglyceridemia at baseline. The mean levels of blood pressure and fasting plasma glucose and BMI of subjects with hypertriglyceridemia and without hypertriglyceridemia were within the normal range. But subjects with hypertriglyceridemia were significantly more obese ($p < 0.001$) and had significantly higher blood pressure ($p < 0.001$) and a higher glucose concentration ($p < 0.001$) than subjects

without hypertriglyceridemia.

Risk factors for development of impaired fasting glucose and diabetes mellitus

Of 7,222 initially normoglycemic subjects, 638 subjects (8.8%) developed impaired fasting glucose and 114 subjects (1.6%) developed diabetes mellitus during the follow-up. In Cox regression model, the cumulative incidences of impaired fasting glucose are 32% in obesity and 16% in non-obesity subjects in 9 years (Fig. 1). Otherwise, the cumulative incidences of diabetes mellitus are 8% in obese and 4% in non-obese subjects. The relative risks of obesity for the development of impaired fasting glucose and diabetes mellitus are respectively 1.87 (95% CI 1.58–2.21, $p < 0.001$) and 2.12 (95% CI 1.44–3.13, $p < 0.001$).

The cumulative incidences of impaired fasting glucose are 34% in hypertensive subjects and 17% in normotensive subjects (Fig. 2). The cumulative incidences of diabetes mellitus are 7% in hypertensive subjects and 4% in normotensive subjects. The relative risks of hypertension for the development of impaired fasting glucose and diabetes mellitus are respectively 2.17 (95% CI 1.53–2.19, $p < 0.001$) and 1.81 (95% CI 1.18–2.78, $p < 0.006$).

The cumulative incidences of impaired fasting glucose are 33% in hypertriglyceridemia and 17% in normotriglyceridemia (Fig. 3). The cumulative incidences of diabetes mellitus are 8% in hypertriglyceridemia and 4% in normotriglyceridemia. The relative risks of hypertriglyceridemia for development of impaired fasting glucose and diabetes mellitus are respectively 1.87 (95% CI 1.57–2.23, $p < 0.001$) and 2.03 (95% CI 1.34–3.07, $p < 0.001$).

Sex, age, BMI, family history of diabetes, hypertension, cigarette smoking, and fasting plasma glucose at baseline were adjusted. In multivariate-adjusted Cox regression model, age, obesity, hypertension, and hypertriglyceridemia had respectively 1.009-fold (95% CI 1.001–1.018, $p = 0.035$), 1.30-fold (95% CI 1.09–1.55, $p = 0.003$), 1.29-fold (95% CI 1.07–1.55, $p = 0.007$), and 1.38-fold (95% CI 1.15–1.66, $p = 0.001$) risk for development of impaired fasting glucose (Table 2). Obesity, hypertension, and hypertriglyceridemia in multivariate-adjusted Cox regression model of diabetes mellitus did not have a sig-

Table 1. Clinical Data of Subjects at Baseline According to the Baseline Serum Triglyceride Levels

	Normotriglyceridemia	Hypertriglyceridemia	p-value
n (m/f)	5,999 (2,512/3,487)	1,223 (794/429)	
Age (yr)	52.3 $\pm$ 10.5	53.3 $\pm$ 10.3	ns
Systolic BP (mmHg)	118.4 $\pm$ 16.7	122.4 $\pm$ 17.8	0.001
Diastolic BP (mmHg)	75.6 $\pm$ 10.8	78.8 $\pm$ 10.8	0.001
BMI (kg/m ²)	22.6 $\pm$ 2.7	24.4 $\pm$ 2.7	0.001
Fasting plasma glucose (mg/dl)	90.2 $\pm$ 8.2	92.2 $\pm$ 8.1	0.001
Triglyceride (mg/dl)	87.3 $\pm$ 27.8	216.9 $\pm$ 85.8	0.001

Values are shown in means $\pm$ SD.

Figure 1. Incidence of newly developed impaired fasting glucose and diabetes in obesity and non-obesity.

Figure 2. Incidence of newly developed impaired fasting glucose and diabetes in hypertension and normotension.

nificant Hazard ratio. However, the levels of body mass index and triglyceride had 1.30-fold (95% CI 1.02–1.16, $p=0.003$), and 1.003-fold (95% CI 1.001–1.005, $p=0.013$) risk for the development of diabetes mellitus (Table 3).

Discussion

In other studies, the incidence of the development of impaired glucose tolerance and diabetes mellitus has ranged from 15 to 45% for over 10 years (15, 23, 24). In this study, the cumulative incidences of development of impaired fasting glu-

Risk Factors for IFG and Diabetes Mellitus

Figure 3. Incidence of newly developed impaired fasting glucose and diabetes in hypertriglyceridemia and normotriglyceridemia.

Table 2. Cox Regression Model of Impaired Fasting Glucose Incidence, Adjusted for Age, Obesity, Hypertension, and Hypertriglyceridemia

	Hazard ratio	95%CI	p-value
Age	1.009	1.001–1.018	0.035
Obesity	1.30	1.09–1.55	0.003
Hypertension	1.29	1.07–1.55	0.007
Hypertriglyceridemia	1.38	1.15–1.66	0.001
Sex	0.91	0.76–1.01	ns
Fasting plasma glucose at baseline (mg/dl)	1.38	1.14–1.16	0.001
Family history of DM	1.26	1.03–1.56	0.027

Table 3. Cox Regression Model of Diabetes Mellitus Incidence, Adjusted for Age, Obesity, Hypertension, and Hypertriglyceridemia

	Hazard ratio	95%CI	p-value
Age	1.02	1.00–1.04	0.046
BMI (kg/m ²)	1.30	1.02–1.16	0.003
Hypertension	1.21	0.79–1.87	ns
Triglyceride (mg/dl)	1.003	1.001–1.005	0.013
Sex	0.79	0.51–1.23	ns
Fasting plasma glucose at baseline (mg/dl)	1.19	1.16–1.23	0.001
Family history of DM	2.38	1.59–3.57	0.001

case and diabetes mellitus in 9 years were respectively 20% and 4.5%. We have shown that hypertriglyceridemia, obesity, hypertension, and age were the independent risk factors for the development of impaired fasting glucose in the Japanese. Also, hypertriglyceridemia and obesity were independent risk factors for the development of diabetes mellitus. However, hypertension was not an independent risk factor for the development of diabetes mellitus.

A family history of diabetes, obesity, hypertension, insulin resistance, low insulin secretion, low physical activity, and cigarette smoking are known risk factors for type 2 diabetes and impaired fasting glucose (25–28). Clustering of dyslipidemia, diabetes, obesity, and hypertension was reported in many cross-sectional studies. These risk factors for diabetes mellitus are related to insulin resistance (29). In those reports, fasting hyperinsulinemia was an independent risk factor. In this study, obesity, hypertriglyceridemia, and hypertension had independence. Therefore, it could be suspected that not only insulin resistance but also other mechanisms are the fundamental risks for impaired fasting glucose and diabetes mellitus.

The level of fasting glucose in normal fasting glucose was an independent risk factor for the development of impaired fasting glucose and diabetes mellitus. Impaired fasting glucose has a high prevalence of impaired glucose tolerance. (30, 31). Similar progression rates to diabetes are reported in impaired glucose tolerance/normal fasting glucose and impaired fasting glucose/normal glucose tolerance groups. In impaired glucose tolerance/ impaired fasting glucose, the progression rate to diabetes is two fold (11, 32).

Hypertension was an independent risk factor for the development of impaired fasting glucose in this study. Otherwise,

hypertension was not an independent risk factor for the development of diabetes mellitus. This suggests that impaired fasting glucose and diabetes mellitus correspond to different stages of impaired glucose metabolism (15). Impaired fasting glucose has hyperinsulinemia whereas diabetes mellitus has low insulin secretion (33). Hypertension is more strongly related to hyperinsulinemia.

In this study, subjects with hypertriglyceridemia were significantly more obese and had a significantly higher blood pressure and higher glucose concentration than subjects without hypertriglyceridemia at baseline. However, after adjusting for BMI, hypertension, and fasting glucose at baseline hypertriglyceridemia were independent risk factors for the development of impaired fasting glucose and diabetes mellitus. But hypertriglyceridemia was not a risk factor for diabetes mellitus in the Paris prospective study (12). Perhaps, this is because the duration of follow-up in the Paris study was only 3 years and thus too short to evaluate the risk factors for diabetes mellitus. In the Framingham study, very low density lipoproteins and obesity were independent predictors of glucose intolerance for a 14-year follow-up period (11). In that study however, diabetes mellitus was not differentiated from impaired glucose tolerance. The fasting triglyceride level was positively associated with the 2-hour glucose level in the oral glucose tolerance test after 6 years in Chinese (20). However, half of the subjects in their study already had impaired glucose tolerance at baseline. In the present study, all subjects had normal fasting glucose at baseline. In a small group of familial hypertriglyceridemia patients, the level of serum triglyceride was an independent predictor for the development of impaired glucose tolerance and type 2 diabetes (34). Moreover, our study showed that hypertriglyceridemia was an independent risk factor for the development of impaired fasting glucose and diabetes mellitus in the general Japanese population. Triglyceride-rich lipoproteins and free fatty acids may directly interfere with peripheral binding and the action of insulin (35–37); an increased hepatic flux of free fatty acids may also increase hepatic glucose production (38). In recent reports, obesity and type 2 diabetes have been associated with low plasma adiponectin concentrations; adiponectin decreases insulin resistance by decreasing the triglyceride content in muscle and liver in obese mice (39, 40). Adiponectin may also have an important role for the development of diabetes mellitus.

In conclusion, hypertriglyceridemia is an independent risk factor for the development of impaired fasting glucose and diabetes mellitus in Japanese. In the future, the relationship between hypertriglyceridemia and the pathogenesis of diabetes mellitus should be studied.

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