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Risk Factors for Development of Pre-Diabetic State from Normal Glucose Regulation

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Orisaka, M., Nakai, K., Tominaga, M. and Suwabe, A. *Risk Factors for Development of Pre-Diabetic State from Normal Glucose Regulation*. Tohoku J. Exp. Med., 2006, **210** (4), 279-283 —— As a strategy to prevent the progression of diabetes mellitus, it is important to screen out the subjects who will develop a pre-diabetic state (PDS) in the future. To find out the potential risk factors for PDS, we employed the values of fasting plasma glucose and hemoglobin A1c (HbA1c), which are routinely measured in our health checkup. We selected 3,879 individuals who had normal glucose regulation at both fasting plasma glucose < 6.1 mmol/l and HbA1c < 5.5% in 1997 and investigated whether they would develop PDS in the next 5 years. PDS is defined at fasting plasma glucose ≧ 6.1 mmol/l and HbA1c ≧ 5.5%. Among 3,879 individuals, 21 developed PDS and 2,128 maintained normal glucose regulation in 2001. The remaining 1,730 subjects fit one of the two criteria for PDS. The parameters measured in 1997, including fasting plasma glucose, HbA1c, triglyceride, alanine aminotransferase, γ-glutamyltranspeptidas, cholinesterase, uric acid, red blood cells, hemoglobin, percent body fat and diastolic blood pressure, were significantly higher in the individuals who developed PDS than in those who maintained normal glucose regulation. On the other hand, hematocrit was significantly lower in PDS than in normal glucose regulation. Logistic regression analysis identified alanine aminotransferase ≧ 40 U/l, triglyceride ≧ 1.69 mmol/l, low-density lipoprotein cholesterol ≧ 3.62 mmol/l and hematocrit < 38% as valuable factors for predicting the development of PDS. The present study demonstrates that the subjects with high risks for PDS could be identified from several clinical parameters and that they should be encouraged to improve their living habits not to develop diabetes mellitus. ———— glucose; diabetes mellitus; pre-diabetic state; lifestyle; laboratory data
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Ninety-eight % of all patients with diabetes have type 2 diabetes mellitus, and the rate has been increasing, particularly in those aged 40 or older (Tajima 1999). Besides the complications of diabetes, i.e., retinopathy, nephropathy and neuropathy, complications involving the large blood vessels, such as myocardial infarction and cerebrovascular disorders, also weigh heavily on

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the healthcare system, posing a social problem.

Because patients with type 2 diabetes have no subjective symptoms, they are also expected to spend four to seven years with the disease before diagnosis (Harris et al. 1992). Ten to 20% of patients with diabetes have already developed complications such as arteriosclerosis, when they are diagnosed with diabetes (Harris et al. 1992).

It is important to detect and intervene in mild cases of diabetes mellitus and even conditions with impaired glucose regulation ([IGR]; impaired glucose tolerance plus impaired fasting glucose) at an earlier stage. However, no factor predictive of the onset of IGR has been identified. To identify such factors, we conducted a study of individuals in whom IGR was newly found, and investigated which clinical tests had previously shown abnormal results and what factors were involved in the onset of IGR.

Subjects and Methods

A total of 27,193 people who received a complete medical checkup by the Iwate Health Service Association during the five-year period from 1997 through 2001 were included in our study after excluding those who were receiving treatment for hyperlipidemia, fatty liver, thyroid diseases, gynecologic diseases, or diabetes.

The diagnosis of diabetes was based on the 1999 report by the Diagnosis Criteria Exploratory Committee of the Japan Diabetes Society (1999). According to this criteria, fasting plasma glucose (FPG) levels less than 6.1 mmol/l were defined as normal glucose regulation (N). The hemoglobin A1c (HbA1c) value was regarded as normal when it was less than 5.5%. Because our health checkup program does not include a 75-g oral glucose tolerance test (OGTT), we could not diagnose IGR precisely according to the Japan Diabetes Society criteria. Therefore, a patient whose FPG was 6.1 mmol/l or greater and whose HbA1c was 5.5% or greater was defined as being in a pre-diabetic state (PDS). When FPG was 7.0 mmol/l or greater or when HbA1c was 6.1% or greater, the individual was diagnosed as having diabetes, according to the Instructions for Diabetes Examination of the Elderly Health Law in Japan (Ministry of Health and Welfare 2001).

Of 3,879 people who had normal glucose regulation in 1997, those who still had normal glucose regulation in 2001 were categorized as the N-N group and those who showed PDS in 2001 as the N-PDS group. In 1997, twenty-five items consisting of 17 biochemical indicators including FPG and HbA1c, five hematological indicators, percent body fat, and systolic (SBP) and diastolic (DBP) blood pressures in the two groups were compared. The LDL-cholesterol (LDL-C) level was calculated using the Friedewald equation (excluding those with triglyceride [TG] levels of 4.52 mmol/l or greater).

In statistical analyses, the results were expressed as means ± S.D. Unpaired Student's *t*-test and logistic regression were used, and differences of $p < 0.05$ were regarded as significant. The SPSS program was used for statistical analyses.

Table 1. Backgrounds of the subjects at the start of the study in 1997.

	N-N	N-PDS	*p* value
n (male/female)	2,128 (1,302/826)	21 (17/4)	
Age (years)	52 ± 9.8	49 ± 7.2	0.158
Body fat (%)	24.8 ± 5.7	27.5 ± 6.8	0.029
SBP (mmHg)	118 ± 17.0	125 ± 15.5	0.057
DBP (mmHg)	73 ± 11.0	78 ± 8.2	0.036

N-N, the subjects with normal glucose regulation from the baseline (1997) to the end of the follow-up (2001). N-PDS, the subjects with normal glucose regulation at the baseline (1997) who thereafter developed a pre-diabetic state by the end of the follow-up (2005).

Student's *t*-test was used to compare N-N and N-PDS.

SBP, systolic; DBP, diastoric.

Results

Of 3,879 people who received a complete medical checkup in 1997 and excluding those who answered that they were receiving treatment for the diseases mentioned earlier, 2,128 people (54.9%) were categorized in the N-N group and 21 people (0.5%) in the N-PDS group. They were 52.5 ± 9.8 and 49.3 ± 7.2 years old on average, respectively. Percent body fat and DBP in 1997 were significantly greater in the N-PDS group than in the N-N group (Table 1).

The FPG and HbA1c values were significantly greater in the N-PDS group than in the N-N group. No significant difference was observed in total cholesterol (TC) and LDL-C in serum lipid between the two groups. In the N-PDS group, however, TG was significantly higher while HDL-cholesterol (HDL-C) was significantly lower (Table 2).

Other than lipid parameters, alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), cholinesterase (CHE), uric acid, red blood cell count (RBC), hemoglobin (Hb) and hematocrit (Ht) were significantly greater in the N-PDS group than in the N-N group (Table 2).

Logistic regression analysis identified ALT $\geqq$ 40 U/l, TG $\geqq$ 1.69 mmol/l, LDL-C $\geqq$ 3.62

Table 2. Laboratory data at the start of the study in 1997.

	N-N	N-PDS	p value
FPG (mmol/l)	5.1 ± 0.4	5.7 ± 0.2	< 0.0001
HbA1c (%)	5.1 ± 0.3	5.3 ± 0.2	< 0.0001
TC (mmol/l)	5.02 ± 0.83	5.20 ± 0.88	0.324
HDL-C (mmol/l)	1.50 ± 0.38	1.22 ± 0.25	< 0.0001
LDL-C (mmol/l)	3.03 ± 0.76	3.08 ± 0.76	0.762
TG (mmol/l)	1.13 ± 0.69	2.00 ± 1.26	0.005
AST (U/l)	24 ± 9	42 ± 53	0.132
ALT (U/l)	26 ± 18	51 ± 43	0.014
γ-GTP (U/l)	35 ± 38	70 ± 54	0.007
LDH (U/l)	352 ± 66	344 ± 49	0.587
ALP (U/l)	142 ± 41	162 ± 79	0.259
CHE (U/l)	170 ± 34	192 ± 41	0.003
UN (mmol/l)	5.4 ± 1.2	5.0 ± 1.2	0.124
Creat (μmol/l)	80 ± 20	88 ± 20	0.065
UA (μmol/l)	290 ± 80	350 ± 110	0.021
RBC ($10^4/\mu$l)	463 ± 41	494 ± 28	< 0.0001
WBC ($10^3/\mu$l)	5.6 ± 1.5	6.4 ± 2.1	0.093
Hb (g/dl)	14.2 ± 1.4	15.0 ± 1.1	0.009
Ht (%)	43.0 ± 3.8	45.3 ± 2.8	0.006

N-N, group with normal glucose regulation from the baseline to the end of the follow-up; N-PDS, group with normal glucose regulation that developed PDS by the end of the follow-up; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglyceride; AST, aspirate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CHE, cholinesterase; UN, urea nitrogen; UA, uric acid; RBC, red blood cell count; WBC, white blood cell count; Hb, hemoglobin; Ht, hematocrit.

Student's t-test was used to compare N-N and N-PDS.

TABLE 3. Values predicting the pre-diabetic states (logistic regression analysis).

	Beta	Odds ratio	95% interval	*p* value
ALT (≧ 40 U/l)	0.742	2.100	1.7 – 2.7	< 0.0001
TG (≧ 1.69 mmol/l)	0.457	1.579	1.3 – 1.9	< 0.0001
LDL-C (≧ 3.62 mmol/l)	0.510	1.665	1.3 – 2.1	< 0.0001
Ht (< 38%)	0.530	1.699	1.4 – 2.1	< 0.0001

ALT, alanine aminotransferase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; Ht, hematocrit.

mmol/l and Ht < 38% as significant factors for predicting the onset of PDS (Table 3).

DISCUSSIONS

People who had normal glucose regulation on a complete medical checkup in 1977 were followed for five years, and classified into N-N or N-PDS groups in 2001. The clinical test results in these groups were compared to identify the characteristics of people who developed PDS thereafter.

Analysis of a total of 25 items consisting of 17 biochemical indicators, five hematological indicators, percent body fat, SBP and DBP revealed that people in the N-PDS group already had significantly higher percent body fat, DBP, and TG five years before, when their glucose regulation was normal. The combination of these abnormal but not severe test results seems to constitute metabolic syndrome or fatty liver. Both metabolic syndrome and fatty liver are known to be risk factors for developing disorders of glucose metabolism (Matsumoto et al. 2005).

Patients in the pre-diabetic condition that is named IFG if diagnosed only with FPG, or impaired glucose tolerance (IGT) if diagnosed with 2-h plasma glucose (PG) after glucose load, have been shown to develop coronary heart diseases at a significantly higher rate than healthy people and at almost the same rate as patients with diabetes (Fuller et al. 1983; Fujishima et al. 1996; Laakso 1996; Tominaga et al. 1999). Furthermore, factors such as hypertension, FPG and TG, which were originally regarded as indicators of progression from IGT to diabetes, are also considered risk factors for coronary diseases (Stern 1995). Like these reports our analysis also suggested that hypertension, FPG, and TG were prognostic factors for the onset of PDS.

Our study demonstrated that an individual who would develop PDS had already shown certain abnormal test results five years before when their glucose regulation had been normal. It has also been reported that individuals with higher TG values, even within the normal range, develop cardiovascular diseases more frequently than those with lower TG values (Miller et al. 1998). Our present results were also supported by several reports from large-scale clinical trials, which showed that a higher TG value *per se* is one of the risk factors for cardiovascular diseases (Phillips et al. 1993; Hokanson and Austin 1996).

From this finding, it seems essential for even people with normal glucose regulation to be motivated to improve their living habits so that PDS will not be induced. One way to motivate them would be informing them of their test results.

According to surveys of diabetes conducted by the Ministry of Health, Labor and Welfare (MHLW) in Japan, the number of patients suspected of diabetes was estimated at 6.9 million in 1997 and expected to increase to 7.4 million five years later (Ministry of Health 1997). In the diabetes screening test conducted by our association as a mandatory item in a complete medical checkup, public health examinations, medical examinations at industrial healthcare centers, and lifestyle disease-preventive checkups for school children, the percentage of people in whom IGR is found has been increasing each year. This trend can be considered to support the announcements of the MHLW.

It is obvious that if the number of people with IGR or diabetes increase, the number of patients with strokes and coronary diseases such as myocardial infarction will also increase as a result. In addition, although it has been proven that even patients who have already developed diabetes can prevent the development and progression of diabetic complications by controlling blood glucose levels more strictly (the Diabetes Control and Complications Trial Research Group 1993; UK Prospective Diabetes Study Group 1998), it is more important to prevent the cardiovascular diseases due to PDS and diabetes.

A reduction in the rate of increase in the number of people with PDS or diabetes is very important in contemporary Japan. Our present study has demonstrated that the subjects with high risks for PDS could be identified from several clinical parameters and also that they should be encouraged to improve their living habits not to develop diabetes mellitus.

References

Fujishima, M., Kiyohara, Y., Kato, I., Ohmura, T., Iwamoto, H., Nakayama, K., Ohmori, S. & Yoshitake, T. (1996) Diabetes and cardiovascular disease in prospective population survey in Japan, the Hisayama study. *Diabetes*, **45**, Suppl., 314-316.

Fuller, J.H., Shipley, M.J., Rose, G., Jarrett, R.J. & Keen, H. (1983) Mortality from coronary heart disease and stroke in relation to degree of glycaemia. The Whitehall study. *Br. Med. J.,* 287867-287870.

Harris, M.I., Klein, R., Welborn, T.A. & Knuiman, M.W. (1992) Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*, **15**, 815-819.

Hokanson, J.E. & Austin, M.A. (1996) Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J. Cardiovascular. Risk,* **3**, 213-219.

Japan Diabetes Society (1999) Guideline for treatment of diabetes mellitus. Tokyo. Japan. (in Japanese)

Laakso, M. (1996) Insulin resistance and coronary heart disease. *Curr. Opin. Lipidol*., **7**, 217-226.

Matsumoto, K., Ozaki, M., Fujita, N. & Miyake, S. (2005) Insulin resistance and metabolic syndrome contribute significantly to the transition of borderline glucose tolerance to type 2 diabetes mellitus. *Journal of the Japan Diabetes Society*, **48**, 849-854.

Miller, M., Seidler, A., Moalemi, A. & Person, T.A. (1998) Normal triglyceride levels and coronary artery disease events: The Baltimore Coronary Observational Long Term Study. *J. Am. Coll. Cardiol.*, **31**, 1252-1257.

Ministry of Health (1997) Labor and Welfare, National Diabetes Survey.

Ministry of Health and Welfare (2001) *The Manual of Checkup for Diabetes Mellitus According to the Health Act for the Elderly Nihon Koushu Eisei Kyokai*, edited by Division of Health for the Elderly, Health and Welfare Bureau for the Elderly, Tokyo, Japan. (in Japanese)

Phillips, N.R., Waters, D. & Havel, R.J. (1993) Plasma lipoprotein and progression of coronary artery disease evaluated by angiography and clinical events. *Circulation*, **88**, 2762-2770.

Stern, M.P. (1995) Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes,* **44**, 369-374.

Tajima, N. (1999) Differentiation between insulin dependent diabetes mellitus (NIDDM) and insulin dependent diabetes mellitus (IDDM). *Doctor. Salon.,* **43**, KYORIN Pharmaceutical Co., Ltd., 120-124.

The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.*, **329**, 977-986.

Tominaga, M., Igarashi, K., Eguchi, H., Kato, T., Manaka, H. & Sekikawa, A. (1999) Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care,* **22**, 920-924.

UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS33). UKPDS Group. *Lancet,* **352**, 837-853.