Original Article

Fasting plasma glucose and its relationship to future diabetes mellitus and white blood cell count: a longitudinal study in a rural Japanese population.

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We examined the longitudinal change of the fasting plasma glucose (FPG) level and its relationship with the development of diabetes and inflammation in a rural Japanese community. The records of an annual health screening in a Japanese community from 1981-1984 were used as the baseline data and compared with follow-up data obtained in 1993. 156 subjects with initial FPG values <7.0mmol/L at the baseline period had been monitored for a mean of 11.5 years. In 1993 FPG-diagnosed diabetes was found more in individuals with baseline FPG values >=5.6 than those with <5.6mmol/L. The subgroup with FPG >=5.6 had a higher mean white blood cell count than that with FPG <5.6mmol/L. A cross sectional analysis in the 1993 data showed the diabetes subgroup had higher mean levels of body mass index, systolic and diastolic blood pressures, C-reactive protein, insulin, triglycerides, white blood cell count, HbA1c and fructosamine, than the non-diabetes subgroup. In conclusion, 'impaired fasting glucose' defined as FPG level with >=5.6mmol/L could identify future risk of diabetes, and it may be related to the development of sub-clinical inflammation in a rural Asian population.

(Key words : fasting plasma glucose, diabetes, subclinical inflammation, prospective study, rural Japan)

Introduction

In 1997, the American Diabetic Association (ADA) revised criteria for the diagnosis of diabetes[1], which was followed by World Health Organization (WHO) in 1998[2] and the Japan Diabetes Society in 1999[3]. These three criteria for diagnosis are fundamentally identical, particularly with respect to the fasting plasma glucose (FPG) levels. The cut-off levels of the FPG were set at 6.1mmol/L for normal, 6.1 to 7.0mmol/L for impaired fasting glucose (IFG), and 7.0mmol/L for diabetes. Recently, fasting plasma glucose (FPG) levels within the conventional 'normal range' have been reported to be associated with a gradient risk of diabetes[4]. Based on data published since 1997, the ADA's 2003 Follow-up Report on the Diagnosis of Diabetes Mellitus reduces the lower limit for the diagnosis of "impaired fasting glucose (IFG)"

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from 6.1 to 5.6mmol/L, and redefines "normal" as a FPG of less than 5.6mmol/L[5].

It has been indicated that in terms of progression to future diabetes, the lower an individual's FPG value is, the better the long-term result is. The incidence of diabetes is reported to relate with IFG[4].Even a FPG level of the 'new normal range' (<5.6mmol/L) is associated with a clear gradient of risk for future diabetes[6]. However, the susceptibility and progression of diabetes are different among racial groups and geographic areas. Little is known about a relation between IFG (5.6<=FPG<7.0mmol/L) and the development of diabetes in Asian populations as well as in rural populations. In this retrospective cohort study, therefore, we attempted to analyze the association in a rural Japanese population.

Some studies reported an association of inflammation with diabetes in Caucasians, African Americans, and Latinos[7-9]. Chronic inflammation is now speculated to be one of the risk factors for future diabetes. However, all of these studies were conducted in non-Asian populations. More importantly no study has been conducted for investigating the relationship between inflammation and diabetes in rural populations.

Epidemiological studies have indicated the demography of diabetes is different between urban and rural areas. Diabetes and its major risk factors are more prevalent and the speed of transition from glucose intolerance to diabetes is faster in urban than in rural populations[9-11]. Urbanization is a social risk for diabetes, which has been authenticated by the World Health Organization (WHO)[12]. Although these facts indicate the necessity of diabetes research in rural settings, the number of such researches has been limited.

In this study, therefore, we examined the relationships between fasting plasma glucose, future diabetes, and inflammation in a rural Japanese population. Using the newly defined ADA criterion, we classified rural Japanese residents into normal, IFG, and diabetes subgroups, and quantitatively evaluated their associations with various inflammatory and metabolic markers. Then we discuss the applicability of past study results to rural Asian populations.

Methods

This is a retrospective cohort study. At first we collected 'follow-up' data in an annual health screening which have been conducted in Okawa in 1993, a small rural mountain village in Kochi prefecture whose population was 527. This screening has been conducted as a part of the mass screening program at the nation level, according to the Health and Medical Service Law for the Aged Act of 1981. The local government of Okawa sent, by mail, the invitations to this screening to all the eligible subjects who were 15 years old or older. Then, we tracked information of the subjects back to the same screenings which had been conducted between 1981 and 1984. The information between 1981 and 1984 was used for the baseline data. In all the screenings, data collection was conducted in the same manner. Blood samples were obtained from the participants, drawn from the antecubital vein of seated participants in the morning after overnight fasting. Plasma glucose was measured by an enzymatic method within one hour. Present or past history of diabetes had been documented on medical records and the screening interview. From the four years between 1981 and 1984, FPG data of the earliest year was used for repeated screening participants. According to the baseline FPG level subjects were divided

into two subgroups at the cut-off level of 5.6mmol/L and the results were analyzed. Detailed information on the screening has been reported elsewhere[13]. The data of the 1993 screening was also used as baseline statistics in another study: the Jichi Medical School Cohort Study[14]. All participants were native Japanese.

In the 1993 screening, serum concentrations of total cholesterol, HDL cholesterol, triglycerides, glucose, fructosamine, HbA1c, fibrinogen, insulin, Lp(a) and C-reactive protein (CRP) were also measured. We used two criterion for diagnosing diabetes. One is high FPG level (FPG>=7.0mmol/L) found at the time of follow-up. This FPG criteria accords to the ADA criteria[1]. Another criteria is "known diabetes" which had been developed during the follow-up period and was clinically diagnosed at any medical institution during the period. We analyzed this category, separated from the first criteria group. The "known diabetes" was assessed using an interviewed questionnaire developed for the study, which consisted of four categories: no history of diabetes, diabetes presently treated, diabetes previously treated, and present or past non-treated diabetes. The latter three categories were considered a "known diabetes."

In the 1993 screening, two hundred and thirteen (213) villagers participated in the study[14]. The response rate for all eligible individuals in 1993 was 46%. Among the 213 participants of the study, 157 subjects (72%), who participated in the screening for the baseline in 1981-1984, were enrolled for this study. One subject with a baseline FPG value>=7.0mmol/L was excluded from the analysis so that we would follow up only subjects whose initial FPG values were<7.0mmol/L. No subject had a present or past history of diabetes at the baseline. For insulin and CRP measurements, results below the detection limit were excluded from the analysis. CRP levels were measured by high-sensitive CRP measurement, using nephelometry, a latex particle-enhanced immunoassay (NA Latex CRP Kit, Dade Behring, Tokyo, Japan).

Statistical analyses were performed using SPSS for Windows, Release 8.0 (SPSS Inc., Japan). One-way analysis of covariance with adjustment for age, sex, and body mass index was used to compare the mean values. In using these parametric procedures, the values of insulin, triglycerides, lipoprotein(a), and CRP were transformed to natural logarithms because of their highly skewed distributions. A significant difference was defined as $p<0.05$.

Results

One hundred and fifty-six subjects (67male and 89female) were followed for a mean of 11.5 years. Table1 shows the summary of baseline data. At the baseline in 1981-1984, 125subjects had normal FPG values(<5.6mmol/L) and 31subjects had IFG (FPG>=5.6mmol/L). Among the overall 156subjects, seven(4.5%) developed FPG-diagnosed diabetes and eight (5.1%) developed "known diabetes" at follow-up in 1993. Among the 31subjects with IFG, five (16.1%) developed FPG-diagnosed diabetes and seven(22.6%) developed "known diabetes" at follow-up. There was no significant difference of age between the normal FPG and IFG subgroup: 47.4± 8.1years versus 48.4±6.6years (mean±SD; $p=0.559$, unpaired t test).

The results of longitudinal analysis are shown in the Table2. Subjects with baseline FPG levels>=5.6mmol/L (IFG group) had significantly higher FPG, HbA1c, fructosamine, insulin, and white blood cell (WBC) counts at follow-up than those with baseline FPG levels<5.6

Table 1. Subject characteristics at baseline (1981-1984)

	N	
Total number	156	
Sex		
Male	67	(42.9%)
Age (mean±SD)		(47.2±8.5)
Female	89	(57.1%)
Age (mean±SD)		(47.8±7.3)
FPG level		
Diabetes 7.0mmol/L<=FPG	0	(0.0%)
Impaired Fasting Glucose 5.6<=FPG<7.0mmol/L	31	(19.9%)
'Lower IFG' 5.6<=FPG<6.1mmol/L	26	(16.7%)
Normal FPG<5.6mmol/l	125	(80.1%)

Table 2. Subject characteristics at follow-up (1993) clasified according to the fasting plasma glucose level at baseline (1981-1984).

		Baseline FPG<5.6mmol/l			5.6mmol/l=<Baseline FPG<7.0mmol/l				
		N	Mean	Range(Mean+-SD)	N	Mean	Range(Mean+-SD)	P*	P**
Follow-up	FPG(mmol/l)	125	5.2	4.7-5.6	31	6.3	4.5-8.1	<0.01	<0.01
	Hemoglobin Alc(%)	125	5.4	5.0-5.8	31	6.1	4.6-7.7	<0.01	<0.01
	Fructosamine(μmol/l)	125	248.1	229.8-266.5	31	274.9	222.2-327.6	<0.01	<0.01
	Insulin(μU/ml)	97	4.9	2.9-8.2	23	6.0	3.6-10.2	0.04	0.12
	LDL cholesterol(mg/dl)	125	114.5	81.1-147.8	31	110.2	93.4-127.0	0.93	0.90
	HDL cholesterol(mg/dl)	125	50.9	38.0-63.7	31	49.4	34.5-64.4	0.65	0.82
	Triglycerides(mg/dl)	125	86.3	54.4-136.7	31	93.5	60.0-145.7	0.30	0.41
	Lipoprotein(a) (mg/dl)	125	14.0	5.1-39.0	31	14.9	6.2-35.8	0.52	0.46
	C-reactive protein(mg/dl)	120	0.215	0.069-0.671	30	0.297	0.052-1.705	0.19	0.39
	Fibrinogen(mg/dl)	125	246.3	189.6-303.0	31	236.4	169.0-303.7	0.58	0.48
	WBC(/μl)	124	4446	3138-5755	31	5168	3445-6891	0.02	0.06
	Systolic blood pressure(mmHg)	124	128.2	103.7-152.8	31	132.6	111.8-153.5	0.46	0.68
	Diastolic blood pressure(mmHg)	124	76.0	62.0-90.1	31	79.0	68.5-89.5	0.43	0.67
	Body mass index(kg/m²)	125	23.2	20.2-26.2	31	23.7	20.4-27.0	0.21	
		N	%		N	%			
	FPG<7.0mmol/l	123	98.4		26	83.9		<0.01	<0.01
	FPG>=7.0mmol/l	2	1.6		5	16.1			
	Known'DM(-)	124	99.2		24	77.4		<0.01	<0.01
	Known'DM(+)	1	0.8		7	22.6			

Geometric mean and S.D. are used for insulin, triglycerides, lipoprotein(a), and C-reactive protein. Analysis of coveriance was used. Unpaired t-test was used for body mass index.

*Controlled by age and sex

**Controlled by age, sex and body mass index

mmol/l (normal FPG group). When adjusted by age, sex and BMI, the statistical significance of WBC count and insulin has been lost. Subjects with baseline FPG values>=5.6mmol/L were10times more likely to develop diabetes whose FPG levels satisfy the ADA criteria than those with baseline FPG levels<5.6mmol/L. Among eight subjects with a "known diabetes" at follow-up, five (62.5%) satisfied the ADA criteria (FPG>=7.0mmol/l). Subjects with FPG levels>=5.6mmol/L were 28times more likely to have a "known diabetes" than the lower FPG group. We also made a subgroup comparison between 125subjects with baseline FPG levels<5.6mmol/L and 26subjects with baseline FPG levels from 5.6mmol/L to 6.0mmol/L in order to examine the potential influence of the 'lower IFG' group on developing diabetes.

Table 3. Cross-sectional analysys of subgroups at follow-up divided by diabetic criteria for fasting plasma glucose

	FPG<7.0mmol/l(Non-diabetes)			FPG>=7.0mmol/l(Diabetes)				
	N	Mean	Mean+-SD	N	Mean	Mean+-SD	*P**	*P***
Age	149	59.8	52.0-67.6	7	57.3	48.5-66.1	0.41	
Hemoglobin Alc(%)	149	5.4	4.8-5.9	7	8.0	5.3-10.7	<0.01	<0.01
Fructosamine(μmol/l)	149	250.0	231.2-268.9	7	325.9	232.7-419.0	<0.01	<0.01
Insulin(μU/ml)	113	4.9	3.1-7.7	7	10.4	4.1-26.1	<0.01	0.02
LDL cholesterol(mg/dl)	149	113.6	82.3-144.8	7	149.9	95.2-134.5	0.89	0.43
HDL cholesterol(mg/dl)	149	50.9	37.8-64.0	7	44.1	28.9-59.3	0.16	0.53
Triglycerides(mg/dl)	149	86.1	54.5-136.0	7	128.5	100.8-163.7	0.03	0.16
Lipoprotein(a) (mg/dl)	149	14.5	5.5-38.3	7	9.4	2.3-37.8	0.21	0.16
C-reactive protein(mg/dl)	143	213.3	66.1-688.1	7	1018.3	94.1-11022.1	0.02	0.03
Fibrinogen(mg/dl)	149	242.4	186.0-298.9	7	284.3	189.8-378.8	0.08	0.09
WBC(/μl)	148	4489	3144-5834	7	6743	5297-8188	<0.01	<0.01
Systolic blood pressure(mmHg)	149	128.3	104.9-151.7	7	146.3	118.0-174.5	0.04	0.35
Diastolic blood pressure(mmHg)	148	76.1	62.9-89.4	7	87.3	11.2-163.4	0.02	0.24
Body mass index(kg/m²)	148	23.1	20.3-25.9	7	27.9	23.3-32.4	<0.01	

Geometric mean and S.D. are used for insulin, triglycerides, lipoprotein(a), and C-reactive protein. Analysis of coveriance was used. Unpaired t-test was used for age and body mass index.

*Controlled by age and sex

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Almost the same trend as that shown in Table1was recognized. No statistical difference existed between the normal FPG and 'lower IFG' subgroups with regard to all the variables shown in Table2 except for FPG value. This indicates the 'lower IFG' with baseline FPG from 5.6mmol/L to 6.0mmol/L affects future FPG, but associates neither with definite diabetes nor with inflammation.

Table3 shows the cross-sectional analysis of subjects divided by the ADA criteria of diabetes in 1993. Subjects with FPG values of >=7.0mmol/L in 1993 had significantly higher triglycerides, C-reactive protein, blood pressures, body mass index, white blood cells, HbA1c, fluctosamine, and insulin than those with FPG values<7.0mmol/L. When adjusted by age, sex and BMI, the statistical significance of triglycerides, systolic and diastolic blood pressure has been lost.

Discussion

Our results agree with results from some prospective studies performed in Caucasian and other ethnic populations in urban settings[7-9]. This study shows that a FPG level which accords to the ADA-defined IFG may lead to future diabetes. IFG might lead to sub-clinical inflammation which is indicated by high level of white blood cell count. Compared with previous urban-based studies, our study had several features. It consisted of a single homogenous Asian cohort and integrated the factors relating to glycemic control, metabolic disorders, and inflammatory process seen in diabetes. In addition, we excluded individuals with diabetes at the time of baseline collection. This study focused solely on the subjects with normal FPG or IFG.

The cross-sectional analysis in Table3 showed subjects with FPG levels>=7.0mmol/L at follow-up had significantly higher values as markers not only for diabetes but also for inflam-

mation than those subjects with FPG levels<7.0mmol/L at the follow-up. The same trend in WBC and CRP was also seen in the longitudinal analysis shown in Table2, although a statistical significance in CRP was not obtained because of a possible type II error. The rise of WBC and CRP may indicate an activation of inflammatory process in the development of diabetes. The possible cause-effect relationship between inflammation and diabetes is now attracting attention. The increase of WBC in type2 diabetes has been documented in prospective studies of Caucasian populations[7], but not in Asians. The association of type2 diabetes and other acute phase markers was also reported[7], supporting the inflammatory process in the pathogenesis of the disease. This hypothesis, however, needs further longitudinal investigations. Regrettably our study was unable to confirm the cause-effect relationship between FPG values and inflammation because we obtained WBC and CRP values at the follow-up but not at the baseline.

Obesity apparently confounds the association between diabetes and inflammation. Obesity is well known to relate both with high WBC count and diabetes. In our study as well, adjustment by BMI diluted the strength of relationships between inflammatory markers and diabetes as shown in Table2 and Table3. However, statistical significance of CRP and WBC count remained positive even after the adjustment by BMI in the cross-sectional analysis at follow-up (Table2). These results indicate that obesity is one of the factors which plays a part in the diabetes-inflammation interaction, but obesity alone cannot explain the whole mechanism of the complex interaction between the two conditions.

The data of this study was gathered between 1981 and 1993. This is the period in which the number of diabetes cases had increased most rapidly in Japanese history: 200% increase from 6,200 to 12,500 cases per 1,000,000 population[15]. The socio-epidemiological context of this study, therefore, is similar to the situation in which most developing countries are currently embedded: 170% increase in diabetes cases from 84 million in 1995 to 228 million in 2025[16]. Thus, although we focused on native Japanese in this study, the results of this study may be generalized to other Asia-Pacific populations which are now experiencing an unprecedented rise in diabetes morbidity.

There are some limitations. Retrospective nature of this study narrowed the range of available data, particularly that of biochemical markers at baseline. All we could use at baseline was age, sex and FPG levels of the subjects, which rendered our analysis and inference on the interrelationship between FPG and inflammation limited. Using single FPG value as the only diagnostic measure may have biased the results of this study. The diagnosis of diabetes requires two independent measurements of FPG[1]. Moreover oral glucose tolerance test (OGTT) was not used to confirm the diagnosis. This may decrease the sensitivity of the diagnosis and underestimate the incidence of diabetes. Another limitation is the inclusion of "known diabetes" as study subjects. Because some of the "known diabetes" cases may have received medical treatment and maintained normal FPG level, we considered detecting the "known" cases was needed to reduce the chance of under-estimation of the disease. But the diagnostic criteria of "known" cases was unknown, which may have led to a biased result.

In conclusion, this study indicated that the baseline level of FPG would be a predictor of

diabetes in an Asian population. IFG, which did not meet ADA criteria for diabetes, may identify individuals who will develop diabetes later, and interventions to these categories could be crucial for preventive measures. This study also suggested a relationship between inflammatory processes and IFG in a rural Asian population.

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空腹時血糖と糖尿病および白血球数との関係についての後ろ向きコホート研究

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要　約

空腹時血糖と糖尿病や炎症との関連について過去に多くの報告があるが，そのほとんどは非アジア人種かつ都市部住民を対象としたものである。今回我々は空腹時血糖が将来の糖尿病と炎症の発症にどう影響するか，へき地の住民を対象に後ろ向きコホート研究によって調べた。1981年から1984年までの住民検診データをベースラインとし，1993年時点での追跡データをアウトカムとした。ベースラインにおいて空腹時血糖が7.0mmol/L未満の対象者156名を平均11.5年間追跡した。ベースライン時に空腹時血糖5.6mmol/L以上だった群はそれ以外の群に較べて有意に糖尿病の発症率が高く，白血球数も増加していた。アウトカムデータの横断分析では，糖尿病群は非糖尿病群に較べてbody mass index，収縮期および拡張期血圧，C-reactive protein，インスリン，中性脂肪，白血球数，ヘモグロビンA1c，フルクトサミンが有意に高値であった。本研究によって日本のへき地住民においても，空腹時血糖5.6-7.0mmol/Lのimpaired fasting plasma glucose群は日本の僻地住民において糖尿病の発症に関連し，また炎症にも関連している可能性が示された。

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