Clinical Investigations

A Slight Increase of Fasting Plasma Glucose after 2 Years Was Associated with Electrocardiogram Changes Suggestive of Coronary Heart Disease in Normal Subjects

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Summary

Background: Much attention has been focused on the primary prevention of ischemic heart disease (IHD), but the prevalence and prognostic indicators of IHD remain unclear in healthy Japanese subjects.

Hypothesis: The purpose of this study was to determine the predictors for the transition of IHD in healthy adult subjects using data from annual medical examinations.

Methods: We analyzed clinical data on 2,710 healthy subjects (1,836 men and 874 women aged 26–76 years in 2000) who underwent medical examinations in both 2000 and 2002. Ischemic changes in the electrocardiogram (ECG) suggestive of IHD were defined as the existence of abnormal Q-wave and/or ST-T abnormalities without left ventricular high voltage. We assigned the subjects to two groups: the ischemic heart group (Group I), including subjects with normal ECG findings in 2000, followed by suspicious ischemic changes in the ECGs in 2002; and the normal group (Group N), including subjects with normal ECGs in both 2000 and 2002.

Results: Fifty-nine subjects (2%, 20 women) were assigned to Group I and 2,538 subjects (96%, 810 women) were assigned to Group N. There were significant differences between the two groups in baseline age (Group I vs. Group N: 53 vs. 47 years, $p < 0.001$), body mass index (24 vs. 23 kg/m², $p = 0.036$), systolic blood pressure (132 vs. 122 mmHg, $p < 0.001$), diastolic blood pressure (83 vs. 76 mmHg, $p < 0.001$), and fasting

plasma glucose (109 vs. 96 mg/dl, $p < 0.001$). Fasting plasma glucose significantly increased in Group I (from 109 to 113 mg/dl, $p = 0.034$) during the study. Multivariate analysis showed significant differences in age ($p < 0.001$) and fasting plasma glucose ($p = 0.0053$).

Conclusion: Advanced age and relatively elevated fasting plasma glucose appeared to be significant predictors of ECG findings suggestive of IHD in normal subjects in the short period of 2 years.

Key words: ischemic heart disease, primary prevention, electrocardiogram, fasting plasma glucose

Introduction

The primary prevention of ischemic heart disease (IHD) has been attracting much attention in the last few years.¹ Many Japanese have easy access to hospitals and frequently undergo medical examinations, yet the prevalence and prognostic indicators of IHD remain unclear in healthy Japanese subjects. The Framingham Heart Study² and the Hisayama study³ have shown the long-term natural prognosis of IHD, but their findings provide only limited help to people in the prime of their lives who wish to know the most important parameters likely to disturb and threaten their present quality of life and portend disadvantages in the future due to IHD. We sought to identify prognostic indicators for IHD in the short term, an issue scarcely evaluated by previous studies. Thus, the purpose of this study was to determine the predictors for the transition of IHD in healthy adult subjects using data from annual medical examinations.

Methods

In all, 3,228 subjects underwent medical examination at our hospital in both 2000 and 2002. Of these, we studied 2,710 healthy adults (26–72 years old, 68% men) who showed normal electrocardiograms (ECGs) and no apparent symptomat-

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ic diseases or history of chronic diseases in 2000. Subjects with serum creatinine levels > 1.0 mg/dl, transaminase levels > 40 mg/dl, and active inflammatory changes were excluded.

The subjects were assigned to two groups based on the outcome of the ECGs in 2002: those with warning ischemic ECG changes in 2002 were allocated to the ischemic heart group (Group I) and those with normal ECG in both 2000 and 2002 were allocated to the normal group (Group N). Subjects showing other ECG abnormalities such as bundle-branch blocks, atrial fibrillation, and ectopic beats were excluded from the study. Our comparison of the data collected from the examinations of the two groups focused most closely on parameters related to IHD and risk factors for atherosclerosis. We used multivariate analysis to clarify the predictors of IHD in Group I and also studied the differences and changes of the parameters in Group I between 2000 and 2002.

Criteria for Warning Ischemic Electrocardiographic Changes

Warning ischemic ECG changes were defined as the presence of more than two leads with abnormal Q-wave and/or ST-T abnormalities without left ventricular high voltage. Normal-variant Q waves in leads V_{1-2} , III, and aVf were excluded from abnormal Q waves in this study. ST-T abnormalities included horizontal or downsloping ST-segment depressions of > 0.05 mV, any type of ST-segment depression of > 0.1 mV, and flat or inverted T waves in leads other than V_{1-2} , III, or aVf. Subjects with other abnormal ECG changes unrelated to warning ischemic ECG changes were excluded from this study, as were subjects with heart rate > 100 beats/min at rest in ECG. Representative ECG changes are shown in Figure 1.

Predictive Parameters

Data from the annual medical examinations of the two groups were used to study parameters known to be related to

IHD and atherosclerosis, including the subjects' age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol profile, serum uric acid (UA) concentration, and fasting plasma glucose (FPG) level. The changes in these parameters between 2000 and 2002 were also studied.

Statistics

The Student's *t*-test was used to compare the values between Group I and Group N and between 2000 and 2002. The values were expressed as mean $\pm$ standard deviation (SD). Logistic regression analysis was used to compare the predictive parameters in Group I. We used computer software to analyze the clinical data (StatView for Windows, Ver.6, SAS Institute Inc., Cary, N.C., USA). P values < 0.05 were considered to be significant in this study.

Results

Two percent ($n = 59$) of the study population were assigned to Group I and 96% ($n = 2,538$) to Group N. The remaining 2% had other ECG abnormalities such as bundle-branch block, atrial fibrillation, and ectopic beats. The clinical characteristics of the two groups in 2000 are shown in Table I. Mean age, BMI, SBP, DBP, and FPG level were higher in Group I than in Group N. Multivariate analysis for predictors of Group I is shown in Table II. Age and FPG were the only parameters to show significant predictive value, suggesting that advanced age and relatively elevated FPG level may be significant predictors for the appearance of warning ischemic ECG changes.

Table III shows the changes of the values in Group I between 2000 and 2002. In Group I, BMI, SBP, DBP, and cholesterol profile remained unchanged between 2000 and 2002, whereas FPG increased significantly in only 2 years (Fig. 2).

FIG. 1 (A) Representative electrocardiogram (ECG) change in 2000 to 2002. Electrocardiogram of a 54-year-old man who had hypertension in 2002. The ECG in 2002 showed horizontal ST-segment depression of over 0.05 mV in leads II, III, aVF, and V_{5-6} , and flat T waves in leads V_{5-6} . He showed positive treadmill exercise test and was proved to have ischemic heart disease (IHD) by coronary angiogram. (B) Representative ECG change in 2000 to 2002. Electrocardiogram of a 57-year-old woman who had impaired glucose tolerance and hypertension in 2002. The ECG in 2002 showed horizontal ST-segment depression of over 0.1 mV in leads II, III, aVF, and V_{5-6} . She showed positive treadmill exercise test and was also proved to have IHD by coronary angiogram.

TABLE I Clinical characteristics

Baseline data (in 2000)	Group I	Group N	p Value
Age (years)	53 ± 8	47 ± 8	<0.0001
Male (%)	66	68	NS
BMI (kg/m ²)	24.0 ± 2.8	23.2 ± 3.0	0.034
SBP (mmHg)	132 ± 21	122 ± 16	0.0007
DBP (mmHg)	83 ± 12	76 ± 11	0.0002
T.Chol (mg/dl)	206 ± 44	206 ± 36	NS
TG (mg/dl)	133 ± 71	124 ± 102	NS
UA (mg/dl)	5.2 ± 1.5	5.2 ± 1.4	NS
FPG (mg/dl)	109 ± 26	96 ± 16	0.0002

Values are expressed as mean ± standard deviation.

Abbreviations: BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, T. Chol. = total cholesterol, TG = triglyceride, UA = uric acid, FPG = fasting plasma glucose, NS = not significant.

TABLE II Multivariate analysis for predictors in Group I

	Odds ratio	95% confidence interval	p Value
Age	1.090	1.054–1.126	0.0001
BMI	1.004	0.911–1.107	NS
SBP	1.022	0.982–1.063	0.29
DBP	1.016	0.955–1.082	NS
T. Chol	0.995	0.987–1.003	0.22
TG	1.001	0.998–1.004	NS
UA	0.927	0.748–1.149	NS
FPG	1.013	1.004–1.023	0.0053
Δ BMI	0.929	0.750–1.150	NS
Δ SBP	1.028	0.991–1.067	0.13
Δ DBP	0.990	0.936–1.047	NS
Δ T. Chol	0.998	0.986–1.010	NS
Δ TG	1.002	0.999–1.004	0.17
Δ UA	0.971	0.698–1.352	NS
Δ FPG	1.005	0.994–1.016	NS

Parameters are baseline data in 2000.

Δ = absolute change in 2000 to 2002.

Abbreviations as in Table I.

TABLE III Changes of values from 2000 to 2002 in Group I

	In 2000	In 2002	p Value
BMI (kg/m ²)	24.0 ± 2.8	24.0 ± 3.1	NS
SBP (mmHg)	132 ± 21	132 ± 20	NS
DBP (mmHg)	83 ± 12	81 ± 12	NS
T.Chol (mg/dl)	206 ± 44	207 ± 45	NS
TG (mg/dl)	133 ± 71	152 ± 129	NS
UA (mg/dl)	5.2 ± 1.5	5.5 ± 1.5	NS
FPG (mg/dl)	109 ± 26	113 ± 33	0.034

Values are expressed as mean ± standard deviation.

Abbreviations as in Table I.

Of the 59 subjects in Group I, 34 (58%) underwent a treadmill exercise test. The test indicated suspected IHD in 22 patients (65%), and 14 of these were diagnosed with IHD because of a luminal diameter stenosis of > 75% in at least one major coronary artery on coronary angiogram. Only 4 (7%) of the 59 subjects in Group I described chest symptoms in their daily lives; only 2 subjects had abnormal Q waves accompanied by left ventricular asynergy by ultrasonic echocardiogram and were thereby proven to have IHD by coronary angiogram.

Discussion

Two percent of healthy adult subjects who underwent the same annual medical examination in 2000 and 2002 manifested warning ischemic ECG changes at the second examination. These subjects had significantly higher BMI, SBP, DBP, and FPG levels than the other subjects, but their BMI and cholesterol profiles remained unchanged during the 2-year interval. Multivariate analysis showed that aging and elevated FPG level were the strongest predictors of the appearance of warning ischemic ECG changes in 2 years. On this basis, we estimated that the predictors of these changes were stronger than increases in BMI, SBP, DBP, or cholesterol profile.

The primary prevention of IHD has been attracting much attention.¹ The Hisayama study³ indicated a decreased number of strokes but no reduction of coronary heart disease (CHD) in Japan. The reasons for these findings and the most important risk factors for CHD will have to be identified if CHD is to be prevented more effectively. The Framingham Heart Study² identified risk factors for CHD in the general population of the United States, as well as the quantitative relationships among them.⁴ These previous studies have mainly focused on long-term risk factors and predictors of CHD; no studies have explored short-term predictors of the occurrence of CHD.

Advanced age was included as a risk factor in the Framingham Heart Study due to an increased absolute risk with aging.² Age has also been shown to be strongly predictive as a risk factor for cardiovascular disease (CVD) and CHD mortality in

FIG. 2 Fasting plasma glucose (FPG) level in Group I.

many cohort studies performed in the United States.⁵ As the plaque burden increases with age, there is a tendency toward developing coronary atherosclerosis as a risk factor for future coronary events. As proved in many studies, advanced age is a strong risk factor for CHD that cannot be avoided. In this study, only 2 years of aging appeared to strongly affect the incidence of warning ischemic ECG changes.

Diabetes mellitus (DM) and glucose intolerance are also known as major risk factors for CHD and have been studied extensively.⁶ The control of glucose tolerance and the interval for developing DM and impaired glucose tolerance (IGT) both affect the incidence of CHD.⁶ The subjects in this study were normal adults who were not diagnosed as having DM or IGT at the study entry. Eight subjects (16%) in Group I were diagnosed with DM during the study and commenced treatment within the 2-year period. Only six subjects (12%) in Group I underwent oral glucose tolerance test, and four of these (8%) proved to have IGT. The first observed abnormality in plasma glucose with insulin resistance is IGT, and many prospective studies have shown that IGT is a risk factor for CVD.^{6,7} Therefore, in this study, a slight increase in FPG may have strongly affected the occurrence of warning ischemic ECG changes and portended the occurrence of IHD in the future. We emphasize that the increase in FPG may be more important than the change of BMI and cholesterol profile in the short term for the prediction of the onset of IHD.

Not all subjects in Group I underwent coronary angiogram or cardiac scintigram to prove the presence of IHD; however, we observed the warning ischemic ECG changes in subjects who were not definitely diagnosed as having IHD in this study. Of the subjects in Group I, 17 (29%) had hypertension, fulfilling the criteria of SBP > 140 mmHg and/or DBP > 90 mmHg at rest, but none of the subjects had left ventricular hypertrophy by ultrasonic echocardiogram. Two subjects (4%) in Group I had borderline dilatation of the left ventricle, and one of these had a moderate level of aortic valvular regurgitation. Seventeen subjects were prescribed calcium antagonists (71%) and/or angiotensin-converting enzyme (ACE) inhibitors (56%) for hypertension, eight subjects (14%) were given H₂ blockers for gastrointestinal disease, and the other subjects had no apparent diseases and were not prescribed drugs. None of the subjects in Group I were prescribed digitalis, psychotropic agents, antiallergic agents, or any other drugs capable of producing ECG changes. However, abnormalities in the resting ECG have been shown to be strongly associated with subsequent CVD, CHD, and all other causes of mortality in a population based on random samples.⁸ Moreover, persistent nonspecific minor ST-T abnormalities have been shown to be associated with increased long-term risks of mortality due to CVD and all other causes.⁹ These previous studies emphasized and proved that minor ECG changes are related to the occurrence of CHD and poor prognosis. On this basis, the occurrence of warning ischemic ECG changes in 2 years may indeed suggest insufficient prognosis of IHD in this study. Careful observation will be needed.

In this study, we tentatively identified the main predictors of the appearance of IHD in the short term. Aging and relatively

elevated FPG level are noteworthy predictors of warning ischemic ECG changes. Moreover, an increase of FPG by only 4 mg/dl over 2 years significantly predicts the appearance of warning ischemic ECG changes. This may suggest not only the presence of IHD, but also a cardiac burden which may induce cardiac events in the future.

Clinical Implications

The primary prevention of IHD is also an important issue on the medical economy and the rapidly growing aging population in Japan. The prevention of IHD can be considerably improved by identifying the most important risk factors of the condition and reducing their occurrence. In the Hisayama study,³ stroke mortality continuously declined and survival significantly improved. In contrast, the only parameter linked to an increased incidence of CHD and CHD mortality was advancing age. Severe hypertension and current smoking decreased significantly, while glucose intolerance, hypercholesterolemia, and obesity increased greatly among this cohort. Although the incidence of hospitalized infarction decreased overall, the burden of CHD shifted toward elderly people.^{2,5} In this study, the control of plasma glucose levels and the prevention of transitions to impaired glucose tolerance and DM were important factors, especially among the elderly subjects who complied with the lifestyle practices we recommended.

Limitations

This was an observational study with a short follow-up period; however, it was successful in identifying factors predictive of the appearance of warning ischemic ECG changes in only 2 years. Our study was meaningful in that it focused not on the long-term but on the short-term predictors of IHD in normal subjects. Only 34 subjects (58%) in Group I underwent the treadmill exercise test, far too small a number to confirm the existence of ischemic events. We recommended that all subjects in Group I undergo annual examinations and treadmill exercise tests. However, resting ECG in an annual medical examination will be useful enough from an economic standpoint in the screening for patients with IHD.

This study did not consider a history of habitual smoking, family history of IHD, or serum high-density lipoprotein (HDL) cholesterol level. Twenty-five subjects (49%, 18 men) in Group I were active habitual smokers and 10 subjects (20%) had a family history of ischemic events with onset before the age of 55; these are indeed important risk factors. However, besides these, we emphasize that elevated FPG and advanced age are prominent risk factors for warning ischemic ECG changes. This study did not prove whether elderly subjects with relatively elevated FPG actually showed an increased incidence of IHD or faced a poor prognosis. Further study will be needed to clarify this point.

The limitations of this study make it difficult to assess properly whether the subjects have definite IHD based solely on the analysis of resting ECGs and the results of annual medical examinations. However, we can assert that the screening for IHD

in annual medical examinations will be useful. The physicians performing this annual screening should carefully watch for rises in FPG and changes in resting ECG changes, particularly in elderly subjects.

Conclusion

Aging and relatively elevated FPG appeared to be significant predictors of the incidence of suspicious IHD in healthy adult subjects screened over a short-term period.

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