Hyperinsulinemia and the Development of ST-T Electrocardiographic Abnormalities

An 11-year follow-up study

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OBJECTIVE — It has been suggested that insulin resistance and consequent hyperinsulinemia promote atherosclerosis, but few prospective studies have reported the relationships between hyperinsulinemia and the development of ST-T abnormalities in the 12-lead resting electrocardiogram (ECG) in populations in which atherosclerosis is rare.

RESEARCH DESIGN AND METHODS — A total of 304 Japanese men and women, aged 20–69 years, selected for having high blood glucose or more than a trace-positive urine glucose from a population-based health examination in 1981, were followed for 11 years. Of these, 33 died, 1 from myocardial infarction, while 260/271 living were reexamined in 1992. The 237 subjects with a normal ECG at the baseline examination were analyzed.

RESULTS — Incident ST-T abnormalities occurred in 13/237 people. Insulin concentrations were positively associated with the development of ST-T abnormalities (relative risk ~8, comparing those in the highest versus lowest quartile of insulin values). Adjustment for age, sex, and systolic blood pressure or other risk factors had little effect on this relationship.

CONCLUSIONS — Hyperinsulinemia was related to the development of ST-T abnormalities in ECGs in the absence of the development of clinical signs of atherosclerosis, independent of blood pressure and other risk factors in men and women with mild glucose intolerance.

Hyperinsulinemia may contribute to atherogenesis and may be one of the important risk factors for coronary heart disease (CHD). Several prospective studies (1–3) have also reported a relationship between hyperinsulinemia and the development of ST-T abnormalities on an electrocardiogram (ECG), assuming that ST-T changes are a manifestation of CHD. However, ST-T changes may reflect abnormalities other than atherosclerotic heart disease. In this paper, we investigated whether incident ST-T abnormalities are associated with hyperinsulinemia in a Japanese population in which atherosclerosis is rare.

RESEARCH DESIGN AND METHODS

— A total of 393 people, aged 20–69 years, with high casual blood glucose concentrations were selected from 2,732 participants (>20 years of age; 1,195 men and 1,537 women) who had had a health examination in 1979 and 1980 in the farming community Tanushimaru. The detailed protocol for selection has been described elsewhere (4). These 393 people were rescreened, following a protocol similar to that used in the Seven Countries Study (5), and were offered a 50-g oral glucose tolerance test (OGTT) in 1981. Insulin users and oral hypoglycemic agent users were not included in the baseline examination. Of the 393 subjects, 72 refused to have an OGTT and two pregnant women were excluded; 319 participants finally underwent an OGTT. Five subjects who had undergone gastrectomy, one with a fasting plasma insulin concentration >700 pmol/l, and all subjects with missing insulin data were excluded from the analysis. Glucose tolerance status was classified using reference values from the Japan Diabetes Society classification (6), which have been shown to correspond to the World Health Organization classification (7), using a 75-g OGTT.

A complete data set was available in 304 participants. A follow-up examination of these 304 participants was carried out in 1992, using the same protocol as in 1981, except for omission of the OGTT in 1992.

In the 11 years after the original study, 33 subjects died (15 of cancer, 5 of stroke, 1 of myocardial infarction, 2 of congestive heart failure of unknown etiology, and 10 of other diseases or accidents). Six subjects moved and were lost to follow-up, and five subjects refused to participate in the follow-up examination. Thus, follow-up data were available for 260 participants. Of these, 23 participants with abnormal ECGs at baseline examination were excluded from the analysis. Finally, data for 237 people whose ECGs were normal or had an isolated diagnosis of high R waves were available for the analysis.

Height and weight were measured, and BMI was calculated as an index of obesity. Age, current smoking, alcohol intake, and medical history were ascertained by a questionnaire. Alcohol intake was expressed as the average amount of Japanese sake (15% ethanol content) consumed in a day. Alcohol intake was divided into two groups: ≥360 ml vs. <360 ml of sake per day.

Resting 12-lead ECGs were recorded in supine subjects who had been fasting for at least 12 h before blood drawing. They were assessed independently of the metabolic results, using the Minnesota coding system categories 1, 3, 4, 5, 6, 7, 8, and 9 (8). The

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Abbreviations: CHD, coronary heart disease; ECG, electrocardiogram; OGTT, oral glucose tolerance test.

Table 1—*Baseline (1981) and 1992 ECG findings in study participants*

ECG findings	1981 Total	1981 Without ST-T abnormality	1992
n	304	237	237
Normal	215 (70.7)	189 (79.7)	187 (78.9)
High voltage (3.1)* without ST-T abnormalities	55 (18.1)	48 (20.3)	27 (11.4)
ST-T abnormalities with high voltage (3.1)*	7 (2.3)	0 (0.0)	5 (2.1)
ST-T abnormalities without high voltage (3.1)*	14 (4.6)	0 (0.0)	8 (3.4)
Atrial fibrillation (8.3.1)*	0 (0.0)	0 (0.0)	3 (1.3)
Others (6.4, 7.1, 7.2, 9.8.1)*	13 (4.3)	0 (0.0)	7 (2.9)

Data are *n* (%). *Resting 12-lead ECGs were assessed using the Minnesota coding system categories 1,3–9. The high voltage code was 3.1, and the ST-T abnormality codes were 4.1, 4.2, 4.3 or 5.1, 5.2, 5.3.

high voltage code was 3.1, and ST-T abnormality codes were 4.1, 4.2, 4.3, or 5.1, 5.2, 5.3. Blood pressure was measured after 5-min sitting rest three times at 3-min intervals by a team of physicians using an upright standard sphygmomanometer. The third blood pressure measurement of systolic and fifth-phase diastolic pressure was used.

Blood was drawn from an antecubital vein to determine insulin, glucose, glycosylated hemoglobin A_1, uric acid, creatinine, and lipid concentrations in the morning after 12-h fast. Then, after a 50-g oral glucose load, blood was drawn 60, 120, and 180 min later to determine insulin and glucose levels. Serum insulin was measured by a modification of the immunoassay technique of Herbert et al. (9). The plasma glucose concentration was measured by the glucose oxidase method (10). Total cholesterol and triglyceride levels were enzymatically determined (11,12). HDL cholesterol was measured enzymatically after precipitation by sodium phosphotungstate and magnesium chloride (13), with a slight modification (14).

Because of skewed distributions, the natural logarithmic (ln) transformations were performed for triglyceride, glucose, and insulin concentrations. Geometric means and approximate standard errors are presented. The difference between two groups was determined by Student's *t* test. The difference among groups was performed by analysis of variance. χ^2 tests were used for categorical parameters and for contingency tables to test differences between and among groups. Statistical significance was defined as $P < 0.05$. The summed values of the insulin concentrations at 0, 60, 120, and 180 min (sum insulin) were divided into quartiles of

Table 2—*Baseline characteristics of the subjects stratified by quartiles of the sum of insulin values*

	Sum of insulin (pmol/l) by quartile Q1	Q2	Q3	Q4	Probability†
n	60	59	59	59	
Range	144–366	372–534	540–846	852–4,332	
Mean ± (SE)	277.2 (7.7)	447.6 (6.5)	679.8 (11.6)	1,462.8 (99.4)	—
Age (years)	51.9 ± 1.3	49.5 ± 1.4	52.5 ± 1.3	54.6 ± 1.3	0.06
Systolic blood pressure (mmHg)	125.9 ± 2.6	128.6 ± 2.5	129.8 ± 2.4	132.6 ± 2.6	0.31
Diastolic blood pressure (mmHg)	75.8 ± 1.6	74.5 ± 1.5	76.3 ± 1.5	80.7 ± 1.4	0.02
Heart rate (beats/min)	66.3 ± 1.1	69.8 ± 1.5	71.4 ± 1.7	70.8 ± 1.7	0.09
BMI (kg/m^2)	21.5 ± 0.3	21.9 ± 0.4	22.8 ± 0.4	25.1 ± 0.4	<0.001
Cholesterol (mmol/l)	4.77 ± 0.11	4.88 ± 0.13	5.21 ± 0.11	5.13 ± 0.14	0.04
HDL cholesterol (mmol/l)	1.27 ± 0.04	1.17 ± 0.03	1.19 ± 0.03	1.08 ± 0.03	<0.001
Triglycerides (mmol/l)*	0.96 ± 0.04	1.06 ± 0.05	1.16 ± 0.04	1.44 ± 0.06	<0.001
Uric acid (μmol/l)	225.2 ± 8.85	222.8 ± 7.81	222.8 ± 9.37	233.2 ± 9.89	0.81
Creatinine (μmol/l)	96.3 ± 3.54	93.7 ± 3.54	87.5 ± 1.77	90.2 ± 2.64	0.23
HbA_1 (%)	7.2 ± 0.2	6.9 ± 0.1	7.1 ± 0.2	7.2 ± 0.1	0.37
Sum of glucose (mmol/l)*	25.5 ± 1.05	24.3 ± 1.03	25.8 ± 1.03	28.7 ± 1.03	0.01
Sex (% men)	75.0	47.5	44.1	32.2	<0.001
Antihypertensive medication (% yes)	3.3	5.1	10.2	10.2	0.35
Current smoking, ≥20 cigarettes/day (% yes)	50.0	35.6	28.8	16.9	<0.01
Alcohol intake, ≥360 ml sake (15% ethanol)/day (% yes)	41.7	25.4	20.3	11.9	<0.01
Diagnostic criteria					
Normal	76.6	76.3	64.4	39.0	<0.001
Impaired glucose tolerance	10.0	11.9	22.0	39.0	<0.001
Diabetes	13.3	11.9	18.6	22.0	0.39

Data are means ± SE or %, unless otherwise indicated. *Log-transformed values were used for the calculation of means and exponentiated geometric means are presented. †One-way analysis of variance was used for differences in continuous and categorical parameters across categories of quartiles.

increasing sum insulin concentrations, and absolute risks of incident ST-T abnormalities were computed.

Multiple logistic regression analyses were performed to evaluate the power of the various parameters for predicting the development of ST-T abnormalities. The association of hyperinsulinemia with the development of ST-T abnormalities was assessed controlling for age, sex, systolic blood pressure, and every other potential risk factor. All analyses were performed using the SPSS system.

RESULTS — The baseline and 1992 ECG findings are presented in Table 1 for the 237 subjects who were free of ECG abnormalities (except for 48 who had high R waves) at the baseline examination in 1981; 13 people developed ST-T abnormalities by 1992; 5 of the 13 ST-T changes were severe (Minnesota codes 5.2; 5.2 and 4.3; 5.2 and 3.1; 4.2 and 3.1; and 4.3 and 3.1). Baseline characteristics of the subjects stratified by quartile of the sum of insulin values are shown in Table 2. Factors statistically significantly related to baseline sum of insulin values were diastolic blood pressure, BMI, cholesterol, HDL cholesterol, triglyceride, sum of glucose concentration, female sex, current smoking, alcohol intake, and having normal and impaired glucose tolerance. Cholesterol concentration, current smoking, and alcohol intake lost their significance after adjusting for sex.

Baseline characteristics of the subjects stratified by the development of ST-T abnormalities are given in Table 3. Pre– and post–glucose load insulin levels were significantly higher in the group with than without ST-T abnormalities. Nearly 62% of ST-T changes (8/13) developed in those in the highest quartile of sum of insulin values. Risk for incident ST-T changes was 1.7% (1/60) for people in the lowest quartile, 1.7% (1/59) in quartile 2, 5.3% (3/59) in quartile 3, and 13.6% (8/59) in quartile 4. Systolic and diastolic blood pressure, uric acid, and taking antihypertensive medication were also statistically significantly higher in those who developed ST-T abnormalities than in those who did not. Mean levels of several other variables were also higher in those with ST-T abnormalities, but did not achieve statistical significance, perhaps because of the small number of incident cases.

Multiple logistic regression analyses were performed separately for each independent variable with age and sex as covariates (Table 4). Systolic and diastolic blood pressure, taking antihypertensive medication, uric acid, and pre– and post–glucose load insulin levels were significantly related to the development of ST-T abnormalities. Comparing these variables per standard deviation unit, systolic blood pressure at the baseline examination demonstrated the strongest positive association with the future development of ST-T abnormalities; insulin, whether fasting, post–glucose load, or summed, was somewhat less predictive than blood pressure.

The insulin regression coefficients remained significant in the multiple logistic regression, including sex, age, insulin concentration, and every other single factor listed in Table 4. Neither age, sex, nor any other single factor except blood pressure approached statistical significance in this regression. A multiple logistic regression prediction equation for the probability of new ST-T abnormalities in 1992 is $1/(1 + e^{-z})$, where $z = -18.42 + 0.060 \times$ systolic blood pressure (in conventional millimeters of mercury) $+ 1.211 \times$ ln(sum of insulin [in microunits per milliliter]).

Table 3—*Baseline characteristics of the subjects stratified by the development of ST-T abnormalities in ECG*

Baseline, 1981 characteristics	Incident ST-T abnormalities in 1992		
	No	Yes	Probability
n	224 (94.5)	13 (5.5)	<0.001
Sex (% men)	111 (49.6)	7 (53.8)	0.99
Age (years)	51.9 ± 0.67	55.9 ± 3.34	0.17
Systolic blood pressure (mmHg)	127.8 ± 1.24	154.0 ± 5.64	<0.001
Diastolic blood pressure (mmHg)	76.1 ± 0.75	88.6 ± 2.83	<0.001
Antihypertensive medication (% yes)	13 (5.8)	4 (30.8)	<0.01
Heart rate (beats/min)	69.3 ± 0.76	73.6 ± 5.00	0.21
BMI (kg/m^2)	22.7 ± 0.21	24.5 ± 1.00	0.06
Cholesterol (mmol/l)	4.99 ± 0.06	5.15 ± 0.34	0.55
HDL cholesterol (mmol/l)	1.18 ± 0.02	1.22 ± 0.10	0.56
Triglycerides (mmol/l)*	1.12 ± 0.04	1.37 ± 0.20	0.06
Uric acid (μmol/l)	223.8 ± 4.68	265.4 ± 18.7	0.03
Serum creatinine (μmol/l)	88.4 ± 1.77	88.4 ± 4.42	0.28
HbA_1 (%)	7.1 ± 0.07	7.2 ± 0.28	0.88
Current smoking, ≥20 cigarettes/day (% yes)	75 (33.5)	3 (23.1)	0.64
Alcohol intake, ≥360 ml sake (15% ethanol)/day (% yes)	55 (24.6)	4 (30.8)	0.86
50-g OGTT			
Glucose concentrations (mmol/l)*			
0 min	5.78 ± 0.004	5.73 ± 0.017	0.87
60 min	9.07 ± 0.005	9.42 ± 0.022	0.73
120 min	6.01 ± 0.005	6.32 ± 0.022	0.67
180 min	4.71 ± 0.005	4.50 ± 0.020	0.61
Sum	26.00 ± 0.005	26.35 ± 0.018	0.87
Insulin concentrations (pmol/l)*			
0 min	46.8 ± 0.66	70.8 ± 3.00	<0.01
60 min	295.2 ± 0.78	503.4 ± 3.36	<0.01
120 min	123.0 ± 0.90	240.0 ± 4.32	<0.01
180 min	52.8 ± 0.78	79.2 ± 3.36	0.03
Sum	555.6 ± 0.78	943.2 ± 3.36	<0.01
Diagnostic criteria			
Normal	143 (63.8)	9 (69.2)	0.92
Impaired glucose tolerance	47 (21.0)	2 (15.4)	0.90
Diabetes	34 (15.2)	2 (15.4)	0.71

Data are means ± SE or %, unless otherwise indicated. Of 224 subjects with no ST-T abnormalities in 1992, 27 had 3.1, 2 had 8.3, etc.. Of 13 subjects with ST-T abnormailities in 1992, 5 had 3.1. *Log-transformed values were used for the calculation of means and standard errors and exponentiated; geometric means are presented.

Table 4—*Association of various parameters with the development of ST-T abnormalities adjusted for age and sex*

Parameters	β*	Probability
Systolic blood pressure	1.137	0.001‡
Diastolic blood pressure	1.047	0.001‡
Antihypertensive medication	0.470	0.008‡
Heart rate	0.399	0.124
BMI	0.543	0.053
Serum cholesterol	0.108	0.699
HDL cholesterol	0.174	0.522
Triglycerides†	0.396	0.076
Uric acid	0.572	0.047‡
Serum creatinine	−0.464	0.283
HbA_1	−0.001	0.999
Current smoking	−0.507	0.172
Alcohol intake	0.144	0.676
Glucose concentrations†		
0 min	−0.118	0.754
60 min	−0.054	0.865
120 min	0.042	0.884
180 min	−0.198	0.552
Sum	−0.068	0.828
Insulin concentrations†		
0 min	0.738	0.007‡
60 min	0.761	0.009‡
120 min	0.789	0.007‡
180 min	0.500	0.049‡
Sum	0.799	0.004‡

Each row reports a separate logistic regression model of new ST-T abnormalities on age, sex, and the given factor. *Standardized regression coefficients; †log-transformed values were used. ‡$P < 0.05$.

CONCLUSIONS — We found an eightfold excess risk of new ST-T abnormalities occurring during the 11 years between 1981 and 1992, comparing those in the highest versus the lowest quartiles of sum of insulin values at a population-based health examination in 1981 in Japan. Many authors assume that ECG abnormalities are synonymous with CHD (1–3), but ST-T abnormalities do not necessarily represent ischemia in Japan where CHD rates are low (15). In fact, of the 13 subjects whose ECGs showed the development of ST-T abnormalities, only one had obvious evidence of angina pectoris. Furthermore, the cause of death was myocardial infarction in only one of the 33 who died before 1992.

Previous research on insulin and ECG abnormalities has been conducted in Oxford, U.K., where atherosclerosis is common and the incidence of CHD is high. Hillson et al. (1) studied diabetic individuals and reported a positive relationship between hyperinsulinemia and ECG abnormalities (including ST-T abnormalities). Other studies (2,3) regard ECG findings as a measure of CHD without verification of this assumption. Collins et al. (2) studied the relationship of serum insulin and ECG abnormalities in the populations of Mauritius and Nauru. Tuomilehto et al. (16) reported that CHD was rare in Nauru, but Mauritius had a high CHD mortality rate. The Collins study (2) found a relationship between insulin levels and ECG abnormalities in longitudinal analyses in Mauritius, but did not find such a relationship either cross-sectionally or longitudinally in Nauruans or cross-sectionally in Mauritians. They suggested that the inconsistency might be a consequence of the relative nonspecificity and insensitivity of the prevalent ECG as an indicator of CHD. Liu et al. (3) reported a prospective study in Pima Indians. Neither endogenous fasting nor 2-h postload serum insulin was associated with the subsequent development of ECG abnormalities (including ST-T abnormalities) in NIDDM patients or nondiabetic subjects. The lack of significant association may be related to lower serum cholesterol levels and less heavy smoking in Pimas than in the general U.S. population (3). CHD is relatively rare in Pima Indians (17), and the prevalence of ECG abnormalities is low, despite the high prevalence of NIDDM (18). Inconsistencies among these studies (1–3) and our findings may be due to several factors including proneness of the population to CHD or differences in the race or sex of subjects (19,20) or in diabetic status (1,21). In our study, all subjects had mild glucose intolerance on screening in 1979, but only ~30% had impaired glucose tolerance or diabetes on reexamination in 1981.

Based on our findings, we suggest that glucose intolerance and hyperinsulinemia may be predictive of ST-T abnormalities. Our data show nonsignificant increases in risk of incident ST-T abnormalities for other CHD risk factors, such as serum triglycerides, HDL cholesterol, BMI, heart rate, and uric acid. Cigarette smoking was nonsignificantly inversely associated with development of ST-T changes. However, the low statistical power of this study should be borne in mind when interpreting these negative findings.

In our data, the independent predictors of incident ST-T findings were systolic blood pressure and insulin. Both predictors are part of the insulin resistance syndrome, which is associated with alterations in myocardial repolarization. Two mechanisms may be involved: *1*) an insulin-induced increase in sympathetic activity (22), and 2) a direct effect of high insulin, impaired glucose utilization, or both on membrane activity of myocardial cells. Although hyperinsulinemia promotes vascular smooth muscle proliferation and growth of cardiac myocytes (23), we found no association of insulin with high R waves (data not shown), and the more likely explanation for ST-T wave findings is a sympathetic nervous system (SNS)-induced alteration in repolarization. High blood pressure may alter cellular electrophysiological properties and the time course of repolarization and increase SNS activity. This study points out that the mechanism of ST-T abnormalities may not be progressive ischemic heart disease.

Another possibility is the influence of medication given to reduce blood pressure or to treat glucose intolerance. Some such medications may cause repolarization changes as a side effect. Nearly 77% of people who had incident ST-T changes (10/13) were taking some kind of medication in 1992, compared with 18% (41/224) of subjects who did not develop ST-T changes. However, we could not investigate this pos-

sibility further because specific medication names were not recorded in 1992.

A limitation of this study is the small number of cases of incident ST-T abnormalities on which it is based. Nevertheless, the differences in insulin and blood pressure levels between those who did and did not develop ST-T abnormalities are striking and worthy of further investigation. The pathogenesis of incident ST-T abnormalities is related to both coronary and noncoronary mechanisms and, as such, should be viewed as a nonspecific finding. The use of ST-T abnormalities as an index of coronary disease may not be justified in populations with low prevalence of CHD. We conclude that both insulin and blood pressure may influence ST-T abnormalities in the absence of atherosclerosis.

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