Clustering of Cardiovascular Risk Factors in Urban Asian Indians

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OBJECTIVE — To study the prevalence of cardiovascular risk factors in native urban Asian Indians and to look for the occurrence of clustering of these factors.

RESEARCH DESIGN AND METHODS — The study included 953 subjects (532 men and 421 women), aged ≥40 years, selected from a population survey for diabetes, which was conducted in 1994 in Madras, Tamil Nadu, India. Measurements of anthropometry, blood pressure, plasma lipid profile, glucose tolerance, plasma insulin response, and electrocardiogram were made. Based on the normal ranges derived from the population study, abnormalities in anthropometric values, plasma lipids, and insulin values were determined. Age-adjusted prevalences of the abnormalities were calculated using data from a 1991 urban census in Madras. The expected prevalences of the abnormalities in isolation and in combinations were calculated and compared with the corresponding observed figures.

RESULTS — The prevalences of risk factors were in the order of central adiposity > dyslipidemia > hyperinsulinemia (2-h) > glucose intolerance > obesity > hypertension. The age-adjusted prevalence of coronary heart disease (CHD) was 3.9% (3.5% in men and 4.5% in women, NS), and T wave inversion was seen in an additional 10.3%. Isolated prevalences of all factors, except hypertension, were in lower frequency than expected. Combinations of each risk factor with one or two more risk factors occurred more frequently (1.3–4 times) than expected by chance. Impaired glucose tolerance and dyslipidemia showed association with hyperinsulinemia, whereas hypertension did not show such an association.

CONCLUSIONS — Clustering of the cardiovascular risk factors or the components of insulin resistance syndrome occurs in the native Asian Indian population. This finding underscores the need for preventive aspects of metabolic disorders and CHD.

Reaven (1) in 1988 described syndrome X, which was later called insulin resistance syndrome (IRS). The syndrome consisted of several features, i.e., compensatory hyperinsulinemia, glucose intolerance, hypertension, and dyslipidemia. Later on it was observed that overall obesity and, particularly, abdominal obesity were also features of IRS (2). In 1984, Jarret (3) speculated that both diabetes and cardiovascular disease (CVD) shared common antecedents rather than one being a complication of the other. Recent developments have added further credence to the fact that they share common genetic and environmental antecedents, i.e., that they spring from a "common soil" (4). The common occurrence of a pentad—obesity, NIDDM, hypertension, atherosclerotic CVD, and dyslipidemia—occurs more frequently than by chance in westernized societies, and it is also associated with hyperinsulinemia (5). Clustering of the above-mentioned risk factors common for diabetes and CVD has been demonstrated in populations, especially in those with a high prevalence of NIDDM, such as Mexican-Americans, Japanese Americans, Micronesians, and Caucasians (6–10).

Asian Indians have high rates of diabetes and impaired glucose tolerance (IGT) (11–15). Hyperinsulinemia is also a characteristic of Indians (12–14,16–19). Although there is evidence of increased coronary heart disease (CHD) mortality in migrant Indians (13,18,19), there are no such records on mortality or prevalence of cardiovascular risk factors in native Asian Indians. In this study, we are reporting clustering of the cardiovascular risk factors in urban Indians living in the homeland.

RESEARCH DESIGN AND METHODS

We studied conventional cardiovascular risk factors in subjects ≥40 years of age as a part of the population-based diabetes survey conducted in 1994 in Madras city, Tamil Nadu, India. The parameters studied included anthropometry, blood pressure, plasma lipid profile, glucose tolerance, plasma insulin responses, and electrocardiogram (ECG) records. Data were analyzed in 953 subjects (532 men and 421 women). Details of the prevalences of diabetes and IGT in the whole population were reported separately (11), and details of the population were described there as well.

All subjects fasted overnight (for a minimum of 10 h), and the period of fasting was ascertained by asking the study subjects before registration. After registration, a fasting blood sample was collected. A 75-g anhydrous glucose load was given orally in 250 ml of water. A second blood sample was drawn 2 h later.

The blood samples were aliquoted into two tubes: one in an oxalate-fluoride mixture for plasma glucose estimation and the other in a plain tube for separation of serum for immunoreactive insulin (IRI) estimation. Fasting serum samples were also used for the estimation of total cholesterol, HDL cholesterol, and triglycerides (TGs). Glucose and insulin were measured in the fasting and 2-h samples. Samples were transported in ice to the laboratory. Plasma glucose, total cholesterol, and TGs were measured on the same day.

Plasma glucose was measured by the glucose oxidase procedure, total choles-

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Abbreviations: CHD, coronary heart disease; CV, coefficient of variation; CVD, cardiovascular disease; dBP, diastolic blood pressure; ECG, electrocardiogram; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; IRS, insulin resistance syndrome; O/E, observed/expected; OR, odds ratio; sBP, systolic blood pressure; TG, triglyceride; WHR, waist-to-hip ratio.

Table 1—*Age-adjusted prevalence of risk factors in isolation and in combination*

	Hypertension	Glucose intolerance	Increased 2-h insulin	Dyslipidemia	Obesity	WHR
Prevalence (age-adjusted)	21.8	39.1	55.1	60.8	27.0	61.1
Isolated						
Observed	1.2	0.44	2.3	2.4	0.44	3.0
Expected	0.8	1.5	3.0	3.7	1.0	3.6
O/E ratio	1.5	0.29	0.77	0.65	0.44	0.83
Plus one other factor						
Observed	9.2–16.7	10.2–28.7	16.7–37.3	14.5–39.3	9.2–20.7	15.6–39.3
Expected	4.4	7.7	12.7	16.0	5.2	15.8
O/E ratio	2.1–3.8	1.3–3.7	1.3–2.9	0.91–2.4	1.8–4.0	1.0–2.5
Plus two other factors						
Observed	4.7–11.2	4.7–20.2	7.4–20.1	6.1–25.5	4.7–19.5	6.6–25.5
Expected	8.2	13.3	19.6	20.1	11.4	21.2
O/E ratios	0.6–1.4	0.4–1.5	0.38–1.0	0.3–1.3	0.4–1.7	0.3–1.2
Plus three other factors						
Observed	3.4–7.1	3.4–14.6	4.5–14.6	3.4–7.4	3.4–11.7	3.8–14.6
Expected	7.6	11.6	14.5	14.1	9.2	15.2
O/E ratio	0.4–0.9	0.3–1.3	0.3–1.0	0.2–0.5	0.2–1.3	0.3–0.96

Data are %. Expected value is calculated. Observed values are combinations of various factors; the lowest and the highest prevalence of the combinations are shown.

terol and TGs by enzymatic procedure, and HDL cholesterol by the phosphotungstate-magnesium precipitation method. All tests were conducted on a Hitachi 704 autoanalyzer using Boehringer Mannheim (Mannheim, Germany) reagents.

Serum samples were kept at −20°C for radioimmunoassay of insulin. A kit from Bhabha Atomic Research Centre (Bombay, India) was used. It uses a modified procedure of Herbert et al. (20) with a second antibody:polyethyleneglycol mixture for separation of bound and free radioactivity. The intra-assay coefficient of variation (CV) was <5% and the inter-assay CV was <7%.

Clinical details were filled in a computerized proforma that included history of heart disease and family history of diabetes, heart disease, and hypertension. Height, weight, waist, and hip measurements were made by standard procedures. BMI and waist-to-hip ratio (WHR) were calculated. Glucose tolerance was classified according to World Health Organization criteria (21).

The means and SDs of normal values were derived from the values obtained in 700 normoglycemic nonhypertensive subjects (20–85 years of age) in a previous survey (16), after deleting the upper and lower percentile values. The cut-off values obtained when using the mean ± 1 SD were as follows: BMI: 24.9 kg/m^2; WHR: men 0.9, women 0.85; cholesterol: 209 mg/dl; HDL cholesterol: <35 mg/dl for men, <40 mg/dl for women; TGs: 165 mg/dl; fasting insulin: 16 μU/ml; and 2-h insulin: 41 μU/ml. The presence of one or more abnormal lipid parameters was termed dyslipidemia in this study.

Blood pressure was measured in all the subjects in sitting position using a mercury sphygmomanometer, in the right arm. The average of two readings measured 5 min apart was recorded. Hypertension was defined as the presence of a systolic blood pressure (sBP) of ≥160 mmHg and/or a diastolic blood pressure (dBP) of ≥95 mmHg or as any person being treated with antihypertensive drugs.

A 12-lead ECG was recorded for 953 people. Probable CHD was diagnosed if there was *1)* a history of myocardial infarction based on records of treatment for heart disease in a hospital or 2) a pathological Q wave (major Q wave abnormalities) in an ECG recording (Minnesota codes 1.1.1–1.2.7) and 3) ST segment depression (codes 4.1–4.2). T wave abnormalities were marked separately (codes 5.1–5.4). The ECG records were read independently by one resident and one physician, and the interpretations were recorded as per the Minnesota code. All abnormal ECGs were again coded by a person certified for Minnesota coding (Dr. Bonita Peachey, London, U.K.)

Statistical analysis

The prevalence of CHD was age-adjusted to the urban population of Madras, as recorded in a 1991 census, using the direct standardization method. The overall prevalence of each abnormality was age-adjusted in a similar manner. The prevalence of risk factors in men and women was compared by χ^2 test. Pearson correlation analysis was done to look for the linear association of various anthropometric, hemodynamic, and metabolic variables with plasma insulin.

The expected prevalence estimates were calculated using the overall prevalence of each condition. The calculations were similar to those described by Zimmet et al. (9). Estimates of isolated risk factors and combinations of two, three, and four risk factors were calculated and compared with the corresponding observed prevalence.

Student's *t* test was used for comparison of group means. Plasma insulin values were adjusted for BMI and waist measurements by using a regression equation in all the calculations involving plasma insulin values. Multiple logistic regression analyses were carried out to find the associated parameters for hypertension and combinations of risk factors. Study subjects with an absence of the respective risk factors served as control subjects. Diabetic subjects (n = 226) were omitted from the analyses including insulin because of its influence on β-cell function.

RESULTS — The age-adjusted prevalences of the risk factors are shown in Table 1. The prevalences of risk factors were in the

Table 2—*Comparison of anthropometric variables in subjects with and without various abnormalities*

	BMI (kg/m²)	WHR	Waist circumference (cm)
Nonhypertension	23 ± 4.0	0.89 ± 0.07	82.7 ± 10.3
Hypertension	23.9 ± 4.2	0.884 ± 0.07	84.2 ± 10.7
	$P = 0.02$		
NGT	22.9 ± 4.0	0.89 ± 0.07	82.6 ± 10.2
IGT	24.3 ± 4.4	0.89 ± 0.07	84.8 ± 10.9
	$P = 0.003$		$P = 0.049$
Normal lipids	22.6 ± 4.2	0.876 ± 0.07	81.4 ± 10.6
Dyslipidemia	23.7 ± 4.0	0.897 ± 0.07	84.5 ± 10.0
	$P = 0.004$	$P = 0.001$	$P < 0.001$
Nonhypertension + NGT	23.1 ± 4.0	0.89 ± 0.07	82.2 ± 10.3
Hypertension + IGT	25.8 ± 5.1	0.89 ± 0.07	87.6 ± 10.7
	$P = 0.006$		$P = 0.012$
Nonhypertension + NGT	23.1 ± 4.1	0.89 ± 0.07	82.5 ± 10.4
Hypertension + dyslipidemia	24.5 ± 4	0.9 ± 0.06	86.3 ± 9.8
	$P = 0.006$		$P = 0.003$
Nonhypertension + NGT + nondyslipidemia	23.1 ± 4.0	0.89 ± 0.07	82.9 ± 10.3
Hypertension + IGT + dyslipidemia	23.5 ± 5.5	0.91 ± 0.06	88.9 ± 11.4
	$P = 0.07$		$P = 0.011$

Data are means ± SD. NGT, normal glucose tolerance.

order of central adiposity > dyslipidemia > hyperinsulinemia (2-h) > glucose intolerance > obesity > hypertension. Women had higher prevalences of increased 2-h insulin (64.2 vs. 49%, $P < 0.001$), glucose intolerance (43.5 vs. 35.6%, $P < 0.003$), and obesity (33.4 vs. 21.4%, $P < 0.001$), but lower central adiposity (56.6 vs. 64.1%, $P < 0.001$) compared with men. The age-adjusted prevalence of probable CHD was 3.9% (3.5% in men and 4.5% in women, NS), and T wave inversion was seen in an additional 10.3%.

Results of Pearson correlation analysis showed that fasting plasma insulin had a significant correlation with BMI ($r = 0.286$, $P < 0.001$), WHR ($r = 0.08$, $P = 0.03$), waist circumference ($r = 0.228$, $P < 0.001$), cholesterol ($r = 0.118$, $P < 0.001$), and TG ($r = 0.197$, $P < 0.001$), while 2-h insulin showed correlations with BMI ($r = 0.185$, $P < 0.001$), cholesterol ($r = 0.181$, $P < 0.001$), and TG ($r = 0.093$, $P < 0.015$). Age, sBP, and dBP did not show significant correlations with either of the measurements of insulin. Therefore, values for analyses involving plasma insulin were adjusted for BMI and waist circumference.

Table 1 also shows the observed and expected occurrence of the risk factors in isolation and in combination. Isolated prevalences of all factors, except hypertension, were in lower frequency than expected. Combinations of each risk factor with one and two more risk factors occurred more frequently (1.3–4 times) than expected by chance; with three additional abnormalities, the observed/expected (O/E) ratios were <1.

Results of Table 2 showed that hypertension was associated with higher BMI compared with nonhypertension. IGT, dyslipidemia, and hypertension plus IGT were associated with higher values of waist circumference. All combinations except hypertension plus IGT plus dyslipidemia were associated with BMI. BMI was the most common variable associated with hemodynamic and metabolic abnormalities. Waist circumference also showed association with all abnormalities except hypertension.

Table 3 showed that hypertension was the only variable that showed no association with increased levels of fasting or 2-h insulin values, except when it was in combination with IGT and dyslipidemia. Maximum clustering of abnormalities occurred with dyslipidemia and the least with hypertension.

Table 4 shows the results of multiple logistic regression analyses after adjusting for age, sex, BMI, and waist circumference. IGT plus hypertension, IGT plus dyslipidemia, and a combination of IGT plus hypertension plus dyslipidemia showed significant associations with 2-h insulin values against cases not having the tested combinations.

In a multiple logistic regression equation excluding subjects with diabetes and treated cases of hypertension, hypertension was found to be associated with age ($\beta = 0.30$, $SE\beta = 0.126$, $P = 0.02$, odds ratio [OR] = 1.35) and family history of CHD ($\beta = 0.99$, $SE\beta = 0.36$, $P = 0.0056$, OR = 2.6) only. Sex, 2-h glucose, BMI, WHR, and fasting and 2-h plasma insulin values were not significantly associated with hypertension.

Table 3—*Comparison of plasma insulin responses in normal subjects and subjects with abnormalities*

	Fasting plasma insulin (μU/ml)	2-h plasma insulin (μU/ml)
Nonhypertension	15.3 ± 11.0	62.4 ± 56.8
Hypertension	16.4 ± 10.5	67.6 ± 60.3
NGT	14.6 ± 10.6	52 ± 48
IGT	19.2 ± 11.3	107 ± 68
	$P < 0.001$	$P < 0.001$
Normal lipids	13.1 ± 9.6	52 ± 51
Dyslipidemia	17.8 ± 11.5	74 ± 61
	$P < 0.001$	$P < 0.001$
Nonhypertension + NGT	15.3 ± 10.8	60.3 ± 55.1
Hypertension + IGT	21 ± 12.3	122.2 ± 70
	$P = 0.014$	$P < 0.0001$
Nonhypertension + nondyslipidemia	15.4 ± 10.8	62.7 ± 57
Hypertension + dyslipidemia	17.1 ± 11.6	70.8 ± 64
Nonhypertension + NGT + nondyslipidemia	15.4 ± 10.6	62 ± 56
Hypertension + IGT + dyslipidemia	20.3 ± 14.3	116 ± 71
		$P < 0.001$

Data are means ± SD. NGT, normal glucose tolerance.

Table 4—*Results of multiple logistic regression analyses after correcting for age, sex, BMI, and waist circumference*

Dependent variables	Log fasting plasma insulin				Log 2-h plasma insulin			
	β	SEβ	*P*	OR (95% CI)	β	SEβ	*P*	OR (95% CI)
IGT + hypertension vs. NGT + nonhypertension	−0.468	0.424	0.27	0.63 (0.27–1.44)	1.665	0.36	<0.0001	5.29 (2.61–10.7)
Hypertension + dyslipidemia vs. nonhypertension + nondyslipidemia	0.282	0.26	0.27	1.33 (0.80–2.21)	0.147	0.18	0.421	1.16 (0.81–1.65)
IGT + dyslipidemia vs.NGT + nondyslipidemia	0.375	0.283	0.186	1.45 (0.84–2.53)	1.64	0.25	<0.0001	5.166 (3.16–8.41)
IGT + hypertension + dyslipidemia vs. NGT + nonhypertension + nondyslipidemia	−0.205	0.59	0.726	0.814 (0.26–2.59)	2.01	0.50	0.0001	7.493 (2.8–19.89)

NGT, normal glucose tolerance.

CONCLUSIONS — We have recently reported a rising prevalence of NIDDM in the urban population in India (11). There is a paucity of data on cardiovascular risk factors in native Indians. Migrant Asian Indians have increased mortality from CHD in the U.K. compared with Europeans (13,18). The excess cardiovascular risk was not explained by any conventional factors, such as obesity or smoking (18).

This study reports the prevalence of CHD and the cardiovascular risk factors in the native urban Indian population. The study highlights the fact that native Indians who have a high prevalence of diabetes also have a clustering of cardiovascular risk factors or syndrome X. The observed frequency of isolated risk factors, except for hypertension, was lower than the expected value, showing that the risk factors occurred more frequently in combination. Combinations of each risk factor with one or two more risk factors occurred more frequently than expected by chance. Hyperinsulinemia was an associated feature in the combinations with IGT. Zimmet et al. (9) noted that in the mixed population of Mauritius, clustering of cardiovascular risk factors, especially the association of three or more combinations, was about four times greater than expected. The study group consisted of Asian Indians, Creoles, and Chinese, and intergroup differences were absent in the results. Both the present study and the study by Zimmet et al. found that values of the risk factors were higher when in combination than when occurring in isolation.

Hyperinsulinemia was shown to be a characteristic feature of native Indians (16) and also migrant Asian Indians living in several countries (12–14,17,18,22). Therefore, it is likely to have a major role in the causation of metabolic abnormalities associated with syndrome X. Hyperinsulinemia, indicated by high 2-h plasma insulin, was associated with IGT, with dyslipidemia, and with clusters in which IGT was a component. But it was noted that hypertension was not associated with increased insulin values. The prevalence of hypertension was higher among those with IGT and diabetes. In a prospective analysis of the San Antonio Heart Study cohort, Haffner et al. (7) noted that the basal fasting insulin was predictive of a cluster of metabolic disorders in Mexican-Americans and non-Hispanic whites. Ferrannini et al. (29) felt that this was not applicable to all populations. Zimmet et al. (9) found that such a relationship did not apply to the population of Mauritius.

The lack of an association of insulin concentration with hypertension has been previously reported in many ethnic groups, including Mauritians (23), Micronesians, Polynesians and Melanesians (24), Pima Indians (25,26), American blacks (26), and some European populations (27,28). In the Mauritian study, insulin concentration was not significantly different between normotensive and hypertensive Asian Indian, Creole, and Chinese subjects in any glucose tolerance group (10). Ethnic differences in the role of insulin in determining blood pressure are evident from the above studies. Although elevated insulin levels can cause several metabolic changes that lead to hypertension (27), the mechanisms underlying such a link are not clearly understood. Saad et al. (26) have clearly demonstrated racial differences in the relationship between blood pressure and insulin in a study comparing Pima Indians, whites, and American blacks. While a positive relation between the two parameters was observed in the whites, it was absent in the other two races.

We have not analyzed the association of CHD with glucose intolerance and hypertension because the number of subjects with CHD was small. The prevalence of CHD was 3.9% in the study population, aged ≥40 years. There was no sex difference with respect to the occurrence of CHD. Similar observations had been recorded by McKeigue et al. (12,13,18) in South Asians in the U.K. The prevalence of CHD in urban Indians appear to be similar to that reported in migrant Asian Indians. McKeigue et al. noted a higher prevalence of ischemic ECG abnormalities among South Asians than among Europeans (17 vs. 12%, $P < 0.001$), with an excess of major Q waves in younger South Asian men. CHD was seen in 4% of Asian men aged 40–59 years in their study, while it was 3.9% in our analysis. There are no mortality data from CHD in Indian populations that could be compared with the data available in migrant Indians. However, two studies from northern India showed that the prevalence of CHD was 3.2% (30) and 2.8% (31) in the urban population.

Among the components of prevalences of glucose intolerance, hyperinsulinemia and upper body adiposity have already been reported in urban Indians (11,32,33). This study shows the clustering of these with other components of IRS in the native Indian population. Central adiposity, indicated by a high WHR, has been found to be a characteristic feature of Asian Indians (13,14,32,33). This study shows that the waist circumference, rather than the WHR, is more strongly associated with insulin resistance. Efforts need to be targeted to prevent the metabolic abnormalities, to combat the rising prevalence of diabetes and CHD.

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