Insulin resistance, high prevalence of diabetes, and cardiovascular risk in immigrant Asians.

Genetic or environmental effect?

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Abstract

Objectives—To compare the prevalence of diabetes, hyperinsulinaemia, and associated metabolic abnormalities in immigrant Asians, Asians in India, and native white British men.

Design—Case control study.

Setting—Wythenshawe Hospital, Manchester, United Kingdom, and Maulana Azad Medical School, New Delhi, India.

Subjects—Men with angiographically proved coronary artery disease; 83 British Asians, 87 white men, and 30 Indian Asians with age matched controls.

Interventions—Fasting lipid concentrations, serum glucose, and total insulin concentrations were measured in the fasting state and one and two hours after a 75 g glucose load by mouth. All subjects had a physical examination by the same observer.

Results—Asians in the United Kingdom and in India had a higher prevalence of diabetes and impaired glucose tolerance than the white British men. Patients in all three ethnic groups had higher total insulin concentrations than their controls in the fasting state and after the glucose load. British Asian and Indian Asian patients and controls had higher total insulin concentrations than the white men in the fasting state and after the glucose load. Total insulin concentrations were similar in British and Indian Asians, though fasting concentrations were higher in British Asians than Indian Asians. White men had similar cholesterol, lower triglyceride, and higher high density lipoprotein cholesterol concentrations than Asians in the United Kingdom and in India. British Asian patients had higher cholesterol concentrations and British Asian controls had higher triglyceride concentrations than the Indian Asian groups. Asian patients and controls were more active. British and Indian Asian patients had higher waist to hip ratios than controls. The waist to hip ratio was positively correlated with insulin and triglyceride concentrations and negatively correlated with the high density lipoprotein cholesterol concentration. Fasting insulin and high density lipoprotein concentrations were independent predictors of coronary artery disease in white men, whereas in British Asians the waist to hip ratio was the strongest independent predictor. In

Indian Asians the waist to hip ratio and high density lipoprotein concentration were independent predictors of coronary artery disease.

Conclusions—Central obesity in the subgroups of Asians studied showed a close association with hyperinsulinaemia and the risk of coronary artery disease. A predisposition to insulin resistance and its metabolic abnormalities in this group of Asians seems to be genetically determined, environmental changes after migration having only a small additional effect.

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The United Kingdom has one of the highest death rates from coronary artery disease. Evidence has emerged that male and female migrants from the Indian subcontinent have a higher mortality from coronary artery disease than the native white population.^{1,2} Immigrants from the Indian subcontinent belong to differing geographical, cultural, and religious groups; however, the high mortality is shared by the various groups of Asians.^{3,4}

Established risk factors such as increased plasma cholesterol concentrations, hypertension, and smoking do not explain this high mortality from coronary artery disease in immigrant Asians.¹ Studies in Asian communities in the United Kingdom have suggested that a higher prevalence of non-insulin dependent diabetes mellitus, lower plasma high density lipoprotein cholesterol concentrations, and higher plasma triglyceride concentrations may be additional risk factors for coronary artery disease in this racial group.⁵⁻⁷ Insulin resistance has been suggested as the underlying common mechanism in immigrant Asians, leading to diabetes mellitus and lipid abnormalities.⁷ Hyperinsulinaemia has also been shown in survivors of first myocardial infarction in Asians in the United Kingdom compared with the native white population.⁵

Hughes *et al*⁸ have reported that first myocardial infarction in mainly Gujarati Asians from London occurs at a significantly younger age than in white subjects. Hughes *et al*⁵

reported significantly higher concentrations of insulin in Asians than in white survivors of first myocardial infarction. Only two hour insulin concentrations after glucose given by mouth were measured in their study. They suggested that insulin may be responsible for

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"atherogenic" lipid abnormalities in the Asian patients studied, and also for enhanced atherosclerosis and, as a consequence, the increased mortality from coronary artery disease seen in Asian immigrants.

Central obesity has been associated with hyperinsulinaemia⁹ and it has been suggested that the over production of insulin may act as an energy conserving mechanism under conditions of periodic famine and low energy intake. It has also been suggested that non-insulin dependent diabetes and other disturbances associated with insulin resistance and central obesity are consequences of environmental influences, such as low physical activity and high energy intake, in Asian immigrants transported into urban British life.^{6,7}

This supposition is only speculative as there are no studies comparing Asians in the Indian subcontinent with Asians in the United Kingdom.

The present work seeks differences in coronary risk factors and the role of insulin resistance, central obesity, and physical activity in patients with coronary artery disease and controls in Asians in the United Kingdom and in India, and explores any effect of environment on these abnormalities after migration.

Subjects and methods

SUBJECTS

Consecutive series of male British Asian patients referred for diagnostic coronary angiography for chest pain between January 1988 and March 1990 were included if they fulfilled the following criteria: (a) 50% or more stenosis in one or more major epicardial coronary arteries; and (b) permanent resident of the United Kingdom. Patients with familial hypercholesterolaemia and those being investigated for a valve disorder but with additional coronary artery disease were excluded.

White patients were randomly selected from the catheter laboratory register throughout the period of the study using the same criteria.

Consecutive series of Indian Asian patients having diagnostic coronary angiography in the G B Pant Cardiac Centre and Maulana Azad Medical School, New Delhi, India, between 24 December 1989 and 24 January 1990 were included in the study using the same angiographic criteria.

CONTROLS

Controls from the United Kingdom were recruited from the lists of five local general practices. They were randomly selected and as far as possible age matched with their respective patient group. After review of the medical records the following patients were excluded: those with a documented history of myocardial infarction, angina, or stroke; those with a primary lipid disorder; patients with hypertension receiving treatment; and temporary residents. Age matched Indian Asian controls were recruited randomly from the

minor surgical outpatients clinic of the same hospital from which patients were recruited. Similar appropriate exclusions were observed as in the controls from the United Kingdom.

PROCEDURE

After an overnight fast, subjects attended between 8.30am and 9.30am and a fasting (venous) blood sample was taken. Anhydrous dextrose (75 g) diluted in 500 ml water was then ingested by all subjects. Further blood samples were taken after 60 and 120 minutes; the 60 minute sample was omitted in the Indian Asians. Those patients receiving a thiazide diuretic were asked not to take this drug for three days before blood sampling and those receiving β blockers had their treatment substituted with a calcium antagonist one month before blood sampling in view of the influence of these drugs on serum lipid concentrations.¹⁰⁻¹¹ Patients with non-insulin dependent diabetes were asked to omit all hypoglycaemic drugs for 24 hours (48 hours for chlorpropamide). Blood samples were not taken from three British Asian patients with insulin dependent diabetes.

A detailed history was taken of demographic details, medical history, smoking habits, social class, and exercise. "Non-sedentary" was defined as those who were either on their feet most of the day as part of their job, or taking regular physical exercise (at least once a week for at least 20 minutes); "sedentary" was defined as those who were on their feet for less than half the day as part of their job and not taking any form of regular exercise. Patients were asked about their levels of physical activity before the onset of their symptoms.

LABORATORY MEASUREMENTS

All laboratory analyses for British Asians and white patients were performed within 24 hours of sampling, except for the insulin measurements, for which serum was separated immediately and stored at -20°C and measurements made within three to five weeks. For Indian Asians, plasma glucose was measured within 24 hours of sampling; serum for insulin measurement was stored at -20°C and transported to the United Kingdom on dry ice. Serum for lipid measurement was transported in an insulated box to the laboratory in the United Kingdom. Blood for lipid measurement was taken after overnight fasting in Indian Asians, no more than four days before transporting the samples to the United Kingdom.

Serum glucose was measured by an automated glucose oxidase method. Subjects were classified as normoglycaemic if their two hour serum glucose concentration was less than 7.8 mmol/l or as having impaired glucose tolerance if their glucose concentration was greater than or equal to 7.8 mmol/l and less than 11.1 mmol/l. Subjects were classified as diabetic if their glucose concentration was greater than or equal to 11.1 mmol/l after glucose challenge.¹²

Plasma total insulin was measured by

Map of Indian subcontinent showing the origin of Asians studied from the UK and India.

radioimmunoassay using a commercially available kit (Diagnostic Products Limited); the tests were performed in duplicate. The interassay variability was less than 6% throughout. All measurements were performed in the same laboratory at Wythenshawe Hospital by the same biochemist (RW).

Data were analysed using the SPSSX software program. Group means were compared using unpaired Student's *t* tests; where appropriate, the raw data were log transformed to normalise distributions. Distributions were compared using χ^2 tests. Unconditional logistic regression analysis was performed to examine the relation between risk factors within the study groups. The relative risk of coronary

atherosclerosis in each ethnic group was computed on univariate analysis. Multiple regression analysis was performed by a backwards stepwise method in an attempt to assess the relative influence of each risk factor on the presence of coronary atheroma in each patient group.

Eighty three male British Asian and 87 white male patients, along with 80 and 81 controls, respectively, 30 male Indian patients, and 30 controls were recruited in the study.

The British Asian patient and control groups consisted predominantly of people who had migrated from the undivided Punjab (now partly in Pakistan and partly in India) (figure). Seventy four British Asian patients

Table 1 Mean (SD) blood pressure and body size morphology, current smokers, and interval (median) between onset of angina and coronary angiography (in patients)

	White subjects		British Asians		Indian Asians		P Value*
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)	
Age (years)	56.7 (8.7)	56.4 (8.9)	51.9 (7.1)	51.6 (7.7)	50.0 (8.6)	49.5 (10.0)	<0.001
Height (cm)	173.1 (6.3)	174.9 (6.7)	169.7 (6.8)	169.1 (5.6)	169.5 (5.3)	168.6 (5.8)	<0.01
Weight (kg)	76.9 (11.0)	76.1 (9.2)	73.5 (9.1)	70.4 (7.9)	68.7 (8.7)	68.5 (8.2)	<0.001
BMI (kg/m ²)	25.7 (3.2)	24.9 (2.4)	25.5 (9.9)	24.6 (2.2)	23.9 (2.9)	24.1 (2.7)	0.02
WHR	0.97 (0.06)	0.96 (0.05)	1.02 (0.05)	0.97 (0.75)	1.00 (0.6)	0.96 (0.06)	<0.001
Systolic BP (mm Hg)	137.8 (24.4)	137.0 (16.6)	130.2 (20.6)	122.1 (18.0)	138.0 (19.5)	132.5 (18.8)	<0.01
Diastolic BP (mm Hg)	81.8 (10.5)	82.4 (7.8)	79.1 (8.3)	77.9 (7.3)	81.0 (7.2)	80.5 (6.5)	<0.05
Time in United Kingdom (yr)	—	—	27.4 (5.9)	27.2 (7.3)	—	—	NS
Non-sedentary (%)	32/37 (37)	30/87 (34)	19/83 (23)	14/80 (17)	16/30 (53)	20/30 (67)	<0.01
Mean lifetime cigarette consumption of ex-smokers and current Smokers (1000s)	212 (164-267)	160 (121-204)	159 (121-203)	139 (92-196)	150 (77-246)	85 (52-127)	NS

BMI = Body mass index; WHR = weight to height ratio; BP = blood pressure. * Analysis of variance.

Table 2 Social class distribution (%)

	White subjects		British Asians		Indian Asians	
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)
Social class 1	11	12	12	12	3	7
Social class 2	38	37	34	34	41	40
Social class 3	44	48	47	48	44	37
Social class 4	7	3	7	6	12	16

χ^2 (15) = 10.5; P = 0.78.

Table 3 Difference in the prevalence of diabetes, impaired glucose tolerance, and normoglycaemia. Values are No (%)

	White subjects		British Asians		Indian Asians	
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)
Diabetic	7 (8)	2 (2)	21 (25)	9 (11)	10 (33)	5 (17)
Impaired glucose tolerance	15 (17)	6 (7)	19 (23)	16 (20)	7 (23)	5 (17)
Normoglycaemic	65 (75)	73 (90)	43 (52)	55 (69)	13 (43)	20 (67)

χ^2 (5) = 30.6; P = 0.00001.

Table 4 Geometric means (95% confidence intervals) of glucose and insulin concentrations at fasting and one and two hours after glucose load by mouth

	White subjects		British Asians		Indian Asians		P Value*
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)	
Glucose (mmol/l)							
Fasting	4.77 (4.5 to 5.0)	4.40 (4.2 to 4.61)	5.34 (4.97 to 5.74)	4.91 (4.53 to 5.32)	5.58 (4.87 to 6.39)	5.01 (4.45 to 5.64)	NS
One hour	7.76 (7.22 to 8.32)	7.24 (6.74 to 7.77)	9.88 (9.17 to 10.66)	8.39 (7.73 to 9.10)	—	—	<0.05
Two hour	6.13 (5.61 to 6.70)	5.19 (4.30 to 5.61)	7.37 (6.64 to 8.19)	6.34 (5.69 to 6.84)	8.08 (6.79 to 9.65)	7.25 (6.3 to 8.35)	<0.10
Insulin (μU/ml)							
Fasting	12.7 (10.8 to 14.9)	7.6 (6.5 to 8.8)	28.2 (24.5 to 31.8)	18.6 (16.4 to 20.9)	18.4 (15.6 to 21.6)	14.2 (12.1 to 16.6)	<0.001
One hour	72.7 (63.0 to 83.8)	51.6 (44.9 to 59.3)	122.0 (104.8 to 142.0)	90.0 (79.3 to 102.3)	—	—	<0.05
Two hour	43.5 (36.5 to 51.9)	26.8 (22.2 to 32.3)	83.3 (70.2 to 96.4)	58.0 (51.2 to 65.1)	8.62 (6.12 to 12.10)	6.53 (4.92 to 8.66)	<0.05

*Analysis of variance.

Table 5 Geometric mean (95% confidence intervals) of insulin concentrations (μU/ml) at fasting and one and two hours after glucose given by mouth by glucose tolerance categories

	White subjects		British Asians		Indian Asians		Significance P < 0.05
	(a) Patients (n = 87)	(b) Controls (n = 81)	(c) Patients (n = 83)	(d) Controls (n = 80)	(e) Patients (n = 30)	(f) Controls (n = 30)	
Diabetic							
Fasting	2.90 (13.6 to 61.9)	14.7*	24.7 (18.6 to 32.9)	33.6 (19.6 to 57.6)	14.9 (10.7 to 20.7)	14.6 (4.9 to 42.9)	
One hour	84.0 (47.4 to 146.9)	25.9*	63.1 (41.6 to 94.6)	69.0 (36.2 to 121.5)	—	—	
Two hour	70.0 (52.4 to 92.7)	25.8*	53.8 (36.2 to 36.2 to 79.0)	67.0 (36.2 to 122.7)	44.4 (29.3 to 66.6)	32.6 (82.2 to 128.0)	
Impaired glucose tolerance							
Fasting	17.6 (11.1 to 27.6)	9.7 (3.7 to 24.7)	36.3 (26.8 to 48.4)	24.0 (18.7 to 30.5)	25.1 (17.9 to 34.4)	17.0 (12.4 to 23.0)	c > a
One hour	85.6 (55.1 to 131.6)	72.1 (38.1 to 134.2)	172.2 (138.3 to 210.6)	117.2 (95.5 to 141.1)	—	—	c > a
Two hour	87.2 (60.9 to 123.9)	59.2 (26.8 to 129.0)	120.4 (93.6 to 152.9)	84.6 (69.4 to 102.5)	133.2 (90.0 to 196.3)	99.8 (89.1 to 111.0)	
Normoglycaemic							
Fasting	10.8 (9.1 to 12.1)	7.3 (6.1 to 8.5)	26.6 (22.6 to 30.8)	15.6 (13.8 to 17.4)	18.3 (14.5 to 22.8)	13.4 (11.5 to 15.3)	c > d, c > a
One hour	68.8 (58.5 to 80.6)	51.2 (43.8 to 59.1)	138.4 (116.7 to 160.7)	87.2 (74.4 to 100.4)	—	—	d > b, a > b
Two hour	35.2 (28.7 to 42.5)	25.1 (20.5 to 30.2)	83.1 (67.3 to 101.5)	50.4 (44.2 to 57.3)	69.4 (48.4 to 98.5)	43.1 (31.2 to 58.5)	c > a, d > b

*Insufficient number for confidence intervals.

had migrated from the Punjab and nine migrated from elsewhere to the United Kingdom (Gujarat, Kenya, Bangladesh); there were 75 British Asian controls who had migrated from the Punjab and five from elsewhere. All the patients and controls studied in Delhi, India, had migrated from the Punjab in 1947 after the partition of India. Thus most British Asians and Indian Asians had origi-

nated from a similar geographical area in the Indian subcontinent. The British Asian patients and controls had been resident in the United Kingdom for a similar length of time (table 1).
British Asian patients and controls were younger, shorter, and lighter in weight than their comparative white patients. No significant difference in age, height, or weight was seen between Indian Asians and British Asians. Social class in the three ethnic groups was similar (table 2) and smoking rates were also similar (table 1). Body mass index was similar in the different racial groups; however, within groups British Asian patients had a higher body mass index than their controls. The only differences in systolic and diastolic blood pressure were between British Asian and white controls (being lower in British Asians).

A striking difference was seen in the waist to hip ratio. Patients had a higher waist to hip ratio than controls in both the Asian groups; British Asian patients and controls had higher waist to hip ratios than white patients. Asian patients and controls from the United Kingdom had similar waist to hip ratios to Asians from India (table 1).
The prevalence of diabetes and impaired

Table 6 Mean (SD or 95% confidence intervals) cholesterol and triglyceride concentrations in patients and controls (all values mmol/l)

	White subjects		British Asians		Indian Asians		P Value*
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)	
Total cholesterol	6.32 (1.14)	6.08 (0.90)	6.16 (1.09)	5.69 (0.96)	5.44 (1.06)	5.04 (1.05)	<0.05
Log HDL cholesterol	1.08 (1.02 to 1.14)	1.29 (1.22 to 1.36)	1.02 (0.97 to 1.07)	1.07 (1.02 to 1.12)	0.89 (0.81 to 0.98)	1.22 (1.11 to 1.35)	<0.01
Total cholesterol/HDL cholesterol							
HDL cholesterol	6.06 (1.95)	4.88 (1.48)	6.11 (1.49)	5.41 (1.30)	6.09 (1.32)	4.20 (1.20)	<0.001
Log triglyceride	1.79 (1.60 to 2.01)	1.30 (1.19 to 1.43)	2.39 (1.64 to 2.16)	1.84 (1.66 to 2.03)	1.91 (1.68 to 2.19)	1.38 (1.16 to 1.64)	<0.01

HDL = High density lipoprotein
* Analysis of variance.

Table 7 Comparison between sedentary and non-sedentary subjects with respect to insulin concentrations, body mass index, lipids, and blood pressure. Values are mean (SD or 95% confidence intervals)

	All subjects		P value
	Sedentary (n = 260)	Non-sedentary (n = 131)	
Log insulin concentrate (μU/ml)			
Fasting	17.1 (15.6 to 18.7)	11.6 (10.3 to 12.9)	<0.0001
One hour	88.2 (80.6 to 92.7)	62.1 (54.5 to 70.8)	<0.001
Two hours	57.9 (52.4 to 64.0)	36.2 (29.3 to 37.3)	<0.001
BMI (kg/m ²)	25.53 (0.16)	23.95 (0.23)	<0.001
Total cholesterol (mmol/l)	5.97 (0.06)	5.88 (0.10)	NS
Log triglyceride (mmol/l)	1.85 (1.73 to 1.95)	1.60 (1.50 to 1.69)	<0.01
Log HDL cholesterol (mmol/l)	1.08 (1.06 to 1.10)	1.12 (1.07 to 1.16)	NS
Systolic blood pressure (mm Hg)	133.9 (1.2)	129.4 (1.8)	<0.05
Diastolic blood pressure (mm Hg)	81.12 (1.1)	78.96 (1.6)	<0.01

HDL = High density lipoprotein.

glucose tolerance was much higher in British Asians than white patients and even higher in Indian Asians. Only 43% of Indian Asian patients and 52% of British Asian patients were normoglycaemic compared with 75% of white patients (table 3).

Fasting serum insulin concentrations were higher in patients than controls in all three racial groups ($P < 0.001$), with British Asian patients having significantly higher concentrations than any other group, and the two Asian groups having significantly higher concentrations than white patients. At one hour after glucose challenge, the patients had higher concentrations than the controls ($P < 0.001$), with British Asians having significantly higher concentrations than white patients (one hour sample was omitted in Indian Asians).

At two hours after the glucose given by mouth, white and British Asian patients had higher concentrations than controls ($P < 0.001$); Indian Asian patients and controls were not different. Asian groups had signifi-

cantly higher concentrations than white patients. Concentrations were comparable in Asians in the United Kingdom and in India (table 4).

As there was a larger proportion of patients with diabetes and impaired glucose tolerance in Asians than white men, the racial groups were subdivided according to glucose category to examine the effect of glucose status on insulin concentrations (table 5). These concentrations were higher in patients with impaired glucose tolerance than in normoglycaemic patients in the same subgroup. Normoglycaemic patients had significantly higher insulin concentrations than controls, except in Indian Asians in fasting, one and two hour samples after glucose by mouth. British Asians and Indian Asians had higher concentrations than white patients at all stages of the oral glucose tolerance test ($P < 0.001$). Indian Asian non-diabetic patients had higher insulin concentrations than controls at two hours: 87.2 (65.3–115.5) v 51.0 (38.0–67.3) μU/ml ($P < 0.01$).

LIPIDS

Triglyceride concentrations were higher in British Asian patients than in any other group except Indian Asian patients ($P < 0.01$). British Asian and white patients had higher concentrations than their controls ($P < 0.01$). In the controls British Asians had significantly higher concentrations than white men and Indian Asians (table 6).

High density lipoprotein concentrations were lower in white patients and Indian Asians than in their controls ($P < 0.01$). White controls had significantly higher concentrations than any other group except

Table 8 Comparison between sedentary and non-sedentary white subjects. Values are mean (SD or 95% confidence interval)

	White patients		White controls		P Value (patients)	P Value (controls)
	No regular exercise (n = 55)	Regular exercise (n = 32)	No regular exercise (n = 51)	Regular exercise (n = 30)		
Log insulin (μU/ml)						
0 hours	15.95 (7.9 to 19.4)	8.41 (7.1 to 9.8)	7.56 (6.29 to 9.0)	7.57 (5.69 to 9.97)	<0.001	NS
One hour	84.77 (75.1 to 99.4)	54.9 (43.8 to 68.1)	52.4 (45.6 to 62.8)	47.9 (37.7 to 60.9)	<0.01	NS
Two hours	56.26 (46.0 to 68.7)	27.66 (22.1 to 34.4)	27.9 (21.9 to 35.5)	24.5 (18.9 to 31.8)	<0.001	NS
Body mass index (kg/m ²)	26.31 (0.43)	24.55 (0.52)	25.13 (0.34)	24.42 (0.42)	<0.01	NS
Total cholesterol (mmol/l)	6.18 (0.13)	6.56 (0.23)	6.11 (0.11)	6.02 (0.18)	NS	NS
Log triglyceride (mmol/l)	1.78 (1.5 to 2.0)	1.80 (1.5 to 2.1)	1.27 (1.12 to 1.43)	1.33 (1.18 to 1.50)	NS	NS
Log HDL cholesterol (mmol/l)	1.07 (1.01 to 1.13)	1.08 (1.0 to 1.1)	1.28 (1.20 to 1.36)	1.29 (1.19 to 1.40)	NS	NS
Systolic BP (mm Hg)	141.8 (3.0)	130.8 (4.6)	138.3 (2.3)	134.6 (2.8)	<0.05	NS
Diastolic BP (mm Hg)	83.8 (16.6)	78.2 (28.8)	82.5 (1.1)	82.1 (1.3)	<0.05	NS

HDL = high density lipoprotein; BP = blood pressure.

Table 9 Comparison between sedentary and non-sedentary British Asian subjects. Values are mean (SD or 95% confidence interval)

	British Asian patients		British Asian controls		P Value (patients)	P Value (controls)
	No regular exercise (n = 61)	Regular exercise (n = 19)	No regular exercise (n = 66)	Regular exercise (n = 14)		
Log insulin (μU/ml)						
0 hours	31.8 (26.0 to 36.5)	18.9 (15.1 to 21.7)	19.6 (17.4 to 22.1)	13.5 (11.1 to 16.6)	<0.001	<0.01
One hour	127.7 (106.6 to 152.9)	125.2 (77.4 to 135.6)	93.6 (81.4 to 107.7)	73.6 (62.8 to 86.4)	NS	<0.05
Two hours	94.6 (80.6 to 111)	50.90 (37.7 to 68.7)	60.9 (54.0 to 68.7)	42.5 (34.4 to 47.4)	<0.001	<0.05
Body mass index (kg/m ²)	25.92 (0.34)	24.32 (0.71)	24.90 (0.27)	23.05 (0.48)	<0.05	<0.01
Total cholesterol (mmol/l)	6.21 (0.14)	5.96 (1.8)	5.65 (0.11)	5.88 (0.29)	NS	NS
Log triglyceride (mmol/l)	2.50 (2.2 to 2.7)	1.95 (1.6 to 2.3)	1.82 (1.6 to 2.0)	1.85 (1.6 to 2.1)	<0.05	NS
Log HDL cholesterol (mmol/l)	1.0 (0.9 to 1.0)	1.09 (1.03 to 1.16)	1.05 (1.01 to 1.09)	1.11 (1 to 1.2)	NS	NS
Systolic BP (mm Hg)	132.5 (2.6)	122.1 (4.1)	124.7 (2.2)	109.7 (3.1)	<0.05	<0.01
Diastolic BP (mm Hg)	79.9	76.3	78.8	73.5	NS	<0.05

HDL = High density lipoprotein; BP = blood pressure.

Table 10 Comparison between sedentary and non-sedentary Indian Asian subjects. Values are mean (SD or 95% confidence interval)

	Indian Asian patients		Indian Asian controls		P Value (patients)	P Value (controls)
	No regular exercise (n = 14)	Regular exercise (n = 16)	No regular exercise (n = 10)	Regular exercise (n = 20)		
Log insulin (μU/ml)						
0 hour	16.7 (12.6 to 21.3)	19.8 (15.1 to 21.7)	16.1 (14.0 to 18.5)	13.1 (11.4 to 15.1)	NS	NS
One hour						
Two hours	64.0 (42.9 to 95.5)	74.4 (55.1 to 100.4)	79.0 (46.9 to 132.9)	36.2 (29.6 to 44.2)	NS	<0.01
Body mass index (kg/m ²)	25.06 (0.7)	22.92 (0.6)	25.56 (0.53)	23.36 (0.65)	<0.05	<0.05
Total cholesterol (mmol/l)	5.61 (0.3)	5.28 (0.2)	5.12 (0.43)	5.00 (0.19)	NS	NS
Log triglyceride (mmol/l)	2.33 (1.9 to 1.1)	1.59 (1.3 to 1.8)	1.58 (1.06 to 2.3)	1.29 (1.1 to 1.4)	<0.01	NS
Log HDL cholesterol (mmol/l)	1.04 (0.9 to 1.1)	1.17 (1.0 to 1.2)	1.28 (1.05 to 1.5)	1.19 (1.9 to 1.3)	NS	NS
Systolic BP (mm Hg)	132.6 (5.7)	142.7 (4.2)	138.0 (6.2)	129.7 (4.0)	NS	NS
Diastolic BP (mm Hg)	80.2 (2.1)	81.6 (1.7)	82.6 (2.4)	79.4 (1.2)	NS	NS

HDL = High density lipoprotein; BP = blood pressure.

Table 11 Pearson correlation coefficients between waist to hip ratio, lipids, and insulin concentrations

	White subjects		British Asians		Indian Asians	
	Patients (n = 87)	Controls (n = 81)	Patients (n = 83)	Controls (n = 80)	Patients (n = 30)	Controls (n = 30)
Total cholesterol	0.08	0.18	-0.008	0.22	0.34	0.18
Log HDL cholesterol	-0.16	-0.27*	0.003	-0.03	0.37*	-0.01
Log triglyceride	0.15	0.23*	0.19	0.29†	0.36*	0.33
Log insulin						
Fasting	0.38†	0.20	0.43†	0.44†	0.10	0.21
One hour	0.17	0.32†	0.20	0.27*	—	—
Two hours	0.38†	0.24	0.32†	0.50†	0.13	0.41*

* P < 0.05. †P < 0.01.

Table 12 Univariate effects of insulin, glucose, Body mass index, waist to hip ratio, and lipids on relative risk of coronary atherosclerosis

	White subjects			British Asians			Indian Asians		
	Relative risk	Relative risk for increase of one unit (95% CI)	P Value	Relative risk	Relative risk for increase of one unit (95% CI)	P Value	Relative risk	Relative risk for increase of one unit (95% CI)	P Value
Log Insulin									
Fasting	2.8	1.7 to 4.8	<0.0001	4.0	2.1 to 7.8	<0.0001	4.4	1.2 to 17	0.02
One hour	2.2	1.4 to 3.7	0.0009	2.2	1.3 to 3.7	<0.003	—	—	—
Two hours	2.0	1.4 to 3.0	0.0002	2.5	1.4 to 4.2	0.0005	2.3	1.1 to 5.1	0.03
Log glucose									
Fasting	4.4	1.1 to 1.7	0.025	1.8	0.7 to 4.7	0.21	2.6	0.5 to 13	0.22
One hour	1.9	0.7 to 4.9	0.21	3.2	1.2 to 8.3	<0.01	—	—	—
Two hours	3.1	1.3 to 7.2	0.006	2.1	1.0 to 4.3	0.04	1.8	0.5 to 6.3	0.32
Log triglyceride	4.0	1.9 to 8.2	<0.0001	3.6	1.7 to 7.7	0.003	7.1	1.6 to 31	0.0003
Cholesterol	1.2	0.9 to 1.7	0.16	1.6	1.2 to 2.2	0.0003	1.4	0.9 to 2.4	0.15
HDL cholesterol	1.2	0.9 to 1.7*	<0.0001	0.92	0.8 to 1.1*	0.22	0.60	0.45 to 0.81*	<0.0001
Cholesterol/HDL ratio	1.5	1.2 to 1.8	<0.0001	1.4	1.1 to 1.8	<0.002	3.8	1.9 to 7.8	<0.0001
Body mass index	1.1	1.0 to 1.2	0.08	1.1	0.9 to 1.1	0.3	1.0	0.9 to 1.2	0.53
Waist to hip ratio	1.7	1.0 to 1.9*	0.061	3.3	1.9 to 5.7*	<0.0001	2.5	1.1 to 6.0*	0.025
Diabetes	3.4	0.7 to 1.7	0.10	2.5	1.0 to 5.9	0.035	2.5	0.7 to 8.7	0.13

* Per 0.1 unit increase.
HDL = High density lipoprotein; CI = confidence interval.

Table 13 Univariate effects of insulin on relative risk of coronary atherosclerosis in Asians, excluding patients with diabetes

	British Asians			Indian Asians		
	Relative risk	Relative risk for increase of P value one unit (95% CI)	P Value	Relative risk	Relative risk for increase of P value one unit (95% CI)	P Value
Log insulin:						
Fasting	7.9	3.2 to 19	<0.0001	31	2.8 to 340	<0.0005
One hour	5.6	2.5 to 12	<0.0001	—	—	—
Two hour	4.5	2.2 to 9.1	<0.0001	3.5	1.2 to 9.9	<0.008

CI = Confidence interval.

Table 14 Multivariate analysis showing independent predictors of coronary atherosclerosis

	Relative risk	Relative risk for One unit increase (95% CI)	P Value
White subjects			
Log Insulin (fasting) concentration	2.4	1.4 to 4.3	<0.0001
Log HDL cholesterol concentration	0.84	0.72 to 0.98*	0.0007
British Asians			
Waist to hip ratio	4.1	2.2 to 7.7*	<0.0001
Indian Asians			
Waist to hip ratio	3.1	0.9 to 10.4	0.009
Log HDL cholesterol concentration	0.53	0.36 to 0.77	<0.0001

* Per 0.1 unit increase.
CI = Confidence interval; HDL = high density lipoprotein.

Indian Asian controls. The timing of lipid measurements was different in the subgroup from India; this may have affected the high density lipoprotein cholesterol concentration.¹³

Cholesterol concentrations were significantly higher in Asian patients from Britain than in patients from India. Concentrations were similar in the patient groups compared with their respective control groups.

Cholesterol (total cholesterol/high density lipoprotein cholesterol) was significantly higher in all patient groups compared with their controls (table 6).

RELATION BETWEEN EXERCISE AND INSULIN CONCENTRATIONS

There were significant differences between sedentary and non-sedentary subjects. Body mass index, systolic and diastolic blood pressures, triglycerides, and insulin concentrations during fasting and at one and two hours after glucose by mouth were significantly lower in subjects who were more active (table 7). Indian Asians had the largest proportion of non-sedentary subjects followed by white patients; British Asians had the lowest proportion (table 1).

Data were further analysed for each ethnic group (tables 8–10) and this also showed clear differences between the physically active and inactive groups.

RELATION BETWEEN WAIST TO HIP RATIO, INSULIN, AND LIPIDS

There was a significant positive correlation between the waist to hip ratio and insulin in most patient and control groups at one or more times of the oral glucose tolerance test. High density lipoprotein cholesterol showed a negative, and triglyceride a positive, correlation with the waist to hip ratio (table 11).

UNIVARIATE EFFECTS ON RELATIVE RISK OF CORONARY ATHEROMA AND MULTIVARIATE ANALYSIS

Table 12 shows the univariate effects of various variables on the relative risk of coronary atheroma in the three patient groups.

In Asians these were also computed separately in non-diabetic subjects to see whether a higher prevalence of diabetes in Asians was overshadowing other risk factors (table 13). In white patients fasting glucose, triglyceride, and insulin concentrations showed the strongest association. In British Asians, fasting insulin followed by triglyceride concentration and the waist to hip ratio showed the strongest association; in Indian Asians, triglyceride and then fasting insulin concentration, cholesterol ratio, and the waist to hip ratio showed the strongest association. In the combined Asian groups, on excluding the diabetic patients, the relative risk from insulin is greatly increased.

In multiple regression analysis (table 14), fasting insulin and high density lipoprotein cholesterol concentrations were independent predictors of coronary atherosclerosis in white men, whereas in British Asians the waist to hip ratio was the strongest independent predictor; high density lipoprotein cholesterol concentrations and waist to hip ratio were independent predictors in Indian Asians.

Discussion

All the patients studied had angiographically proved significant coronary atherosclerosis. Asians studied in India were from the same geographical area from which most of the Asians studied in the United Kingdom had migrated. This study confirms the presence of hyperinsulinaemia, glucose intolerance, low plasma high density lipoprotein cholesterol, and high triglyceride concentrations in this subgroup of Punjabi Asians. Similar abnormalities have been reported in various other subgroups of Asians,^{7 14} however, a comparative analysis of these abnormalities between Asians in the United Kingdom and in India has not been reported previously.

In this study insulin concentrations were measured in the fasting state and one and two hours after glucose given by mouth. At all stages clear differences were seen in insulin concentrations between and within each of the three racial groups. Concentrations in Asians from the United Kingdom and in India were similar, except in the fasting state. This suggests that insulin resistance may be mainly a genetic defect in this subgroup of Asians. Obesity, however, another variable which is under environmental control, was no different in the Asian group from United Kingdom than in Asians from India. This could be due to the predominantly urban groups of Indian Asians in this study. Further comparison with rural Indians would be more revealing. Similar findings in second generation Japanese-American non-insulin dependent diabetic men were seen compared with Japanese men in Tokyo.¹²

In this study central obesity, evidenced by a higher waist to hip ratio, showed a significant correlation with hyperinsulinaemia in Asians and white men; however, only in Asians did it pose a significant relative risk of coronary atherosclerosis. Multivariate analysis showed central obesity to be the most powerful single predictor of coronary atherosclerosis in British Asians and the second most powerful predictor in Indian Asians. Two recent population studies^{6,7} in the United Kingdom in which most of the subjects were from the Punjabi region of the Indian subcontinent have shown a similar striking tendency to central obesity. In the study by McKeigue *et al.*,⁷ Gujaratis had a similar high waist to hip ratio to other subgroups of Asians. Thus this tendency of central obesity may be universally present in the various subgroups of Asians, but the risk of coronary artery disease or myocardial infarction mediated through it may be different. This study is a case control study and thus there remains a possibility that risk factors in the patient groups may alter after the onset of the disease.

Evans *et al.*¹⁵ have shown a positive correlation between increasing degrees of insulin resistance and the waist to hip ratio; a similar correlation was noted in our study.

Central obesity may mediate insulin resistance and its effects through various routes. Fractional hepatic extraction of insulin is reduced in central obesity, thus producing greater posthepatic delivery of insulin.¹⁶ Hypertrophied fat cells associated more with central obesity show resistance to insulin action *in vitro*¹⁷ and hypertriglyceridaemia is associated more with central rather than lower body obesity of equal degree.^{15,18} Prospective studies^{19,20} also support central obesity as a cardiovascular risk factor.

Insulin, apart from the mediation of lipid abnormalities,²¹ has an effect on the cells important in the pathogenesis of atherosclerosis. It promotes the proliferation of cultured smooth muscle cells.²² Insulin may act directly²³ or indirectly through the stimulation of growth factors.^{22,24}

The beneficial effects of exercise or physical activity are clearly seen in this study. Subjects who were physically active had significantly lower insulin concentrations, body mass index, triglyceride concentrations, and there were favourable effects on systolic and diastolic blood pressure. Indian Asians were the most active, followed by white men, and the least physical activity was recorded in British Asians. Another study has also suggested that habitual aerobic exercise reduces central obesity.²⁵ The evidence of the present study suggests that promotion of physical activity in the Asian community in the United Kingdom should be an important measure to protect against coronary artery disease.

Knight *et al.*⁶ and McKeigue *et al.*⁷ speculate that insulin resistance in Asians may be an adaptive energy conserving mechanism under conditions of periodic famine and low energy intake, and the increased incidence of diabetes and other disturbances associated with

insulin resistance noted in migrant Asians may be consequences of their transportation into urban British life, together with a high energy intake. Our data do not fully support this supposition. Similar high insulin concentrations were seen in Asians in the United Kingdom and in India, suggesting that the environment is not making an appreciable difference. Adaptive mechanisms, however, in any population, take a long time to operate,²⁶ also agriculture has been the main occupation of the population in India for centuries and the food supply has been plentiful apart from the latter part of this millennium.

In the present study Indian Asians were mainly recruited from an urban setting; however, they were still more physically active than other groups. In rural India where most subjects follow agricultural occupations with a high level of physical activity, the prevalence of coronary artery disease has been shown to be low.²⁷ High levels of physical activity thus may act as a "protective" mechanism against the deleterious effects of this predisposition to higher insulin concentrations.

Further evidence that predisposition to insulin resistance in Asian migrants may be mainly genetic comes from an historical perspective. The Indus Valley civilisation vanished without trace around the second millennium BC. Its disappearance is almost certainly linked with the rise of a population group, the Nordics, normally known as the Aryans, who were most probably invaders from northern Iran and had earlier broken off from the main nomad tribes in south Russia.²⁸ Studies showing the presence of insulin resistance in Asians overseas, including ours, have been in subgroups of Asians migrating mainly from the north, northwest, and northeast of the Indian subcontinent belonging to the Aryan population group, thus having a common genetic pool. The other major population group in India is the Dravidian, who reside mostly in the southern part of India. It will be interesting to know if people of Dravidian origin in India also show this predisposition. Studies to define possible gene markers (currently under way) in Asians may contribute most to a better understanding of this predisposition.

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