The Relationship Between Obesity, Plasma Immunoreactive Insulin Concentration and Blood Pressure in Newly Diagnosed Indian Type 2 Diabetic Patients

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The association of blood pressure with clinical and biochemical measures was studied in 185 newly diagnosed Type 2 diabetic patients, 74 impaired-glucose-tolerant (IGT) and 128 non-diabetic control subjects. Hyperglycaemic subjects were older than control subjects (controls 40 (24–59) years, IGT 48 (29–64) years, diabetic 43 (29–60) years, median (5th–95th centile) both $p < 0.05$). They were also more obese (body mass index (BMI) controls 23.5 kg m^{-2} (17.2–29.9), IGT 26.0 kg m^{-2} (19.8–33.9), diabetic 24.2 kg m^{-2} (19.3–32.2)) and with a greater waist–hip ratio (controls 0.83 (0.70–0.98), IGT 0.88 (0.75–0.98), diabetic 0.89 (0.75–1.00)). Blood pressure was significantly higher in both IGT (systolic 127 mmHg (108–162), diastolic 80 mmHg (66–99)) and diabetic patients (systolic 130 mmHg (104–160), diastolic 84 mmHg (66–102)) compared to non-diabetic controls (systolic 120 mmHg (100–151), diastolic 80 mmHg (60–94)). Univariate analysis showed that in diabetic patients systolic blood pressure was related to age ($r = 0.17$, $p < 0.05$), BMI ($r = 0.23$, $p < 0.01$) and plasma immunoreactive insulin (fasting and post glucose, $r = \sim 0.25$, $p < 0.01$) but not to C-peptide concentrations; diastolic blood pressure to BMI ($r = 0.35$, $p < 0.001$), waist–hip ratio ($r = 0.23$, $p < 0.01$) and plasma immunoreactive insulin (fasting $r = 0.30$, $p < 0.001$, post glucose $r = \sim 0.20$, $p < 0.05$) but not to C-peptide concentrations. Multivariate analysis revealed that systolic blood pressure in diabetic patients was related to BMI ($p < 0.01$) and fasting immunoreactive insulin ($p < 0.05$) while diastolic blood pressure was related to BMI ($p < 0.001$) and waist–hip ratio ($p < 0.01$). Thus, blood pressure is associated with obesity even in our relatively non-obese population and it is also associated with plasma immunoreactive insulin concentrations. The mechanism of these associations remains to be established.

KEY WORDS **Blood pressure Obesity Body mass index Waist–hip ratio Immunoreactive insulin Asian Indians Type 2 diabetes**

Introduction

Diabetes and hypertension are frequently associated. In subjects who develop Type 2 (non-insulin-dependent) diabetes, blood pressure may be elevated years before glucose intolerance presents.[1] In a large study of Type 2 diabetes, as many as 40 % of men and 53 % of women were hypertensive at the time when diabetes was diagnosed.[2] It has indeed been postulated that Type 2 diabetes, hypertension, and dyslipidaemias may have a common pathogenetic mechanism of insulin resistance.[3–5] The disease complex consisting of insulin resistance, hyperglycaemia, hypertension, and dyslipidaemias progressing to atherosclerotic heart disease is called syndrome X.[3] Most of the data on this syndrome are from white Caucasian populations where obesity is common. We have previously shown, in our relatively non-obese population of native (Asian) Indians, an association of hyperglycaemia with waist hip ratio (a measure of central obesity) rather than with body mass index (a measure of generalized obesity).[6] We also found an association between waist–hip ratio and urinary albumin excretion rate in newly diagnosed Type 2 diabetic patients.[7] Similar association of central obesity with Type 2 diabetes, hypertension, dyslipidaemias, and coronary artery disease has been demonstrated in a migrant Asian population in the UK.[8]

We have now studied blood pressure and its associations with measures of obesity and pancreatic B-cell function in newly diagnosed hyperglycaemic patients.

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Patients and Methods

The design and details of the Wellcome Diabetes Study have been described.[6] Newly diagnosed untreated hyperglycaemic subjects from outpatients and wards were serially enrolled. The following categories of subjects (both hyperglycaemic and non-diabetic controls) were excluded: age > 65 years, pregnant women, recent (within 6 months) myocardial infarction or stroke, other severe illness (cancer, renal failure, etc.), and those on steroid treatment. Approximately 10 % of the eligible subjects declined to participate in the study. Non-diabetic control subjects had either been outpatients for various minor illnesses (n = 96), or were spouses of patients (n = 16) or hospital staff (n = 16) who responded to our appeal for volunteers. None of these had a known family history of diabetes. Subjects with impaired glucose tolerance (IGT) included 40 outpatient volunteers (including nine spouses of diabetic patients) and 34 referred to us for an oral glucose tolerance test (OGTT) because of at least one symptom commonly associated with diabetes (polyuria, polydipsia, polyphagia, weight loss or genital symptoms) and/or a family history of diabetes. Thus, there were 128 non-diabetic controls (73 men, 55 women), 74 IGT subjects (42 men, 32 women), and 185 Type 2 diabetic patients (120 men, 65 women) classified by WHO criteria (1985) for a 75 g (anhydrous) OGTT.[9]

Blood pressure was measured in the supine position after a rest period of 10 min on the morning of the oral glucose tolerance test. A standard mercury sphygmomanometer was used and diastolic pressure was recorded as disappearance of sounds (phase V). Blood pressure was measured by one of the two observers and intra- and inter-observer coefficient of variation was < 5 %. In the majority, the observer was not aware of the glycaemic category of the patient. Six non-diabetic, 11 IGT, and 18 diabetic patients were receiving anti-hypertensive medication when studied.

Anthropometric measurements (height, weight, waist–hip ratio) were recorded as described previously;[6] minimum circumference of the waist between the lower margin of the rib cage and the highest point of iliac crest and the maximum circumference of hips near the level of the greater trochanters were measured, with subjects standing comfortably, arms hanging by the side and during normal respiration, in comfortable indoor clothing. Blood samples were drawn through an indwelling cannula in an antecubital vein. The mean of two samples collected 10 min apart after an overnight 12 to 14 h fast is referred to as 'fasting', subsequent samples were drawn every 30 min for 2 h. Plasma glucose and creatinine were measured on an Abbott VP-Super autoanalyser (Irwing, Texas, USA) using standard kits and HbA_1 by a colorimetric method.[10] Plasma immunoreactive insulin was measured by a double antibody radioimmunoassay[11] using an anti-porcine insulin antibody raised in guinea pig (65–104, ICN Immunobiologicals, Lisle, Illinois, USA) and human insulin standards. This antibody shows full cross-reactivity with proinsulin. Thus, 'immunoreactive insulin' (IRI) measures insulin, proinsulin, and probably its split products in the plasma. The detection limit of this assay is 2 mU l^{-1} and intra- and inter-batch c.v. < 6 % and < 9 %, respectively. Plasma C-peptide was measured by a kit (Novo, Bagswaerd, Denmark) with detection limit of 0.02 nmol l^{-1} and intra- and inter-batch c.v. < 5 % and < 8 %, respectively. Areas under the IRI and C-peptide curves during the oral glucose tolerance test were calculated by the trapezoidal rule.

The data is presented as median (5th–95th centile) except when $n < 20$ where it is median (range). Statistical difference between the groups was tested by Mann-Whitney test and correlations by Pearson's correlation coefficient (r). Multivariate analysis was by multiple linear regression analysis. For correlations and regression, data was 'normalized' by logarithmic transformation where appropriate (i.e. plasma IRI, plasma C-peptide). Subjects on anti-hypertensive treatment were excluded from the correlation and regression analysis of blood pressure. Statistical analyses were performed using SPSS.PC+ (3.1) package (SPSS Inc., Chicago, Illinois, USA).

Results

Type 2 diabetic patients (43 (29–60) years) and IGT subjects (48 (29–64) years) were older than nondiabetic controls (40 (24–59) years, both $p < 0.05$). IGT subjects were more obese (BMI 26.0 (19.8–33.9) kg m^{-2}) than the non-diabetic (23.5 (17.2–29.9) kg m^{-2}, $p < 0.001$) and diabetic (24.2 (19.3–32.2) kg m^{-2}, $p < 0.01$) subjects. Waist–hip ratio was higher in both IGT (0.88 (0.75–0.98)) and diabetic subjects (0.89 (0.75–1.00)) than in non-diabetic controls (0.83 (0.70–0.98), $p < 0.001$ both), while there was no difference between the two hyperglycaemic groups. Similar differences in BMI and waist–hip ratio were obtained between the groups when men and women were analysed separately.[6] Plasma glucose and HbA_1 showed the expected differences between the groups.

Systolic blood pressure was higher in both IGT (127 mmHg (108–162)) and diabetic patients (130 mmHg (104–160)) compared to non-diabetic controls (120 mmHg (100–151), both $p < 0.05$); there was no significant difference between IGT and diabetic patients. Diastolic blood pressure was higher in diabetic patients (84 mmHg (66–102)) compared to both IGT (80 mmHg (66–99)) and non-diabetic controls (80 mmHg (60–94)), $p < 0.05$; and there was no difference between the latter two groups. When men and women in different glycaemic groups were compared separately, very similar differences were seen. However there were no significant differences in blood pressure of men and women except in the IGT group where women had lower diastolic blood pressure than men ($p < 0.05$). Subjects with systolic blood

pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg, together with those taking anti-hypertensive drugs at the time of study, are referred to as 'hypertensive'. A total of 9 (7 %) non-diabetic, 21 (28 %) IGT, and 47 (25 %) diabetic subjects were thus hypertensive.

Table 1 shows the comparison of various measurements between normotensive and hypertensive subjects in each of the three glycaemic groups. Hypertensive non-diabetic subjects were more obese (BMI, $p < 0.05$) as compared to normotensive non-diabetic subjects but all other measurements were similar in the two subgroups. Hypertensive IGT subjects were older than normotensive IGT subjects ($p < 0.01$), but all other measurements were similar. In the diabetic group, hypertensive patients were older ($p < 0.01$), more obese (BMI ($p < 0.01$)), had a tendency to higher waist–hip ratio ($p < 0.07$), and showed higher plasma creatinine ($p < 0.001$) and IRI concentrations (fasting ($p < 0.05$) as well as after oral glucose ($p < 0.01$)) than those in the normotensive diabetic patients. There was no significant difference in plasma glucose and C-peptide concentrations between the two subgroups of diabetic patients. The above mentioned differences in BMI, plasma creatinine, and plasma IRI between hypertensive and normotensive diabetic patients held true for men when analysed separately except waist–hip ratio which was similar in the two groups of men. Hypertensive diabetic women were older than normotensive diabetic women, however there was no significant difference in other parameters.

Fasting plasma IRI concentrations were significantly higher in diabetic patients compared to those in control ($p < 0.001$) and IGT subjects ($p < 0.01$). After oral glucose normotensive diabetic patients showed lower plasma IRI concentrations but hypertensive diabetic patients showed similar plasma IRI concentrations compared to non-diabetic controls. IGT subjects showed the highest IRI concentrations after oral glucose (Table 1).

Table 2 shows correlations of systolic and diastolic blood pressure in different groups. In non-diabetic subjects systolic blood pressure was related to obesity (BMI, $p < 0.01$) and fasting plasma C-peptide concentration ($p < 0.05$) and diastolic blood pressure to BMI ($p < 0.001$), waist–hip ratio ($p < 0.05$), and fasting plasma IRI ($p < 0.05$). In IGT subjects systolic blood pressure was related to age ($p < 0.01$) and diastolic blood pressure to age ($p < 0.05$) and C-peptide area ($p < 0.05$). In diabetic patients systolic blood pressure was significantly related to age ($p < 0.05$), BMI ($p < 0.01$), and to plasma IRI concentrations (fasting ($p < 0.001$), 2 h after oral glucose ($p < 0.01$), and the area ($p < 0.01$)); diastolic blood pressure was related to BMI ($p < 0.001$), waist–hip ratio ($p < 0.01$), and the plasma IRI concentrations (fasting ($p < 0.001$), 2 h after oral glucose ($p < 0.05$) and the area ($p < 0.01$)). In diabetic patients there was no significant relation between blood pressure and plasma glucose or C-peptide concentrations. When analysed separately for men and women in non-diabetic controls there was no difference; in men

Table 1. Comparison of clinical and biochemical characteristics of normotensive and hypertensive subjects

	Controls		Impaired-glucose-tolerant		Type 2 diabetic	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
n	119	9	53	21	138	47
Men, women	67, 52	6, 3	28, 25	14, 7	87, 51	33, 14
Age (yr)	40 (24–59)	50 (28–61)	43 (29–61)	55 (16–66)[b]	43 (28–60)	51 (31–63)[b]
BMI (kg m^{-2})	23.3 (16.9–29.8)	25.4 (19.2–30.5)[a]	25.8 (19.6–33.1)	26.8 (19.3–32.7)	23.9 (18.7–31.0)	25.7 (20.2–34.5)[b]
Waist–hip ratio	0.83 (0.70–0.98)	0.88 (0.74–0.97)	0.88 (0.74–0.98)	0.89 (0.77–0.97)	0.88 (0.75–1.00)	0.90 (0.74–1.04)
HbA_1 (%)	6.3 (5.4–7.3)	6.7 (5.6–7.2)	6.4 (5.3–8.7)	6.7 (5.0–8.8)	8.8 (6.4–14.8)	8.4 (6.0–13.7)
Creatinine (μmol l^{-1})	71 (28–111)	80 (17–106)	65 (27–118)	88 (37–114)	65 (20–97)	78 (28–133)[c]
Fasting glucose (mmol l^{-1})	4.5 (3.8–5.5)	4.6 (4.0–4.9)	5.1 (4.4–6.3)	5.1 (3.7–6.1)	9.2 (5.0–15.3)	8.3 (5.1–17.2)
Fasting IRI (mU l^{-1})	8.5 (1.3–30.3)	12.3 (1.0–52.0)	11.3 (1.0–45.1)	11.0 (1.1–49.7)	14.8 (3.5–37.4)	19.0 (4.8–43.0)[a]
2 h IRI (mU l^{-1})	83 (19–225)	67 (5–164)	145 (30–367)	162 (31–356)	48 (10–181)	86 (10–232)[b]
IRI area (mU l^{-1}) × h	174 (63–387)	138 (36–282)	201 (39–482)	197 (31–613)	80 (18–261)	122 (28–335)[b]
Fasting C-peptide (nmol l^{-1})	0.27 (0.05–0.59)	0.35 (0.16–1.47)	0.43 (0.08–0.89)	0.47 (0.11–1.13)	0.44 (0.13–0.77)	0.44 (0.08–1.20)
2-h C-peptide (nmol l^{-1})	1.42 (0.14–3.21)	1.18 (0.30–2.74)	2.28 (0.23–6.12)	3.25 (0.25–5.32)	1.12 (0.19–4.14)	1.36 (0.10–3.60)
C-peptide area (nmol l^{-1}) × h	2.50 (0.23–5.20)	2.35 (1.01–5.42)	3.68 (0.37–8.13)	4.73 (1.43–6.43)	1.60 (0.50–4.82)	1.98 (0.28–4.60)

Median (5th 95th centile), except when $n < 20$ where it is median (range).
All biochemical measurements on plasma.
Significance refers to the difference between normotensive and hypertensive in each subgroup.
[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$.

Table 2. Correlations of blood pressure in different groups

	Controls (122)		IGT (63)		Type-2 diabetic (167)					
	Sys-BP	Dia-BP	Sys-BP	Dia-BP	Sys-BP			Dia-BP		
					All	Men	Women	All	Men	Women
Age (yr)	–	–	0.34[b]	0.26[a]	0.17[a]	0.19[a]	–	–	–	–
BMI (kg m^{-2})	0.30[b]	0.38[c]	–	–	0.23[b]	0.32[b]	–	0.35[c]	0.51[c]	–
WHR	–	0.23[c]	–	–	–	0.20[a]	–	0.23[b]	0.27[b]	–
Fasting glucose (mmol l^{-1})	–	–	–	–	–	−0.19[a]	–	–	–	–
HbA$_1$ (%)	–	–	–	–	–	–	–	–	–	0.32[a]
Creatinine (μmol l^{-1})	–	–	–	–	–	0.32[b]	–	–	0.25[a]	–
Fasting IRI (mU l^{-1})	–	0.18[a]	–	–	0.28[c]	0.32[b]	–	0.30[c]	0.40[c]	–
2 h IRI (mU l^{-1})	–	–	–	–	0.24[b]	0.32[b]	–	0.18[a]	0.27[b]	–
IRI area (mU l^{-1}) × h	–	–	–	–	0.24[b]	0.33[b]	–	0.21[b]	0.31[b]	–
Fasting C-peptide (nmol l^{-1})	0.21[a]	–	–	–	–	–	–	–	–	–
2 h C-peptide (nmol l^{-1})	–	–	–	–	–	0.20[a]	–	–	–	−0.31[a]
C-peptide area (nmol l^{-1}) × h	–	–	–	0.27[a]	–	0.22[a]	–	–	–	–

IGT: impaired glucose tolerance.
Pearson's correlation coefficient (r): only significant values shown.
[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$.
Separate data for men and women shown only in diabetic patients.

with IGT diastolic blood pressure was significantly related to BMI ($p < 0.05$), IRI area ($p < 0.05$) and fasting plasma C-peptide ($p < 0.01$). In diabetic patients all of the relationships mentioned above were significant only in men; none of the relationships was significant in women.

Multivariate Analysis

Variables included in multivariate analysis were age, gender, BMI, waist–hip ratio, fasting plasma glucose, and creatinine concentrations, and fasting, 1 and 2 h plasma IRI, and C-peptide concentrations. In non-diabetic control subjects both systolic and diastolic blood pressure were related to BMI ($r = 0.34$ and $r = 0.29$ respectively, $p < 0.01$ both) while in IGT subjects there were no significant associations. Systolic blood pressure in diabetic patients was significantly related to BMI ($r = 0.28$, $p < 0.01$) and fasting plasma IRI concentration (partial $r = 0.18$, $p < 0.05$); diastolic blood pressure to BMI ($r = 0.41$, $p < 0.001$), waist–hip ratio (partial $r = 0.23$, $p < 0.01$), and weakly to fasting plasma IRI (partial $r = 0.14$, $p < 0.1$) and C-peptide concentrations (partial $r = -0.14$, < 0.1). Exclusion of 1 and 2 h plasma IRI and C-peptide concentrations in the analysis did not change the results.

Analysed separately for men and women, diabetic men showed a significant relationship between systolic blood pressure and 1 h plasma IRI ($r = 0.37$, $p < 0.02$) and BMI (partial $r = 0.21$, $p < 0.05$), and a significant relationship of diastolic blood pressure with BMI ($r = 0.52$, $p < 0.001$) and fasting plasma IRI (partial $r = 0.23$, $p < 0.05$). Diabetic women did not show any significant relationships of systolic blood pressure, diastolic blood pressure was significantly related to 1 h plasma C-peptide ($r = 0.31$, $p < 0.05$).

Discussion

In our study, a significantly larger number of IGT and diabetic subjects were hypertensive compared to non-diabetic controls. Age and obesity in the hyperglycaemic subjects appear to have contributed to this difference. The direct association between systolic blood pressure and age in our IGT and diabetic patients probably reflects the rise in systolic blood pressure with increasing age due to the loss of compliance of the large blood vessels.[12]

Previous reports of the association of blood pressure, obesity (BMI), and diabetes are mostly in white Caucasian subjects in whom generalized obesity is fairly common. A similar direct association between blood pressure and obesity was also present in our relatively non-obese population, especially men. Hypertensive subjects tended to be more obese than normotensive subjects irrespective of the glycaemic category. BMI (a measure of generalized

obesity) was directly associated with both systolic and diastolic blood pressure, and waist–hip ratio (a measure of central obesity) was associated with diastolic blood pressure. This difference might be a result of the complex interaction between different mechanisms involved in the regulation of systolic and diastolic blood pressure, on one hand, and those involved in the regulation of glucose homeostasis and body fat distribution, on the other. Central obesity even in the absence of generalized obesity appears a more potent risk factor in Asians; plasma glucose levels[6] as well as urinary albumin excretion rate[7] in our subjects were directly related to waist–hip ratio but not to BMI. A comparative study between white Caucasians and migrant Asians attributed the increased prevalence of diabetes, hypertension, and dyslipidaemias in migrant Asians to their marked central obesity.[8]

Many reports have stressed the association between blood pressure and plasma IRI concentrations, especially in diabetic patients.[3, 8, 13–17] It has been proposed that insulin resistance and hyperinsulinaemia are involved in the pathogenesis of hypertension.[3, 4, 14, 16, 18] However, many studies failed to find an association between blood pressure and plasma IRI concentrations.[19–21] It is possible that ethnic-racial factors are important in this association. The inconsistencies in the association in different studies argue against a primary pathogenetic role for insulin in hypertension but it is possible that insulin contributes to the elevation of blood pressure in susceptible subjects when exposed to high circulating IRI concentrations over long periods of time such as Type 2 diabetic patients. In our study we found a significant association between blood pressure and plasma IRI concentration only in diabetic patients. It is also likely that the association of obesity and blood pressure is through hyperinsulinaemia and insulin resistance.

The significant association between blood pressure and plasma IRI but not C-peptide concentrations could reflect the metabolic effects of systemic insulin on mechanisms controlling blood pressure (renal sodium reabsorption, sympathetic activity, etc.[18]) or the different hepatic metabolism of these two molecules leading to different concentrations in peripheral circulation.[22, 23] Obesity is associated with decreased hepatic extraction of insulin.[24] An alternative explanation for this 'differential' association could be that one or more of the insulin-like molecules (proinsulin and its split products) measured in conventional immunoassays of 'insulin' (IRI) but not in the C-peptide assay[25, 26] contribute to this association. In this context, the recent findings of significant associations between plasma concentrations of proinsulin and 32–33 split proinsulin with cardiovascular risk factors, including blood pressure[27] and glucose intolerance,[28] are important. It is perhaps significant that Asian Indians showed higher circulating concentration of these insulin-like molecules than those in white Caucasian subjects.[27]

Higher plasma creatinine concentration in hypertensive than normotensive diabetic patients possibly suggests an early renal impairment in hypertensive patients.

There are few population-based studies of cardiovascular risk factors in native Indians. Difficulties in organizing such studies in developing countries are well known. Hospital-based studies like ours inevitably suffer from a bias of population selection but provide useful clues and guidelines for larger population-based studies. We plan to undertake such a study soon.

In summary, we found an association of obesity (both generalized and central) and plasma IRI concentrations with blood pressure in our newly diagnosed Type 2 diabetic patients. Our data highlight the association of obesity with blood pressure even in a relatively non-obese population. It is possible that central obesity is the more important component of this association. Insulin-like molecules (measured as 'IRI') could underly this relationship.

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