

# Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations

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## Abstract

**Aims/hypothesis.** Insulin resistance/hyperinsulinaemia is implicated in the development of cardiovascular disease and diabetes but its role and causal pathways are not clear. We tested the hypothesis that the insulin-like growth factor system is independently associated with cardiovascular risk within susceptible populations based on previous reports of the links between low circulating insulin-like growth factor binding protein-1 concentrations and increased macrovascular disease in Type II (non-insulin-dependent) diabetes mellitus.

**Methods.** In a population-based study 272 subjects (142 subjects of European and 130 Pakistani of origin) underwent a 75 g oral glucose tolerance test and standardised anthropometry. Fasting concentrations of insulin-like growth factor binding protein-1 (IGFBP-1), insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), intact insulin and lipids were measured and were related to 2-h glucose tolerance test status. Insulin sensitivity was calculated using the homeostasis model assessment (HOMA).

**Results.** Insulin-like growth factor binding protein-1 was significantly lower in subjects with impaired glu-

cose tolerance when compared with normal glucose tolerance in both ethnic groups (Europeans  $F = 6.7$ ,  $p = 0.002$  and Pakistanis  $F = 4.4$ ,  $p = 0.01$ ). Multiple linear regression modelling showed that insulin-like growth factor binding protein-1 was independently associated with 2-h glucose ( $\beta = 0.16$ ,  $p = 0.009$ ) and logistic regression indicated a 40% reduction in risk of impaired glucose tolerance for every 2.7 ng/ml increase in the insulin-like growth factor binding protein-1 concentration [odds ratio 0.6 (CI = 0.49–0.71),  $p = 0.001$ ]. In addition, insulin-like growth factor binding protein-1 was significantly correlated negatively with several established cardiovascular factors, and positively with insulin sensitivity.

**Conclusion/interpretation.** Insulin-like growth factor binding protein-1 is closely related to risk factors for diabetes and cardiovascular disease in people of European and Pakistani origin. It has potential use as a marker of (hepatic) insulin resistance in clinical intervention studies and further implicates the insulin-like growth factor system in the development of macrovascular disease. [Diabetologia (2001) 44: 333–339]

**Keywords** IGFBP-1, glucose tolerance, cardiovascular risk, ethnicity.

Received: 18 May 2000 and in revised form: 22 September 2000

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**Abbreviations:** IGFBP-1, Insulin-like growth factor binding protein-1; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; WHR, waist-hip ratio; HOMA-S, insulin sensitivity; HOMA-B, beta-cell function; BP, blood pressure.

Cardiovascular disease is the leading cause of morbidity and mortality in patients with Type II (non-insulin-dependent) diabetes mellitus accounting for up to 75% of deaths [1]. Although insulin and insulin resistance have been considered major factors in the pathogenesis of cardiovascular disease [2, 3], given the close links between the insulin-like growth factor-system and insulin action we examined the potential role of the insulin-like growth factor-system in the pathogenesis of macrovascular disease.

Growing evidence associates large and small vessel disease with certain effects of the IGF-system. In vitro, IGF-Type I receptor availability is closely linked with vascular smooth muscle cell (VSMC) growth [4]. In vivo animal studies suggest a role for IGF-I as a mediator of hypertrophic/hyperplastic responses in hypertension [5] and implicate IGF-I as a mediator of cardiac hypertrophy [6]. Insulin-like growth factor binding protein-1 regulates the short-term effects of the IGFs and is thought to be inhibitory: low IGF binding protein-1 concentrations result in greater IGF bioavailability and promote IGF-induced effects on major blood vessels, myocardial tissue and lipid metabolism.

We wished to test the hypothesis that the IGF-axis is independently associated with cardiovascular risk based on reports of a link between low IGFBP-1 concentrations and increased risk in previous studies [7, 8]. To this end we examined population samples of two ethnic groups with differing rates of diabetes and cardiovascular disease.

## Subjects and methods

*Subjects and study design.* People of European origin and Pakistani origin (defined as a person of Pakistani ethnic origin, speaking usually Punjabi or Urdu or both and being Muslim) were chosen at random from population registers held at seven health centres in inner city Manchester and they represented at least a 67% response of all subjects invited. These registers are based on the universal availability of free health care in Britain and have been found to include over 97% of the local population. They are the best available sampling frames for names, addresses and age but there is at present no record of ethnicity. Nevertheless, they represent the best available population indices between censuses (which do not include names), because the addresses are updated regularly even though they are still frequently incorrect (hence the 'at least.' response rate described above). They have been used for many years in British population sampling when other methods are not appropriate (e.g. random digit dialling because telephone ownership is not universal; electoral rolls (which do not give age) because they are regarded with suspicion by some sections of the community). The age range sampled was 25–74 years. Ethnicity required 3 out of 4 grandparents to be of that ethnic group and by self-report using the 1991 census categories.

People with known diabetes were excluded from the study. Subjects attended their local health centre having fasted from the previous midnight, between 09.00 hours and 11.00 hours and those without known diabetes had a standard 75-g oral glucose tolerance test (75 g glucose dissolved in 250 ml water) with venous blood samples taken at 0 h and 2 h.

Standardised measures of sitting blood pressure (mean of last 2 of 3 manometer readings) and anthropometry (body mass index (BMI) and waist-hip ratio (WHR)) were taken by trained fieldworkers after subjects had been sitting for 15 min or more answering a detailed lifestyle questionnaire. Ethical permission was granted by the Central Manchester Health District ethical committee with written or independently witnessed consent obtained from each subject.

*Assays.* We measured IGF-I, IGF-II and IGFBP-1 concentrations by previously reported antibody based assays [9, 10, 11]. Respective detection limits were 28 ng/ml, 30 ng/ml and 1 ng/ml and within and between coefficients of variation (CV) were less than 10%. Insulin was measured using the Mercodia ELISA for intact insulin (Uppsala, Sweden). The detection limit was less than 7 pmol/l and within and between assay CVs were less than 8%. Cross-reactivity of the insulin ELISA for proinsulin was less than 0.1%. Insulin sensitivity (HOMA-S) and beta-cell function (HOMA-B) were calculated according to previously described methods [12].

Fasting lipid profiles were measured using the Cobas Mira Autoanalyser (ABX, London, UK). Glucose was assayed using a standard glucose oxidase analyser (Hitachi 747, Roche Reagents, Lewes, Sussex, UK).

Samples were assayed in the order of arrival, with no knowledge of the patients' glucose tolerance status. All samples were assayed in sequential batches over a short period of time. Samples were assayed in duplicate and the analysis was repeated if the coefficient of variation between samples was greater than 10%.

*Statistical analysis.* The data were analysed using the statistical package Intercooled Stata version 5.0 (Stata Corp, Tex., USA). Anthropometric and metabolic data are expressed as arithmetic means with 95% confidence intervals (CI). Comparisons of means was by *t*-test or ANOVA. Logarithmic transformation was done on IGF-I, IGF-II and IGFBP-1 which were non-normally distributed. The relation between glucose tolerance test status (IGT vs normal) and IGFBP-1 was examined using logistic regression (excluding subjects with diabetes). Total group linear regression was carried out to examine the relation between 2-h glucose as a continuous variable and IGFBP-1. Univariate correlation between continuous variables for the whole group used Spearman coefficients (two-tailed test) and multivariate correlation used partial coefficients controlling for age, sex, BMI and 2-h glucose.

## Results

*Prevalence of impaired glucose tolerance and diabetes.* A total of 272 subjects were included (142 Europeans and 130 Pakistanis) which represented a respective response rate of 66% (Europeans) and over 70% (Pakistanis) for the oral glucose tolerance test. Both ethnic groups were of similar age and sex but with established differences for anthropometry (Table 1). The prevalence of new Type II diabetes defined as a 2-h plasma glucose post 75-g oral glucose load of 11.1 mmol/l or more was 9.3% (Europeans) and 17.0% (Pakistanis) and of impaired glucose tolerance (IGT) (defined as a 2-h plasma glucose glucose post 75 g oral glucose load of 7.8 mmol/l or more and 11.0 mmol/l or less was 11.9% (Europeans) and 22.3% (Pakistanis). The BMI was highest in diabetic subjects, intermediate in subjects with impaired glucose tolerance and lowest in those with normal glucose tolerance. Values for metabolic variables by glucose tolerance test status are given in Table 2.

*The IGF axis and glucose tolerance.* Fasting IGFBP-1 (adjusted for age, sex and ethnicity) was significantly

**Table 1.** Anthropometric characteristics of study subjects by sex (males (M) and females (F) and ethnicity: arithmetic means with 95% confidence intervals

		White Europeans	Pakistanis	P value for interethnic difference
Number	M	72	68	N/A
	F	70	62	N/A
Age (years)	M	51.4 (49.6–53.0)	50.4 (47.9–52.9)	NS
	F	52.4 (50.9–54.0)	49.6 (47.2–52.0)	< 0.01
BMI	M	27.2 (26.6–27.7)	27.2 (26.3–28.1)	NS
	F	27.0 (26.3–27.6)	29.2 (28.0–30.4)	< 0.001
WHRatio	M	0.92 (0.91–0.93)	0.95 (0.94–0.97)	< 0.001
	F	0.80 (0.79–0.81)	0.87 (0.85–0.89)	< 0.001
BP systolic	M	133 (130–136)	130 (126–133)	NS
	F	126 (123–128)	126 (121–131)	NS
BP diastolic	M	80 (79–82)	83 (80–85)	< 0.01
	F	77 (76–78)	77 (75–79)	NS

**Table 2.** Biochemical characteristics and BMI for whole group adjusted for age, sex and ethnicity and for age (unadjusted) by GTT status. Arithmetic means with 95% confidence intervals

	Normal ( <i>n</i> = 194)	Impaired glucose tolerance ( <i>n</i> = 44)	New DM ( <i>n</i> = 34)	F value, <i>p</i>
IGFBP-1 (ng/ml)	42.3 (37.5–47.2)	24.2 (13.5–35.0)	39.5 (26.6–52.4)	F = 4.4, <i>p</i> = 0.01
IGF-I (ng/ml)	148.3 (141.9–154.7)	141.2 (126.5–155.8)	132.1 (114.5–149.6)	NS
IGF-II (ng/ml)	581.8 (557.7–605.8)	574.7 (520.2–629.2)	627.7 (562.4–693.0)	NS
Cholesterol (mmol/l)	5.8 (5.6–5.9)	6.0 (5.5–6.4)	5.5 (5.0–6.1)	NS
Triglycerides (mmol/l)	1.6 (0.9–2.3)	3.3 (1.8–4.8)	2.1 (0.3–4.0)	NS
Insulin 0 h (pmol/l)	64.1 (57.6–70.7)	94.1 (80.2–107.9)	84.6 (70.0–99.4)	F = 9.8, <i>p</i> = 0.002
Glucose 0 h (mmol/l) <sup>a</sup>	5.1 (4.9–5.3)	5.6 (5.2–6.1)	8.3 (7.8–8.8)	F = 56.8, <i>p</i> < 0.001
Glucose 2 h (mmol/l) <sup>a</sup>	5.5 (5.1–5.8)	9.0 (8.2–9.6)	16.7 (15.8–17.5)	F = 292.4, <i>p</i> < 0.001
Age (years) <sup>a</sup>	48.1 (46.7–49.4)	54.8 (51.5–58.1)	57.2 (53.3–61.0)	F = 14.6, <i>p</i> < 0.001
BMI	27.1 (26.6–27.6)	28.6 (27.4–29.9)	30.8 (29.3–32.2)	F = 12.4, <i>p</i> < 0.001

F and *p* values refer to comparison by GTT status; NS = not significant; DM, diabetes mellitus

<sup>a</sup> unadjusted values

lower in subjects with IGT (24.2 (13.5–35.0) ng/ml) compared with those with a normal (42.3 (37.5–47.2) ng/ml) or diabetic response (39.5 (26.6–52.4) to oral glucose load (Table 2) This pattern existed in both ethnic groups (Fig. 1).

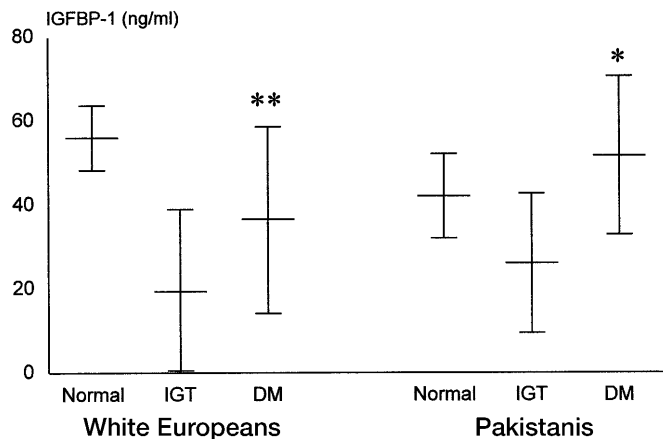
Measurement of IGF-I and IGF-II in the plasma of either ethnic group indicated that the total circulating concentrations of IGF-I and IGF-II were not altered by glucose tolerance (Table 2).

*Relation of IGFBP-1 to insulin sensitivity.* Fasting insulin and post-glucose challenge insulin in both European and Pakistani subjects were lower for those with diabetes than for those with impaired glucose tolerance in each ethnic group (Fig. 2). There was relative hyperinsulinaemia in Pakistani subjects with normal glucose tolerance status compared with Europeans and insulin sensitivity (HOMA-S) was lower in Pakistani with normoglycaemia than in European normoglycaemia (Fig. 3). The HOMA-S was lower in subjects with both impaired glucose tolerance and in subjects with diabetes when compared with subjects who were normoglycaemic in both ethnic groups and cor-

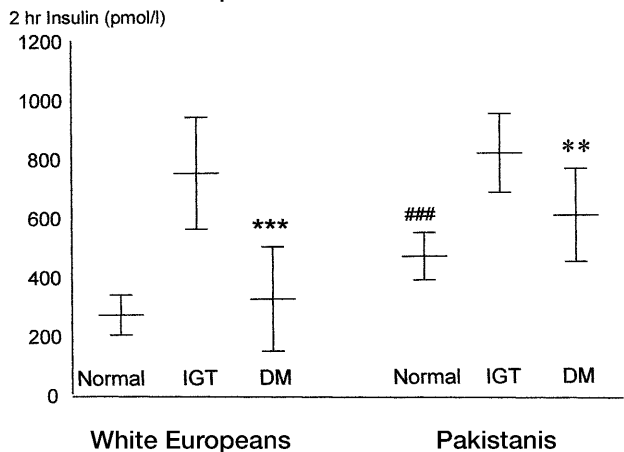
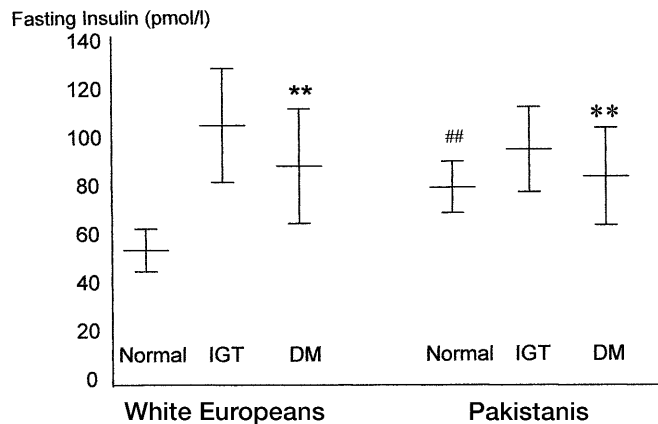
related positively with IGFBP-1 (Table 3). Pancreatic beta-cell function (HOMA-B) was poorer in the diabetic subjects from each ethnic group when compared with normoglycaemic subjects (Fig. 3).

*Relation of IGFBP-1 with established cardiovascular risk factors.* Continuous univariate correlations and multivariate correlations adjusted for age, sex and BMI between IGFBP-1 and metabolic and anthropometric variables were assessed for the whole group (Table 3). IGFBP-1 was negatively correlated with established markers of cardiovascular risk, namely systolic blood pressure (both ethnic groups), diastolic blood pressure (European subjects only), BMI, waist:hip ratio and fasting insulin and triglyceride concentration within each ethnic group (Table 3). The relations remained when adjustment was also made for 2-h glucose. IGFBP-1 correlated positively with insulin sensitivity (HOMA-S) and negatively with pancreatic beta-cell function (HOMA-B).

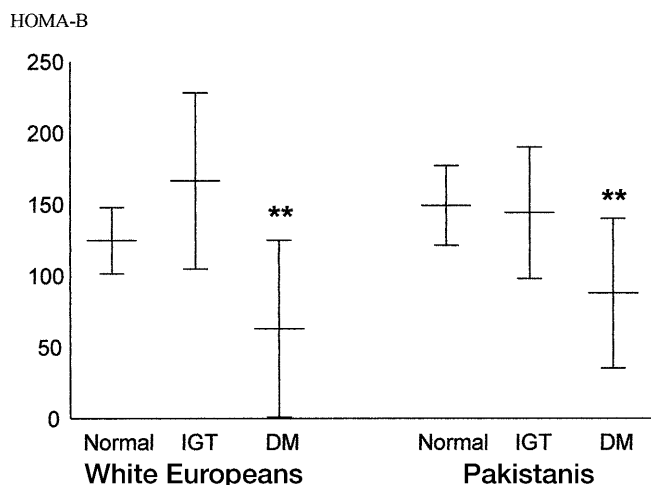
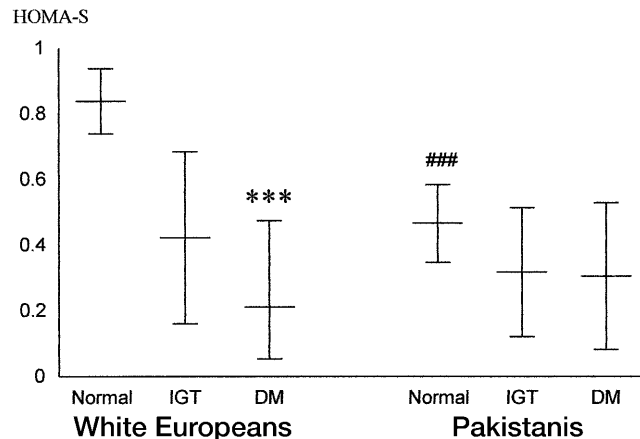
Correlations for HOMA-S with these variables were of a similar degree and direction to those for IG-



**Fig. 1.** Fasting IGFBP-1 by GTT status for each ethnic group: \*\*Europeans  $F = 6.7$ ,  $p = 0.002$  for comparison by GTT status; \* Pakistanis  $F = 4.4$ ,  $p = 0.01$  for comparison by GTT status. The bars display the arithmetic means and 95% confidence limits



**Fig. 2.** Insulin 0 h (upper panel) and insulin 2 h (lower panel) by ethnic group and GTT status. #  $p < 0.01$  for interethnic comparison; ##  $p < 0.001$  for interethnic comparison; \*\*  $p < 0.01$  for diabetes vs impaired glucose tolerance; \*\*\*  $p < 0.001$  for diabetes vs impaired glucose tolerance. The bars display the arithmetic means and 95% confidence limits



**Fig. 3.** HOMA-S (upper panel) and HOMA-B (lower panel) by ethnic group and GTT status; ###  $p < 0.001$  for interethnic comparison; \*\*  $p < 0.01$  for comparison between diabetes and impaired glucose tolerance; \*\*\*  $p < 0.001$  for comparison between diabetes and impaired glucose tolerance. The bars display the arithmetic means and 95% confidence limits

FBP-1 among the group of white Europeans, but much lower or negligible among the Pakistani group. For white European subjects partial  $r_1$  for HOMA-S adjusted for age, sex and BMI with triglycerides was  $-0.43$ ,  $p < 0.001$ ; with WHR it was  $-0.29$ ,  $p = 0.001$ ; with systolic blood pressure (BP) it was  $-0.26$ ,  $p = 0.003$ ; and with diastolic BP it was  $-0.21$ ,  $p = 0.018$ . Among Pakistani subjects, however, these partial  $r_1$  values adjusted for age, sex and BMI were negligible or not significant (NS), with triglycerides  $-0.14$ , NS; with WHR it was  $-0.24$ , NS; with systolic BP it was  $-0.02$ , NS; and diastolic BP it was  $0.05$ , NS. There was no significant correlation of either IGFBP-1 or HOMA-S with fasting cholesterol or HDL-cholesterol level in either of the ethnic groups studied.

*Regression analyses.* IGFBP-1 concentrations were 43% lower in subjects with impaired glucose tolerance than in subjects with normoglycaemia and logis-

**Table 3.** Spearman correlations ( $r_s$ ) and partial correlation coefficient  $r_1$  adjusted for age, sex and BMI for IGFBP-1 for each ethnic group and partial correlation coefficient  $r_2$  adjusted for age, sex, BMI and 2-h glucose

	White Europeans			Pakistanis		
	$r_s$	partial $r_1$	partial $r_2$	$r_s$	partial $r_1$	partial $r_2$
INS 0 h	-0.60 <sup>c</sup>	-0.46 <sup>c</sup>	-0.44 <sup>c</sup>	-0.626 <sup>c</sup>	-0.45 <sup>c</sup>	-0.50 <sup>c</sup>
HOMA-S	0.46 <sup>c</sup>	0.31 <sup>c</sup>	0.41 <sup>c</sup>	0.56 <sup>c</sup>	0.41 <sup>c</sup>	0.48 <sup>c</sup>
HOMA-B	-0.31 <sup>c</sup>	-0.30 <sup>b</sup>	-0.30 <sup>b</sup>	-0.423 <sup>c</sup>	-0.30 <sup>b</sup>	-0.36 <sup>c</sup>
Triglycerides	-0.34 <sup>c</sup>	-0.20 <sup>b</sup>	-0.25 <sup>b</sup>	-0.34 <sup>c</sup>	-0.22 <sup>b</sup>	-0.21(NS)
BMI	-0.51 <sup>c</sup>			-0.315 <sup>c</sup>		
WHRatio	-0.34 <sup>c</sup>	-0.22 <sup>a</sup>	-0.26 <sup>b</sup>	-0.310 <sup>c</sup>	-0.37 <sup>c</sup>	-0.35 <sup>b</sup>
Systolic BP	-0.17 <sup>b</sup>	-0.20 <sup>b</sup>	-0.22 <sup>a</sup>	-0.24 <sup>b</sup>	0.05 NS	0.06 NS
Diastolic BP	-0.33 <sup>c</sup>	-0.19 <sup>a</sup>	-0.23 <sup>a</sup>	-0.02 NS	0.11 NS	0.13 NS

<sup>a</sup>  $p < 0.05$ ; <sup>b</sup>  $p < 0.01$ ; <sup>c</sup>  $p < 0.001$

tic regression analysis showed that for the two ethnic groups combined, for every increase in the IGFBP-1 concentration of 2.7 ng/ml there was a 40% reduction in the risk of impaired glucose tolerance. After adjusting for age and sex, the odds ratio for the association of IGFBP-1 with impaired glucose tolerance among the two ethnic groups combined was 0.60 (CI 0.49–0.71),  $p = 0.001$ ; for European subjects only, 0.50 (0.35–0.74),  $p = 0.001$ ; and for Pakistani subjects 0.66 (0.46–0.90),  $p = 0.01$ . New diabetic patients were excluded from the logistic regression analysis because we aimed to examine the use of IGFBP-1 in identifying insulin-resistant people with impaired glucose tolerance who are at risk of developing diabetes and cardiovascular disease. Diabetic people can be identified by fasting glucose measurement according to already well-established criteria.

For the whole group, IGFBP-1 was also independently negatively related to 2-h glucose in subjects with normoglycaemia and impaired glucose tolerance using multiple regression analysis, (beta coefficient ( $\beta$ ) = -0.16,  $p = 0.009$ ) as were age ( $\beta = 0.22$ ,  $p < 0.001$ ), BMI ( $\beta = 0.20$ ,  $p = 0.001$ ) and fasting insulin ( $\beta = 0.22$ ,  $p = 0.001$ ). Circulating concentrations of IGF-I and IGF-II did not significantly contribute to the variance in IGFBP-1 concentrations when assessed using this model.

## Discussion

These studies show that fasting IGFBP-1 is closely associated with impaired glucose tolerance and cardiovascular risk in population samples of both European and Pakistani origin subjects selected at random and that this relation is independent of standard risk factors. IGFBP-1 was positively related to insulin sensitivity and negatively to blood pressure, BMI, WHR and triglyceride concentrations as found previously in Type II diabetes [7, 8]. Therefore IGFBP-1 has the characteristics to be a marker for both impaired glucose tolerance and cardiovascular risk at a population level. In Type I (insulin-dependent) diabetes

mellitus it is, however, likely that other factors contribute to subject's increased cardiovascular risk because portal insulinopaenia results in high hepatic IGFBP-1 production and free IGF-I concentrations are low [13].

IGFBP-1 has been proposed as a short-term regulator of IGF biological activity [14], is synthesised by the liver and is regulated by insulin. This study clearly shows that defects in insulin secretion or abnormalities causing hepatic insulin resistance greatly influence circulating IGFBP-1 concentrations. Previous studies have investigated the relation between IGFBP-1, cardiovascular risk and insulin resistance in Type II diabetes [7, 8] but our study established a clear relation between IGFBP-1 and cardiovascular risk within a group chosen at random from the general population who were not previously known to have diabetes or impaired glucose tolerance. The relation for IGFBP-1 within the groups studied were similar in degree and direction to those between HOMA-S and established cardiovascular risk factors, as has previously been reported [12] but were much weaker in the generally hyperinsulinaemic and insulin resistant Pakistani group. In multiple regression analysis, however, both IGFBP-1 and insulin were independently associated with 2-h glucose concentrations.

Because hepatic IGFBP-1 production is negatively regulated by insulin [15], with portal insulin concentrations being 2 to 3-fold higher than peripheral insulin concentrations, we examined the relation between IGFBP-1 concentrations and insulin sensitivity. As anticipated, insulin concentrations were higher in subjects with impaired glucose tolerance than in subjects with normoglycaemia for both ethnic groups. Although insulin sensitivity decreased with the development of impaired glucose tolerance, there was a compensatory increase in beta-cell function. As expected fasting IGFBP-1 reflected these changes with a significant fall in IGFBP-1 with the hyperinsulinaemia associated with impaired glucose tolerance. This was reflected in a strong positive correlation of IGFBP-1 and insulin sensitivity and negative correlation of IGFBP-1 with beta-cell function. With the de-

velopment of diabetes insulin secretory capacity was considerably reduced and insulin sensitivity decreased further. The fall in pancreatic insulin-secretory capacity was associated with a rise in circulating IGFBP-1 concentration in accordance with previous results in obese subjects [13]. This trend occurred in both ethnic groups and is likely to reflect a relative lack of insulin inhibition of hepatic IGFBP-1 synthesis in diabetes.

We examined IGFBP-1 as a marker for cardiovascular risk because it forms an important link between the development of hyperinsulinaemia/insulin resistance and the mounting evidence that the IGF/IGFBP system is involved in the development of cardiovascular disease [15]. The time spent in the insulin-resistant (prediabetic) state when circulating IGFBP-1 is low and free-IGF-I potentially high could be critical to the development of cardiovascular disease. In this regard it has been shown that the insulin-resistant state (metabolic syndrome) predisposes people to cardiovascular disease as much as to diabetes with approximately 20% of newly diagnosed patients with Type II diabetes having cardiovascular disease [16]. With the onset of the hyperglycaemia of Type II diabetes further factors increase the person's risk of cardiovascular disease and among these could be the well-described changes in IGFBP-3 proteolysis, with consequent effects on the bioavailability of IGF-I [17].

The concentrations of IGFBP-1 change quickly in relation to insulin production consequently modulating IGF-I and IGF-II access to peripheral tissues. IGF-I mimics the glucoregulatory and lipoprotein effects of insulin [18, 19] and directly stimulates vascular smooth muscle cells which are inhibited by IGFBP-1 [20, 21]. In vitro IGFBP-1 has both inhibitory and stimulatory effects on IGF action depending on experimental conditions [22] and we speculate that this could also be the case in vivo. In the circulation IGFBP-1 could inhibit IGF action, thus preventing IGF-mediated remodelling of the vasculature while in other tissues IGFBP-1 – through its interaction with cell surface membrane proteins like  $\alpha_5\beta_1$  – integrin [23] could deliver IGF-I to tissues. A high IGFBP-1 concentration would thus be of potential benefit by blocking the effects of IGF-I on the vasculature while potentially increasing IGF bioavailability to other metabolically tissues possessing cell membrane receptors with which it can interact.

The high prevalence of impaired glucose tolerance and diabetes found here, particularly among people of Pakistani origin provided adequate support for this analysis. Although samples taken on a single occasion could not characterise adequately the study populations, the anthropometric and metabolic features found here are consistent with earlier population studies showing poorer glucose tolerance and higher insulin concentrations in people in Britain of mainly Hindu Indian origin [23, 24]. In addition as-

says measuring IGFBP-1, IGF-I and IGF-II in these samples are precise, robust and well-characterised so that laboratory measurement errors are minimal.

In agreement with our studies, previous work found that the South Asian population were relatively hyperinsulinaemic compared with the European population [24, 25]. It has been suggested that dietary or hepatic factors rather than peripheral insulin 'resistance' could be responsible. Our study has shown excess fasting and 2-h insulin concentrations in normoglycaemic subjects of Pakistani origin. The IGFBP-1 concentration which is negatively regulated by insulin, was not, however, as low in Pakistani subjects as would be anticipated from the relation between insulin and IGFBP-1 concentrations seen in European subjects. A probable explanation is that Pakistani subjects have relatively greater hepatic insulin resistance so that, for a given portal concentration of insulin hepatic, IGFBP-1 production is not reduced to the same degree. The cause of the increased hepatic insulin resistance is not known but higher portal venous fatty acids have been found to exaggerate hepatic insulin resistance in experimental animal and human studies [26, 27]. Although not measured here, higher portal venous fatty acid flux could be related to the increased waist:hip ratio characteristic of the South Asian population and our Pakistani group and so be a potential factor causing hepatic insulin resistance in this group.

In summary, we have clearly shown that fasting IGFBP-1 is independently related to impaired glucose tolerance and other cardiovascular risk factors. We suggest that IGFBP-1 will prove to be a useful marker for characterising people with adverse cardiovascular risk. This will require testing in prospective cohort and clinical intervention studies.

*Acknowledgements.* We gratefully acknowledge the advice of Professor PN. Durrington of Manchester and also the support of Salford Royal NHS Trust R&D unit. This work was supported by a grant from the Ministry of Agriculture, Fisheries and Food, UK, grant no. 2B069, with other support from the Local and National Health Service Research and Development Programme.

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