Epidemiology of the Insulin-like Growth Factor System in Three Ethnic Groups


The insulin-like growth factor (IGF) system, comprising insulin-like growth factor I (IGF-I), insulin-like growth factor II (IGF-II), and their binding proteins (IGFBPs), is linked to cell growth, the development of cardiovascular disease, and several cancers. Little is known about its epidemiology. The authors studied relations of the IGF system to anthropometric and metabolic variables in three population-based ethnic groups in Manchester, England, in 1994–1998 with differing disease risks: African Caribbean (n = 193), Pakistani (n = 130), and local Europeans (n = 142). Standardized anthropometry, glucose tolerance tests, and serum assays were performed. Body mass indices (BMIs) were high in all groups. IGF-I levels were highest in normoglycemic African Caribbeans and declined with age (r = –0.28). IGF-II levels were greatest in Europeans. IGFBP-1 concentrations increased with age in Pakistanis (r = 0.20) and Europeans (r = 0.29), but not in African Caribbeans (r = 0.06), and were inversely related to BMI (r = –0.37). Age- and sex-adjusted IGFBP-1 was inversely related to fasting insulin and proinsulin in all groups; participants with newly detected diabetes were relatively insulinopenic but had higher IGFBP-1 concentrations. Nonesterified (free) fatty acid (NEFA) concentrations increased with declining glucose tolerance. In multiple regression analysis, IGFBP-1 was independently and negatively related to fasting insulin, BMI, and African-Caribbean compared with European ethnicity but positively related to age, fasting glucose, and NEFA. IGF-I was inversely related only to age, NEFA, and Pakistani ethnicity. IGF-II showed a strong ethnic difference but was unrelated to other variables. These data indicate considerable potential for exploring disease-IGF system relations in population samples. Am J Epidemiol 2001;154:504–13.

differing disease rates between migrant and resident populations can supply important clues to the etiology and, hence, also to the mechanism of disease. For example, compared with the local European population, African Caribbeans in Britain have a higher prevalence of type 2 diabetes mellitus and hypertension (1, 2) but up to 50 percent lower morbidity and mortality from coronary heart disease in the presence or absence of diabetes (3–5). Similar lower coronary disease rates have been found for African-Caribbean migrants to the United States compared with African Americans or American Whites (6).

By contrast, people of South-Asian (Indian subcontinent) origin living in Britain, of all denominations and geographic origin, have a 30–40 percent excess of coronary disease compared with national or local rates (4–7) as well as higher rates of type 2 diabetes than do local Europeans (8–10). These patterns have persisted for at least 20 years (11, 12). Despite these ethnic differences, overall health judged by lower standardized mortality ratios has been generally better for African Caribbeans and South Asians than national England and Wales rates (13).

There is increasing evidence that the insulin-like growth factor (IGF) axis and, in particular, insulin-like growth factor 1 (IGF-I) is intimately involved in the pathogenesis of hypertension (14), atheromatous vascular disease (15, 16), cardiomegaly (17), and cardiac failure (18). IGF bioactivity is modulated by a series of specific high-affinity binding proteins (IGFBPs). Of the six IGFBPs fully characterized to date, insulin-like growth factor binding protein 1 (IGFBP-1) is the principal hour-to-hour regulator of circulating IGF levels that rise and fall in response to hepatic portal blood insulin, its principle negative regulator (19), forming the
link between dietary ingestion, glucose metabolism, and the IGF axis. IGFs and IGFBP-1 may thus be important additional factors acting in synergy with insulin actions to modify lipid and glucose metabolism in a manner that predisposes to cardiovascular disease.

Recently, higher IGF-I levels have been associated with breast cancer in premenopausal women (20) and with prostate cancer in men (21). Such associations and potential actions across a range of different pathophysiological situations likely indicate a central role in cell growth for the IGF system. Population work on the IGF system is sparse, with two studies in elderly people (22, 23). Our study examined the relation of circulating IGF and IGFBP-1 levels to anthropometry, glucose intolerance, and other metabolic variables in population samples of Europeans, Pakistanis, and African Caribbeans living in Britain, with differing cardiovascular disease risks outlined above.

We aimed to test an overall hypothesis that nonesterified fatty acids (NEFAs) in peripheral venous blood, as markers for portal blood fatty acids, might be closely related to and be regulators of IGF system activity, via hepatic insulin sensitivity, in these different ethnic groups. If such a view were supported, this link would provide a dietary route to regulating the IGF system as probable mediators of metabolic activity and perhaps pathology. Here, because we used a cross-sectional, population-based design, our results offer only an initial step in examining that hypothesis by testing for independent associations of the IGF system.

MATERIALS AND METHODS

Study sample

The study design was a population-based community survey in which 465 subjects were randomly sampled from population registers held at seven health centers in inner-city Manchester, England, representing at least a 67 percent response of all subjects invited. Such registers, based on the universal availability of health care free at the time of use in Britain and, when checked, found to contain over 97 percent of the local populace, are the best available sampling frames for name, address, and age but do not, at present, record ethnicity. Nevertheless, they represent the best available proxy for true population indices between censuses (from which names are not available) because addresses are regularly updated but are still frequently incorrect (hence the “at least” response rate above). They have been used for many years in British population sampling (24) when other methods are not applicable (e.g., random digit dialing because telephone ownership was not universal or electoral rolls that lack age and are regarded with suspicion by some sections of the community). Three different ethnic groups in the age range 25–74 years were studied: African-Caribbean, Pakistani, and White European origin. Ethnicity required three of four grandparents in that ethnic group and by self-report using the 1991 census categories. Pakistani was defined as a person of Pakistani origin or birth, usually speaking Punjabi and/or Urdu and being Muslim. Approximate ethnic-specific response rates were derived for Pakistanis, based on name, at 75 percent or more, but no such distinction was possible between African Caribbeans and Europeans, for both of whom the response rate exceeded 67 percent. Other details of local community sampling are given elsewhere (1, 2).

Baseline examination

All subjects attended their local health center and fasted for a standard 75 g glucose tolerance test (GTT) with blood samples taken while fasting and at exactly 2 hours postglucose. New type 2 diabetes was defined according to 1985 World Health Organization criteria as a 2-hour plasma glucose post 75-g oral glucose load (11.1 mmol/liter), and impaired glucose tolerance (IGT) was defined as a 2-hour plasma glucose post 75-g oral glucose load of 7.8 mmol/liter or more and 11.0 mmol/liter or less. Those with known diabetes were not included. Blood samples were centrifuged, and aliquots of plasma or serum were frozen at −70°C until analysis. Standardized measures of anthropometry as body mass index (BMI) (weight [kg]/height [m²]) and waist-hip ratio (WHR) were taken by trained fieldworkers after subjects had responded to a detailed lifestyle questionnaire (1). Not all subjects had all analyses for metabolic variables. Ethical permission was granted by the Central Manchester Health District Ethical Committee, with written or independently witnessed consent by each subject.

Assays

IGF-I, insulin-like growth factor II (IGF-II), and IGFBP-1 levels were determined by previously reported antibody-based assays (25–27) with respective detection limits of 28 and 30 ng/ml and 3 µg/liter and within- and between-assays coefficients of variation (CV) of less than 10 percent. Insulin and proinsulin were measured by using the Mercodia (Uppsala, Sweden) enzyme-linked immunosorbent assay (ELISA) for intact insulin and the DAKO (Ely, United Kingdom) ELISA for intact proinsulin with respective detection limits of less than 7 and less than 2 pmol/liter and within-assay and between-assays CVs of less than 8 percent. Cross-reactivity of the insulin assay for proinsulin and the proinsulin assay for insulin is less than 0.1 percent. Insulin sensitivity (homeostasis model assessment S [HOMA-S]) and β-cell function (homeostasis model assessment B [HOMA-B]) were determined according to the method of Matthews et al. (28). For the homeostasis model assessment procedure, insulin sensitivity is derived from the formula HOMA-S = 146/(fasting insulin × fasting glucose). β-cell function is given by HOMA-B = (3.08 × fasting insulin)/(fasting glucose-3.5). These formulae were modified from the original publication to account for the use of pmol/liter rather than mU/liter for insulin concentrations, assuming 1 mU insulin = 6.5 pmol.

Fasting NEFA concentration was measured using the Wako (Neuss, Germany) ELISA for total NEFA. This is a standard ELISA that is used in our local World Health Organization collaborating laboratory. The Wako enzymatic method relies on the acylation of coenzyme A by the fatty acids to produce hydrogen peroxide. In the presence of a
purple dye, the amount of hydrogen peroxide generated is measured colorimetrically. Assay sensitivity was 0.05 mmol/liter and inter- and intraassay CV was less than 10 percent. Glucose was assayed by using a standard glucose oxidase analyser (Hitachi 747, Roche Reagents, Lewes, Sussex, England).

Statistical analysis

The data were analyzed by using the statistical package Intercooled Stata version 5.0 (Stata Corporation, College Station, Texas). Anthropometric and metabolic data are expressed as arithmetic means with 95 percent confidence intervals. Comparison of means was by t test or analysis of variance. Logarithmic transformation was performed on nonnormally distributed variables. For univariate correlation between continuous variables, Spearman coefficients were used, with partial coefficients for multivariate correlation. Multiple regression was used to examine relations between each component of the IGF axis (IGFBP-1, IGF-I, and IGF-II) in turn, not including each other, and all other variables. The normalized beta coefficients presented allow direct comparison (along a scale of 0–1) of the strength of each association between ethnic groups as well as for the total sample. Numbers may vary between analyses because, due to missing samples, not all subjects had all measurements.

RESULTS

General characteristics

As seen in table 1, men had similar age distributions but women of European origin were older than the other groups. BMIs in men were elevated in all ethnic groups but were higher in African-Caribbean and Pakistani-origin women, with the latter also having the highest WHRs, which were also found in Pakistani men. Rates of glucose intolerance and newly detected diabetes were high, as previously reported for African Caribbeans (1). Fasting plasma glucose values did not differ by ethnic group in men but were higher in Pakistanis, particularly in Pakistani women, whose 2-hour glucose levels were also highest. These levels of glycemia were reflected in the significantly raised concentrations of fasting plasma-specific insulin and non-cross-reacting proinsulin among Pakistanis compared with the other ethnic groups (table 1).

Relation to age and anthropometry

Although there was a significant, if weak, upward trend in IGFBP-1 concentrations with age overall (IGFBP-1 = 9.9 + 0.58age; r² = 0.03; n = 448), this differed by ethnic group, and was strongest in Pakistanis (–35.9 + 1.51age; r = 0.29; r² = 0.09; n = 120), weaker in Europeans (11.3 + 0.8age; r = 0.20, r² = 0.04; n = 142), and indiscernible in African Caribbeans (22.5 + 0.14age; r = 0.06, r² = 0.004; n = 186). IGFBP-1 had a clear negative association with BMI in each ethnic group (r = –0.37 overall), but this was weaker with WHR (r = –0.24), varying by ethnicity (r = –0.17 for African Caribbeans; r = –0.27 for Pakistanis; r = –0.44 for Europeans). There was a negative correlation with IGF-I (r = –0.20, table 2).

The relation of IGF-I with age was inverse in each ethnic group (overall r = –0.28, table 2) and was negative for BMI (r = –0.10) and WHR (r = –0.10), but positive with IGF-II (r = 0.24). IGF-II was unrelated to any of the anthropometric or other metabolic variables measured (table 2).

Relations with glucose tolerance

African Caribbeans had the lowest mean IGFBP-1 levels among those with normal glucose tolerance (F = 9.9, p < 0.0001), at half that in Europeans (figure 1). IGFBP-1 was only weakly associated with fasting glucose (r = 0.09) and was not associated at all in Europeans (r = –0.02). There was also no correlation with 2-hour postchallenge plasma glucose. However, this disguised a complex relation between glucose tolerance status, which varied by ethnic group (figure 1). There was a clear inverse association between IGFBP-1 and fasting insulin concentrations in all ethnic groups (table 2, figure 2), which was somewhat stronger among Pakistanis (β = –0.56, p < 0.0001). As insulin levels increased in the face of IGT, IGFBP-1 levels fell in Europeans and Pakistanis, but rose again with the development of overt diabetes as insulin secretion failed (figure 1). However, in African Caribbeans, IGFBP-1 levels were still decreased in those found to have diabetes (figure 1). Participants with type 2 diabetes generally had fasting insulin concentrations in the mid-lower range, while IGFBP-1 levels were in the upper part of the IGFBP-1 distribution as identified by glucose tolerance status on figure 2.

IGF-I concentrations were highest in African Caribbeans with normal glucose tolerance and, as in Pakistanis, were suppressed in those with diabetes, which did not occur in Europeans whose IGF-II concentrations were higher than in other ethnic groups (table 3).

Fasting proinsulin concentrations, despite being only 10 percent those of insulin, showed the most consistent increase, with declining glucose tolerance status across each ethnic group (figure 3a). Normoglycemic Pakistanis had significantly higher fasting and 2-hour concentrations than did other groups, while African Caribbeans had the lowest levels, which rose least, compared with the steep increase in Europeans. These relative proinsulin patterns were maintained at 2 hours, forming a plateau with glucose intolerance in Pakistan and African Caribbeans but declining in Europeans (figure 3b). Hence, the proinsulin/insulin ratio (figure 3c) showed a consistently higher proportion of proinsulin in those with newly detected diabetes in each ethnic group, with the least excess in African Caribbeans.

Insulin sensitivity

With the HOMA-S index, insulin sensitivity in those participants with 2-hour normoglycemia was least in Pakistanis and declined with decreasing 2-hour glucose tolerance status.
in all ethnic groups (figure 4a). Beta-cell function (HOMA-B) was unchanged between normoglycemic and IGT groups but fell off in those with newly detected diabetes ($p < 0.01$; figure 4b). There were significant positive correlations, both univariate ($\rho$) and after adjustment for age and sex (partial $r$), between IGFBP-1 and HOMA-S in African Caribbeans ($\rho = 0.38$, $p < 0.001$; partial $r = 0.22$, $p < 0.01$), Europeans ($\rho = 0.46$, $p < 0.001$; partial $r = 0.31$, $p < 0.001$), and Pakistanis ($\rho = 0.56$, $p < 0.001$; partial $r = 0.41$, $p < 0.001$).

### Role of NEFA

For subjects with normal glucose tolerance, NEFA were lower in African Caribbeans and Pakistanis than in Europeans (table 3). Total NEFA concentrations were unrelated to age ($r = 0.07$), BMI, WHR, insulin, proinsulin, or fasting glucose ($r = 0.09$), were only weakly related to 2-hour glucose ($r = 0.13$) (table 2), and did not differ by sex (data not shown). NEFAs were associated with levels of

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<table>
<thead>
<tr>
<th></th>
<th>African Caribbean ($n = 82$ males and $11$ females)</th>
<th>European ($n = 72$ males and $70$ females)</th>
<th>Pakistani ($n = 88$ males and $62$ females)</th>
<th>$p$ value for differences (ANOVA$^*$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>52.4 (50.6, 54.2)</td>
<td>51.4 (49.6, 53.0)</td>
<td>50.4 (47.9, 52.0)</td>
<td>NS$^*$</td>
</tr>
<tr>
<td>Female</td>
<td>47.5 (45.8, 49.2)</td>
<td>52.4 (50.9, 54.0)</td>
<td>48.6 (47.2, 52.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI$^*$ (kg/m$^2$)</td>
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<tr>
<td>Male</td>
<td>27.7 (26.1, 27.4)</td>
<td>27.2 (26.6, 27.7)</td>
<td>27.2 (26.3, 28.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>28.8 (28.2, 29.4)</td>
<td>27.0 (26.3, 27.6)</td>
<td>29.2 (28.0, 30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR$^*$</td>
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</tr>
<tr>
<td>Male</td>
<td>0.90 (0.89, 0.91)</td>
<td>0.92 (0.91, 0.93)</td>
<td>0.95 (0.94, 0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.82 (0.81, 0.83)</td>
<td>0.80 (0.79, 0.81)</td>
<td>0.87 (0.85, 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% IGT$^*$</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>12.0 (4.8, 19.1)</td>
<td>8.3 (1.1, 15.3)</td>
<td>22.6 (10.9, 34.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>9.6 (3.8, 15.4)</td>
<td>15.6 (7.2, 23.8)</td>
<td>15.7 (5.3, 26.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% new DM$^*$</td>
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<tr>
<td>Male</td>
<td>8.4 (2.3, 14.5)</td>
<td>11.7 (3.3, 20.0)</td>
<td>13.2 (3.7, 22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>4.8 (0.6, 8.9)</td>
<td>9.1 (2.5, 15.6)</td>
<td>19.6 (8.3, 30.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>5.7 (5.2, 6.1)</td>
<td>5.7 (5.2, 6.1)</td>
<td>6.5 (5.9, 7.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>5.4 (5.0, 5.8)</td>
<td>5.8 (5.3, 6.2)</td>
<td>6.7 (6.1, 7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>2-hour glucose</td>
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</tr>
<tr>
<td>Male</td>
<td>6.6 (5.8, 7.4)</td>
<td>6.5 (5.6, 7.5)</td>
<td>8.1 (7.1, 9.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female</td>
<td>5.9 (5.1, 6.7)</td>
<td>7.3 (6.4, 8.2)</td>
<td>8.1 (7.0, 9.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting insulin†</td>
<td></td>
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<tr>
<td>Male</td>
<td>42.8 (37.4, 49.0)</td>
<td>47.6 (39.9, 56.8)</td>
<td>76.0 (65.2, 88.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>58.2 (52.1, 65.1)</td>
<td>49.4 (42.4, 57.4)</td>
<td>75.3 (64.9, 87.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-hour insulin</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>210.7 (166, 268)</td>
<td>222.1 (159, 311)</td>
<td>503.7 (411, 617)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>276.5 (236, 323)</td>
<td>253.9 (203, 318)</td>
<td>421.2 (332, 534)</td>
<td>0.009</td>
</tr>
<tr>
<td>Fasting proinsulin†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.8 (3.3, 4.3)</td>
<td>4.6 (3.7, 5.7)</td>
<td>8.4 (6.9, 10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>3.3 (2.9, 3.8)</td>
<td>3.7 (3.0, 4.4)</td>
<td>6.3 (5.2, 7.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-hour proinsulin†</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>18.1 (15.1, 21.6)</td>
<td>23.1 (17.8, 29.9)</td>
<td>40.6 (34.1, 48.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>16.1 (13.8, 18.8)</td>
<td>22.8 (18.3, 28.3)</td>
<td>31.6 (25.9, 38.5)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

* ANOVA, analysis of variance; CI, confidence interval; NS, not significant; BMI, body mass index; WHR, waist-hip ratio; IGT, impaired glucose tolerance; DM, diabetes mellitus.
† Geometric mean.
IGFBP-1 ($r = 0.16$) and inversely associated with IGF-I ($r = -0.14$). Levels increased as the glucose tolerance category deteriorated (table 3; $p < 0.01$ for Europeans and Pakistanis and $p = 0.02$ for African Caribbeans).

**MULTIPLE REGRESSION ANALYSIS**

The size of the $\beta$ coefficients allows their direct quantitative comparison between variables in terms of relations within the models that follow. IGFBP-1 was independently and negatively related to fasting insulin ($\beta = -0.360$, $p < 0.0001$), WHR ($\beta = -0.194$, $p = 0.001$), BMI ($\beta = -0.135$, $p = 0.006$), fasting proinsulin ($\beta = -0.119$, $p = 0.041$), and African-Caribbean compared with European ethnicity ($\beta = -0.239$, $p < 0.0001$), was positively related to age ($\beta = 0.224$, $p = 0.0001$) and fasting glucose ($\beta = 0.178$, $p < 0.0001$), and was weakly with NEFA ($\beta = 0.08$, $p = 0.056$). There was no relation to gender or Pakistani origin.

Use of these normalized $\beta$s also showed that IGF-I was independently and negatively related to age ($\beta = -0.274$, $p < 0.0001$), fasting NEFA ($\beta = -0.124$, $p = 0.014$), and Pakistani ethnicity ($\beta = -0.176$, $p = 0.004$), with a borderline positive association with fasting insulin ($\beta = 0.103$, $p = 0.08$). There was no relation between IGF-I and fasting proinsulin or gender.

IGF-II showed a strong inverse association with African-Caribbean ($\beta = -0.264$, $p = 0.001$) and Pakistani ($\beta = -0.240$, $p < 0.0001$) ethnicity compared with European ethnicity but no relations with other variables.

**DISCUSSION**

In this study, we found significant differences in the IGF system between ethnic groups and in the way that the IGF system altered in the presence of IGT and diabetes. Few previous studies have characterized the IGF system and IGFBP-1 at the population level (22, 23), one for IGF-I

![FIGURE 1](image_url)  
**FIGURE 1.** Fasting serum insulin growth factor binding protein 1 (IGFBP-1) plotted against glucose tolerance test (GTT) status, by ethnic group, Manchester, England, 1994–1998. IGT, impaired glucose tolerance; DM, newly detected diabetes mellitus; AfC, African Caribbeans.
only (22), and from our literature search, none have characterized the IGF system and IGFBP-1 across ethnic groups at differing risk of glucose intolerance and cardiovascular disease as here. The three ethnic groups were generally balanced for gender and age, although African-Caribbean women were slightly younger, and were reasonably representative of their respective populations, as indicated under sampling methods.

**TABLE 3. Age- and sex-adjusted mean metabolic data and 95% confidence intervals by ethnic group and glucose tolerance status**, Manchester, England, 1994–1998

<table>
<thead>
<tr>
<th>Variables and 2-hour GTT status</th>
<th>African Caribbean (n = 193)</th>
<th>European (n = 142)</th>
<th>Pakistani (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI†</td>
<td>Mean</td>
</tr>
<tr>
<td>IGF-I† (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>163.0</td>
<td>153.3, 172.8</td>
<td>142.5</td>
</tr>
<tr>
<td>IGT†</td>
<td>158.7</td>
<td>133.2, 184.2</td>
<td>139.1</td>
</tr>
<tr>
<td>New DM†</td>
<td>132.8</td>
<td>96.3, 169.3</td>
<td>168.5</td>
</tr>
<tr>
<td>IGF-II† (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>549.7</td>
<td>513.2, 586.2</td>
<td>647.9</td>
</tr>
<tr>
<td>IGT</td>
<td>485.3</td>
<td>389.9, 580.6</td>
<td>653.6</td>
</tr>
<tr>
<td>New DM</td>
<td>645.0</td>
<td>521.4, 768.5</td>
<td>820.7</td>
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<tr>
<td>IGFBP-1† (ng/ml)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>30.6</td>
<td>23.3, 37.9</td>
<td>56.0</td>
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<tr>
<td>IGT</td>
<td>23.5</td>
<td>4.7, 42.2</td>
<td>19.4</td>
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<tr>
<td>New DM</td>
<td>18.2</td>
<td>0.5, 43.1</td>
<td>36.3</td>
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<tr>
<td>NEFA† (mmol/liter)</td>
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<td></td>
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<tr>
<td>Normal</td>
<td>0.11</td>
<td>0.07, 0.14</td>
<td>0.17</td>
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<tr>
<td>IGT</td>
<td>0.13</td>
<td>0.04, 0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>New DM</td>
<td>0.17</td>
<td>0.05, 0.29</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Defined according to 1985 World Health Organization criteria.
† GTT, glucose tolerance test; CI, confidence interval; IGF-I, insulin-like growth factor I; IGT, impaired glucose tolerance; DM, diabetes mellitus; IGF-II, insulin-like growth factor II; IGFBP-1, insulin-like growth factor binding protein 1; NEFA, nonesterified fatty acids.
African Caribbeans with normal glucose tolerance had lower fasting IGFBP-1 levels than did Europeans or Pakistanis, independently of the other measured variables. African Caribbeans also had no significant differences in IGFBP-1 concentrations between normal, IGT, and diabetes categories. In contrast, in Europeans and Pakistanis, IGFBP-1 concentrations were lower in those with impaired compared with normal GTT results and rose again in those with diabetes, probably directly reflecting the cellular response to secreted insulin arriving at the liver, the principal site of IGFBP-1 synthesis.

The likely mechanism reason for the opposite relation that insulin and glucose have with IGFBP-1 is that lower concentrations of secreted insulin arriving at the liver not
FIGURE 4. Indices of a, insulin sensitivity (HOMA-S) and b, islet β-cell function (HOMA-B) by glucose tolerance test status and ethnic group, Manchester, England, 1994–1998. IGT, impaired glucose tolerance; DM, newly detected diabetes mellitus; AfC, African Caribbean.

only permit more IGFBP-1 secretion (19) but also more hepatic glucose production that is not suppressed. Hence, glucose levels would tend to rise parallel to IGFBP-1 levels in proportion to their hepatic origins. Figure 2 shows that subjects with type 2 diabetes generally do have fasting insulin concentrations in the mid-lower range, while having IGFBP-1 levels in the upper part of the IGFBP-1 distribution. Thus, even at this relatively early stage in the course of type 2 diabetes, there is some degree of insulinopenia that contributes to the higher IGFBP-1 levels found in those with newly detected diabetes.

A previous study compared IGF-I and IGFBP-1 in 57 African-American and 79 “White” (presumably European-origin) pubertal school girls (29). Adjusted IGFBP-1 levels were lower and IGF-I levels were higher in the African-American girls, but because the latter were taller and heavier with greater fat and fat-free mass and had higher levels of maturity, residual confounding will have persisted. The IGF system is generally most active during growth, as shown by our absolute values, which were approximately 25 percent of those in the adolescents. However, the relative ethnic relations were similar in our data as were peripheral blood insulin levels in the African Caribbeans and Europeans here (noting that African Caribbeans and African Americans have quite different recent histories) (30).

The increase in IGFBP-1 with advancing age independent of BMI parallels findings in Finnish volunteers (31). This might imply decreasing levels of circulating insulin with increasing age, but here fasting insulin was unrelated to age, with 2-hour insulin only weakly related (r = 0.13). The increase in fasting IGFBP-I with advancing age was more marked in Pakistanis than in the other groups, perhaps again reflecting “resistance” to portal blood insulin arriving at the liver in older people, and with less hepatic extraction so that more insulin remains detectable in peripheral venous blood. In animal experiments, transgenic mice overexpressing IGFBP-1 developed hyperglycemia and elevated insulin levels and were smaller at birth than were nontransgenic controls (32). The adult heights of the hyperinsulinemic subjects of Pakistani origin here were also less than those of the other two groups (data not shown), perhaps related to the pregnancy programming hypothesis (30, 33).

IGF-I concentrations were higher in African Caribbeans than in the other ethnic groups and declined as glucose intolerance worsened, as concentrations did in Pakistanis. Yet, IGF-I levels in overt diabetes were paradoxically highest in Europeans (table 3). There was no independent relation of IGF-I with BMI in the multiple regression analysis, which was found to be positive in one population-based study in retirees (22) but not in the other (23). In 286 selected Italian obesity clinic patients (34), the IGF-I relation with BMI was negative when only age and BMI (despite many metabolic variables in the model) remained independently (inversely) related to IGF-I. In that study of obesity (34), IGF-I concentrations were related to fasting blood glucose values, and total and free IGF-I fell after glucose challenge as found elsewhere (35, 36), but were not assessed here. These varying data suggest that BMI per se is not a major influence on IGF-I. A randomized trial in middle-aged men at increased cardiovascular risk examined the impact of dietary restriction and exercise on IGFBP-1 and IGF-I by using GTTs (37). IGF-I decreased only in those on diet alone, with fasting insulin levels doing so in the exercise only group, while IGFBP-1 increased with all three interventions (diet, exercise, and both), probably indicating decreased insulin secretion and improved hepatic insulin sensitivity.

Pakistani subjects here with normal glucose tolerance had significantly higher fasting and postglucose challenge insulin and proinsulin, and, hence, lower insulin sensitivity based on HOMA-S than did the other two ethnic groups. These higher insulin levels, both fasting and postglucose challenge, are well established among people of Indian subcontinent origin in all subgroups whether based on current geographic boundaries or on religious or dietary practices (8, 9). A hypothesis that hyperinsulinemia and insulin resistance per se were causes of the excess coronary heart disease in South Asian groups has not been sustained in two separate cohort studies with sufficient incident events (38) (Gandi and McKeigue, unpublished data; Tuomilehto et al., personal communication, 1999). The rise and then decline in circulating insulin levels with GTT status is in keeping with increased insulin secretion and then β-cell failure with the development of diabetes, as found previously with both nonspecific insulin and C-peptide assays in these (8) and other

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In conclusion, these data suggest complex, but identifiable, associations of the IGF system with anthropometric factors that differ between ethnic groups. The interactions of the system with metabolic variables reflect hepatic synthesis of IGFBP-1, probably dependent on concentrations of both insulin and proinsulin arriving at the liver in portal blood modulated also by ambient portal NEFA levels. Both IGF-I and IGF-II vary significantly by ethnic group, unaccounted for by differences in other metabolic or anthropometric variables, as suggested by our multiple regression results. What determines the ethnic variation and whether IGF growth factors and their binding proteins are markers of or direct risk factors for progressive vascular damage, such as arterial intima/media smooth muscle or small blood vessel proliferation or even tumor cell growth, remains to be clarified. How and whether variation in components of the IGF system, measurable as here at the population level, influences cardiovascular and other disease outcomes requires further cohort studies in different ethnic groups (50, 51). We speculate that these growth factors and their binding proteins may be more closely and consistently linked to the causal pathway of disease pathogenesis than inconsistent results have suggested to date for insulin itself.

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