Nonesterified Fatty Acids as Mediators of Glucose Intolerance in Indian Asian Populations

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In India, diabetes is endemic, linked to urbanization (1), and its dispersed migrant populations show a particular vulnerability (2,3). For example, in Britain, diabetes is more frequent among Indian migrants than in the general population (4,5), but reported rates appear to equal those in India (6), although diverse dietary and cultural habits across India are also likely to have an impact (7). Rates of glucose intolerance seem to be similar between particular Indian communities living in East Africa, and British population studies provide increasing support for a causal role of nonesterified fatty acids (NEFAs) in the etiology of type 2 diabetes (8,9). Here, using a standardized comparison of culturally specific Gujarati communities between India and Britain, we hypothesized that factors associated with disordered NEFA suppression following glucose challenge would confer greater glucose intolerance in these populations.

RESEARCH DESIGN AND METHODS

— We compared a Gujarati community who had migrated to Sandwell (West Midlands, Britain) from rural villages around Navsari (Gujarat) with age-, sex-, and caste-matched contemporaries still living in those villages in India (as described elsewhere [10]). Randomly sampled participants from electoral rolls were invited to clinic sessions (beginning 8:30–10:00 A.M.). Participants without known diabetes had glucose tolerance testing (GTT) using a 75-g glucose equivalent (Maxijoul; SHS Supplies, Liverpool, U.K.) with venepuncture at fasting and at 30 and 120 min. Identical procedures for anthropometry in each site included the Leicester height measure (Seca, Birmingham, U.K.), weight (Seca), and waist and hip measurement (metal tapes). The waist was the narrowest circumference above the umbilicus and below the ribs. The hip circumference was measured over thin clothing as the widest horizontal circumference around the buttocks. Measures were rigorously standardized, with fieldworkers locally revalidated monthly and internationally every 4 months.

Plasma glucose was determined by automated glucose oxidase methodology at Sandwell Hospital (U.K.) and at the Mankodi Laboratory (Technicon RA-50; Bayer Diagnostics, Gujarat, India), each under routine quality control. Serum aliquots were stored at −70°C and transported frozen from India to Britain. Serum NEFAs were measured by enzymatic colorimetry (WAKO Chemicals, Alpha Laboratories, Eastleigh, U.K.), insulin was measured by immunoassay with 30% cross-reactivity for proinsulin, and β-cell function and insulin sensitivity were calculated by the homeostasis model assessment (HOMA) (11). Data were analyzed in SPSS v. 9 (SPSS, Chicago, IL) using standard and nonparametric tests, ANOVA, and multiple regression as appropriate.

RESULTS

— Of 537 Gujarati participants enrolled, comprehensive biochemical and anthropometric data were available in 228 from Sandwell and 285 from Navsari. Mean BMIs were >5 kg/m^2 higher in Britain than in India (Table 1). Glucose intolerance (impaired fasting, impaired 2-h values, new diabetes, and known diabetes combined) was higher among Navsari compared with Sandwell men (35.5 [95% CI 27.1–43.9] vs. 21.7% [13.5–29.9]) but not women (28.2 [20.8–35.5] vs. 26.3% [17.8–34.9]).

Glucose levels throughout the GTT were higher in Navsari, while NEFAs were higher in Britain (Table 1). Those without diabetes in Sandwell had greater β-cell function and lower insulin sensitivity than those in Navsari. Mean NEFAs 30 min following the glucose challenge actually increased in Britain; the 0- to 30-min change was used as a measure of suppression (NEFA-S).

In logistic regression, excluding known diabetes and after adjusting for age, sex, site, fasting insulin, and anthropometry, glucose intolerance was associated with NEFA-S (β ± SE: 1.94 ± 0.8, $P = 0.014$). Variation in NEFA-S was correlated with insulin sensitivity (HOMA-S) ($r^2 = 0.18$, $P < 0.001$). In logistic analysis across sites, HOMA-S was associated with BMI (−0.05 ± 0.01) and NEFA-S (−0.81 ± 0.1) and HOMA-β with BMI (0.04 ± 0.01), age (0.01 ± 0.01), and NEFA-S (0.33 ± 0.12), all $P < 0.01$. Fasting glucose (0.54 ± 0.1, $P < 0.001$) was associated with NEFA-S both across and

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Abbreviations: GTT, glucose tolerance testing; HOMA, homeostasis model assessment; NEFA, nonesterified fatty acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Age- and sex-adjusted metabolic factors by diabetes status among Gujarati Indians in Sandwell (U.K.) compared with contemporaries living in Navsari (India)*

	No diabetes			Diabetes†	
	Navsari	Sandwell	No diabetes (*P*)*	Navsari	Sandwell
n	184	168		40	37
BMI (kg/m^2)	20.8 (20.3–21.3)	26.1 (25.6–26.7)	<0.001	22.1 (20.8–23.4)	26.8 (25.1–28.4)
Waist-to-hip ratio	0.82 (0.81–0.83)	0.865 (0.85–0.88)	<0.001	0.85 (0.83–0.88)	0.88 (0.85–0.91)
Fasting plasma glucose (mmol/l)	4.95 (4.86–5.03)	4.88 (4.82–4.95)	0.194	8.10 (6.69–9.50)	9.52 (8.48–0.62)
2-h glucose (mmol/l)	5.64 (5.46–5.82)	5.08 (4.90–5.27)	<0.001	—	—
Fasting NEFA (mmol/l)^A	0.33 (0.29–0.37)	0.41 (0.39–0.45)	<0.001	0.40 (0.27–0.53)	0.55 (0.48–0.62)
30-min NEFA (mmol/l)^B	0.29 (0.26–0.32)	0.45 (0.42–0.49)	<0.001	—	—
2-h NEFA (mmol/l)	0.12 (0.11–0.13)	0.23 (0.20–0.26)	<0.001	—	—
NEFA-S (mmol/l) ($^{A-B}$)	0.01 (0–0.06)	0.04 (0.01–0.08)	0.785	—	—
Fasting insulin (units/l)†	6.8 (6.2–7.5)	10.2 (9.3–11.2)	<0.001	10.3 (8.2–12.7)	12.5 (10.2–15.5)
30-min insulin (units/l)†	44.7 (39.9–50.0)	56.7 (50.9–63.2)	<0.001	—	—
2-h insulin (units/l)†	33.7 (29.8–38.2)	48.7 (43.0–55.2)	<0.001	—	—
HOMA-β (%)†	108 (93–117)	156 (142–177)	<0.001	54.9 (39.0–77.2)	54.1 (39.2–74.7)
HOMA-S (0–1)†	0.68 (0.61–0.75)	0.44 (0.39–0.49)	<0.001	0.28 (0.21–0.37)	0.22 (0.17–0.28)

Data are age-adjusted mean (95% CI) and †geometric mean (95% CI). Postchallenge metabolic measures were available for subjects without reported diabetes. **P* for rural vs. migrant; †includes known and newly detected.

within sites, independently of other variables, but 2-h glucose only correlated with NEFA-S in Sandwell (2.1 ± 0.6, $P < 0.001$).

CONCLUSIONS — The high rates of glucose intolerance in both populations suggest that change in lifestyle from rural India to a British inner city has not worsened glucose tolerance per se. NEFA homeostasis appears disordered in both settings and may be the mechanism that confers glucose intolerance.

Sample sizes were relatively small, and a cross-sectional study design so far can only suggest associations and not causal pathways for incident disease. However, this within-community, transnational design should provide a powerful estimate of the effects of migration as it limits confounding by other environmental factors and minimizes genetic differences. The results may not be generalizeable to other Indian religious and dietary subgroups, although earlier work from Fiji (12) and Tanzania (2) also found a high prevalence of diabetes among rural and urban Indian migrant populations. Despite greater obesity and less glucose intolerance in Britain, these results should not be interpreted to question the role of obesity in the etiology of glucose intolerance. BMI was associated with both insulin sensitivity and β-cell function across both sites.

The supression or change of NEFA at 30 min into the GTT was no different across sites. NEFA supression was related to glucose intolerance and plasma glucose levels and may reflect a mechanism that sustains high levels of plasma glucose, even where dietary energy intake is barely adequate. The change in NEFA following the glucose challenge is likely to be a better marker of metabolic control than absolute fasting or postabsorptive measures. Disordered NEFA regulation promotes higher glucose excursions (13) through delayed glucose disposal (14) and increased endogenous glucose production (15). Their changes here, in India and Britain, were much less than those reported in the British (Anglo-Saxon) Ely population (16). The association between HOMA-S and NEFA suppression indicates that NEFA may also contribute to the major cardiovascular risk of these communities, via lipid metabolism through effects on hepatic insulin resistance (17). Their dual role in South Asian populations may be an important target for intervention.

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