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Adiposity and Hyperinsulinemia in Indians Are Present at Birth

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We studied body size and cord blood leptin and insulin concentrations in newborn urban Indian (Pune, India) and white Caucasian (London, UK) babies to test the hypothesis that the adiposity and hyperinsulinemia of Indians are present at birth.

Indian babies (n = 157) were lighter in weight compared with white Caucasian babies [n = 67; median weight, 2805 g *vs.* 3475 g, respectively; $P < 0.001$, adjusted for gestational age and sex; −1.52 SD score; confidence interval (CI), −1.66, −1.42] and had smaller abdominal (−2.39 SD score; CI, −2.52, −2.09), midarm (−1.47 SD score; CI, −1.58, −1.34), and head (−1.23 SD score; CI, −1.42, −1.13) circumferences. However, their skinfolds were relatively preserved: subscapular (central) skinfold (−0.32 SD score; CI, −0.43, −0.20) was better preserved than triceps (peripheral) skinfold (−0.86 SD score; CI, −0.97, −0.75). Cord plasma leptin (median, 6.2 ng/ml Pune and 6.4 ng/ml London) and insulin (median, 34.7 pmol/liter Pune and 20.8 pmol/liter London) concentrations were comparable in the two populations but were higher in Indians when adjusted for birth weight, confirming relative adiposity and hyperinsulinemia of Indian babies. Indian mothers were smaller in all respects, compared with white Caucasian mothers, except subscapular skinfold, which was similar in the two populations.

Our results support the intrauterine origin of adiposity, central adiposity, and hyperinsulinemia in Indians. Further research should concentrate on elucidating genetic and environmental influences on fetal growth and body composition. Prevention of insulin resistance syndrome in Indians will need to address regulation of fetal growth in addition to prevention of obesity in later life. (*J Clin Endocrinol Metab* 87: 5575–5580, 2002)

THERE IS AN escalating epidemic of type 2 diabetes (1) and coronary heart disease (2) in India, predominantly in urban areas. A recent survey in six cities showed that 12% of adults have diabetes and a further 15% have impaired glucose tolerance (1). The current diabetes epidemic is usually attributed to a thrifty genotype that helped survival in the distant past when food supply was scarce and irregular but has led to obesity and insulin resistance in the modern days of excess and regular food supply (3). Recent research has suggested that a thrifty phenotype at birth, resulting from fetal and perhaps maternal undernutrition and manifesting as intrauterine growth retardation, predicts adult diabetes (4). Indian babies are among the smallest in the world (5), and the thrifty phenotype may have important implications for the diabetes epidemic.

The Indian type 2 diabetic patients differ from the white Caucasian diabetic patients in many ways: they are diagnosed a decade earlier, have a lower body mass index (BMI; *i.e.* are thinner), but are centrally obese and more insulin resistant (6, 7). Recent comparative studies have shown that Indians have a higher percentage body fat for a given BMI compared with white Caucasians and African-Americans but have a lower muscle mass (8–10). Body composition of Indians is partly responsible for their higher insulin resistance (11). There is little information on the origins of the thin-fat, insulin resistant phenotype of Indians.

Abbreviations: BMI, Body mass index; CI, confidence interval(s); CV, coefficient(s) of variation; HDL, high-density lipoprotein.

We have reported that the rural Indian newborn babies who are lighter by 800 g compared with the white Caucasian babies have an almost similar subscapular skinfold thickness (12). This suggests that the thin-fat phenotype of Indians may originate *in utero*. A study of urban newborns in India who are at a very high risk of type 2 diabetes would provide information about whether the characteristic high risk phenotype of Indians is present at birth. This will have important implications for prevention of a diabetes epidemic in India. We therefore studied physical and biochemical features of urban Indian newborns and compared them with those of white Caucasian newborns from an industrialized country who are at a relatively lower risk of type 2 diabetes.

Subjects and Methods

We studied Indian mothers and their newborn babies born at the King Edward Memorial (KEM) Hospital (Pune, India) during the period February 15 to May 15, 1998, and compared them with white Caucasian mothers and their newborn babies born at the Whittington Hospital (London, UK) between July 15 and September 24, 2000. Both hospitals are general hospitals providing obstetric services to the local population. Informed written consent was obtained from all mothers, and an approval was obtained from the ethical review boards of both institutions. We excluded premature deliveries (<37 wk gestation), multiple births, and babies in London if both parents were not white Caucasian.

Measurements

We recorded obstetric history and morbidity diagnosed in the current pregnancy (hypertension, diabetes, and other problems). Gestational age at birth was calculated from the last menstrual period, supported by ultrasound measurements in most cases.

Anthropometry

Anthropometric measurements of mothers and babies were performed in duplicate by the same two observers in both locations, using standardized methods and the same set of instruments (except birth weight). Measurements were performed within 24 h of birth. The coefficient of variation (CV) between two observers (H.G.L. and S.S.R.) for different measurements was less than 2%.

Neonatal measurements included weight [to nearest 0.1 kg, using SECA scale (Marsden, London, UK) in London and ATCO scale (Wadala, Mumbai, India) in Pune]; crown-heel length [to nearest 0.1 cm, using Pedobaby (ETS J.M.B., Brussels, Belgium]; subscapular and triceps skinfolds on the left side of the body [to nearest 0.2 mm, using Harpenden skinfold calipers (CMS Instruments, London, UK)]; and head, mid-upper arm, abdominal, and chest circumferences [to the nearest 0.1 cm, using a nonstretchable fiberglass measuring tape (CMS Instruments)].

Maternal measurements included weight (to the nearest 0.1 kg, using Soehnle electronic scales supplied by CMS Instruments); height [to the nearest 0.1 cm, using Harpenden Stadiometer (CMS Instruments)]; biceps, triceps, subscapular, and suprailiac skinfolds on the left side of the body [to the nearest 0.2 mm, using Harpenden skinfold calipers (CMS Instruments)]; and the head, mid-upper arm, waist, and hip circumferences [to nearest 0.1 cm, using a nonstretchable fiberglass measuring tape (CMS Instruments)].

Hypertension and diabetes

Women were called hypertensive if their blood pressure was at least 140/90 mm Hg or if they were on antihypertensive treatment. Diabetes was diagnosed by World Health Organization criteria for gestational diabetes (2 h plasma glucose $\geq$ 7.8 mmol/liter after 75 g oral anhydrous glucose) during their routine antenatal follow-up.

Cord blood measurements

Cord blood was collected in EDTA tubes from the distal stump and spun in a refrigerated centrifuge within 30 min (4 C; 3500 $\times$ *g*), and the plasma was stored at −80 C. Samples collected in London were carried frozen on dry ice to Pune. All biochemical and endocrine measurements were performed in Pune. Measurements included glucose, albumin, total and high-density lipoprotein (HDL) cholesterol, and triglycerides using standard enzymatic kits on an Abbott Spectrum Biochemistry Analyzer (Abbott Laboratories, Irwing, TX). Plasma insulin concentration was measured using Human Insulin EIA kit (DAKO Diagnostics Ltd., Cambridgeshire, UK; sensitivity, 10.4 pmol/liter; interbatch CV, 5%). Leptin was measured using Human Leptin RIA kit (Linco Research, Inc., St. Charles, MO; sensitivity, 0.5ng/ml; interbatch CV, 4.7%).

Statistical methods

Data are presented as median (interquartile range). Difference between the two populations was tested by Student's *t* test or ANOVA with adjustments for confounding variables. The relationship between measurements was tested by regression analysis. Maternal weight, biceps and suprailiac skinfold thickness, neonatal subscapular skinfold thickness, and cord plasma triglycerides, insulin, and leptin concentrations were log-transformed to ensure normal distribution. Comparisons of different variables in the two populations were made by calculating the SD score using mean and SD for London subjects as a reference. Comparison of Pune and London newborns was also done using pair matching for birth weight. For each London neonate, two Pune neonates were selected with birth weights within 30 g of the London neonate.

Results

Study subjects (Fig. 1)

A total of 463 women delivered in KEM Hospital in Pune during the study period; 315 of these women were born and brought up in urban Pune, and 280 (89%) of them gave informed consent. Of these 280 women, 223 (80%) delivered full term ($\geq$37 wk gestation). We excluded 43 hypertensive and 6 diabetic women. Of the remaining 174 (91 primiparous), anthropometric measurements were available on 152 (87%) mothers and 157 (90%) babies, whereas cord blood measurements were available on 94 (54%). Forty-nine mothers (28%) were delivered by cesarean section, and 50 (29%) received an iv glucose drip at the time of delivery.

Of 688 babies delivered in the Whittington Hospital in London during the study period, 251 were born to white Caucasian couples, and of these, 99 (40%) gave an informed consent for measurements. We excluded 6 premature deliveries and 10 hypertensive and 2 diabetic mothers and their babies. Of the remaining 81 women (33 primiparous), anthropometric data were available on 61 (75%) mothers and 60 (74%) babies, and cord blood measurements on 67 (82%).

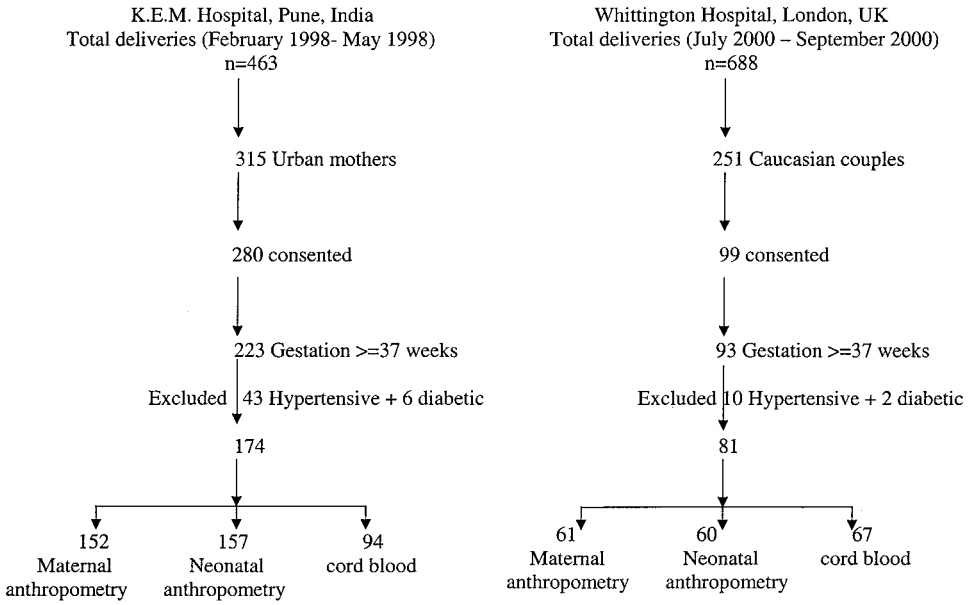

FIG. 1. Flow chart showing selection of mothers and babies in Pune and London.

Thirteen mothers (16%) were delivered by cesarean section, and 4 (5%) received an iv glucose drip at the time of delivery.

In both of the populations, there was no significant difference in gestational age at delivery or in the birth weight of babies whose mothers agreed to be studied and those who did not. In both, there was no significant difference in anthropometric measurements of mothers and babies on whom cord blood measurements were available and of those in whom they were not.

Mothers (Table 1A).

Indian mothers were younger and smaller compared with the white Caucasian mothers. Thus, they were shorter and lighter and had lower BMI and smaller head, midarm, waist, and hip circumferences. Skinfold thicknesses were significantly smaller in the Indian mothers, except for subscapular skinfold, which was similar in the two groups.

Babies (Table 1B and Fig. 2)

Anthropometry. Indian babies delivered on average 9 d earlier than the white Caucasian babies. After adjusting for gestation and sex of the baby, Indian babies were smaller in all measurements compared with the white Caucasian babies. However, different measurements were differentially smaller in Indian babies. When measurements of Indian babies were expressed as SD scores, the smallest measurement was the abdominal circumference (mean, −2.39 SD score); next smallest were chest (−1.61 SD score), midarm (−1.47 SD score), and head (−1.23 SD score) circumferences, whereas the skinfolds were relatively well preserved. The subscapular skinfold was the best preserved measurement in Indian babies (−0.32 SD score), more so than the triceps skinfold (−0.86 SD score).

On multivariate analysis, birth weight was related to gestational age, sex of the baby (boys higher), and maternal size (weight, height, and BMI); but there was still an independent relationship with country of origin (smaller in India). On the other hand, subscapular skinfold thickness was related only to birth weight, not to gestational age, sex, maternal size, and country of origin.

Cord plasma measurements (Table 2). Many of the cord plasma measurements were related to the gestational age and sex of the baby. All comparisons and relations are therefore adjusted for these parameters. Cord plasma concentrations of glucose and insulin were higher in Indian babies whose mothers received iv glucose during delivery compared with those whose mothers did not; these two measurements are therefore also adjusted for cord plasma glucose concentration.

TABLE 1A. Maternal measurements in Pune and London

	Pune	London	*P*
No.	152	61	
Age (yr)	25.0 (22.0–28.0)	32.4 (29.3–35.8)	<0.001
Maternal weight (kg)[a]	51.0 (45.5–58.9)	69.8 (65.1–78.7)	<0.001
Maternal height (cm)	153.2 (149.5–156.7)	163.6 (161.4–168.4)	<0.001
BMI (kg/m^2)	21.7 (20.0–24.2)	26.1 (23.9–28.6)	<0.001
Head circumference (cm)	53.9 (52.0–55.2)	56.0 (54.7–57.1)	<0.001
Midarm circumference (cm)	24.3 (22.7–26.5)	27.6 (26.3–29.9)	<0.001
Waist circumference (cm)	80.5 (75.2–87.2)	96.0 (90.9–102.1)[a]	<0.001
Hip circumference (cm)	92.8 (88.0–98.2)	103.4 (99.2–108.9)	<0.001
Waist/hip ratio	0.87 (0.81–0.91)	0.92 (0.88–0.96)	<0.001
Biceps skinfold (mm)	7.2 (5.6–9.4)	10.2 (7.8–13.7)[a]	<0.001
Triceps skinfold (mm)	13.5 (10.5–17.4)[a]	16.8 (12.4–19.9)	<0.001
Subscapular skinfold (mm)	20.0 (15.4–26.0)[a]	22.5 (16.3–29.5)	NS
Suprailiac skinfold (mm)[a]	16.5 (12.7–21.3)	22.4 (16.5–33.1)	<0.001

Data represent median (interquartile range). NS, Not significant.
[a] Follows log normal distribution.

TABLE 1B. Neonatal measurements in Pune and London

	Pune	London	*P*
No.	157	60	
Gestational age (wk)	39.3 (38.6–40.1)	40.6 (39.7–41.3)	[c]
Birth weight (g)	2805 (2516–3080)	3475 (3200–3905)	[c]
Length (cm)	48.0 (46.3–49.3)	51.0 (49.6–52.5)	[c]
Ponderal index (kg/m^3)	25.3 (23.6–27.7)	26.3 (25.1–28.1)	NS
Head circumference (cm)	33.5 (32.3–34.2)	35.1 (34.0–36.4)	[c]
Midarm circumference (cm)	10.0 (9.3–10.3)	11.2 (10.7–11.9)	[c]
Abdominal circumference (cm)	28.4 (27.2–30.6)	33.4 (32.1–34.4)	[c]
Chest circumference (cm)	32.0 (30.4–33.0)	34.5 (33.0–36.3)	[c]
Subscapular skinfold (mm)[a]	4.1 (3.9–4.7)	4.6 (3.9–5.3)	[b]
Triceps skinfold (mm)	4.3 (3.9–4.9)	5.1 (4.7–5.9)	[c]

Data represent median (interquartile range). NS, Not significant.
[a] Follows log normal distribution.
[b] $P < 0.05$.
[c] $P < 0.001$ (adjusted for gestational age and sex, in case of gestational age only for sex).

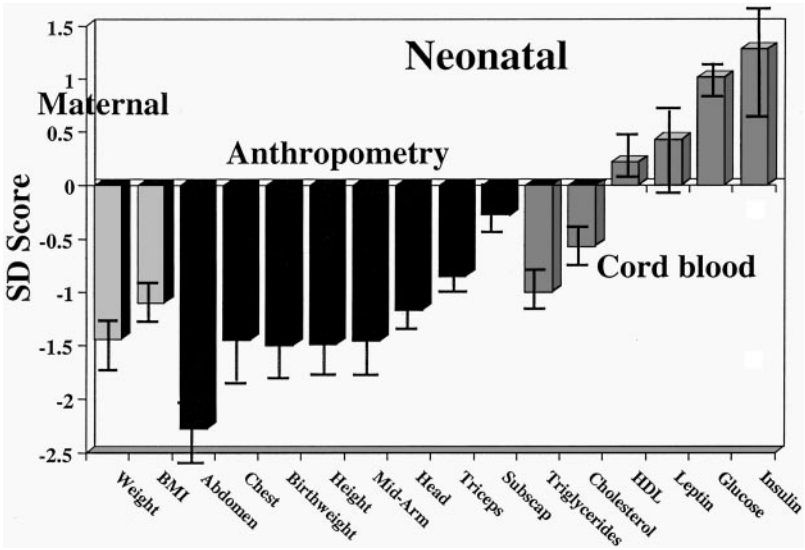

FIG. 2. SD scores for Indian mothers and babies in Pune compared with white Caucasian mothers and babies in London. SD score Indian = individual value − UK mean/UK SD. Mean and 95% CI are shown.

TABLE 2. Cord plasma biochemistry in Pune and London

	Pune	London	P^b
No.	94	67	
Glucose (mmol/liter)	5.3 (4.0–7.0)	4.4 (3.8–5.3)	<0.001[c]
Insulin (pmol/liter)[a]	34.7 (15.3–76.4)	20.8 (13.9–48.6)	0.18[c], 0.57[d]
Leptin (ng/ml)[a]	6.2 (3.3–11.0)	6.4 (4.0–10.5)	0.99[c], 0.75[d]
Cholesterol (mmol/liter)	1.5 (1.3–1.8)	1.8 (1.6–2.1)	<0.001
Triglycerides (mmol/liter)[a]	0.25 (0.19–0.34)	0.51 (0.37–0.78)	<0.001
HDL (mmol/liter)	0.6 (0.5–0.7)	0.6 (0.4–0.7)	0.42
Albumin (g/liter)	36.3 (33.0–39.0)	36.0 (34.0–38.0)	0.68

Data represent median (interquartile range).
[a] Follows log normal distribution.
[b] *P* values adjusted for gestational age and sex.
[c] *P* values additionally adjusted for maternal glucose infusion.
[d] *P* values additionally adjusted for circulating cord glucose.

Differences in the two populations (Table 2 and Fig. 2). Cord plasma concentration of glucose was higher in Indian compared with white Caucasian babies, but those of insulin, leptin, HDL cholesterol, and albumin were similar in the two groups. Cord plasma total cholesterol and triglyceride concentrations were lower in the Indian babies. When further adjusted for the difference in the birth weight of the two populations, Indian babies had higher cord plasma concentration of insulin (41.5 *vs.* 21.3 pmol/liter; $P < 0.001$) and leptin (7.5 *vs.* 4.3 ng/ml; $P < 0.001$) than those in the white Caucasian babies. Adjustment for cord plasma glucose concentration did not alter these findings (insulin, $P < 0.01$; and leptin, $P < 0.001$).

Relation between cord plasma insulin and leptin concentrations and neonatal anthropometry (Table 3). Cord plasma insulin concentration was directly related to birth weight and plasma glucose concentration in both populations. In the Indian babies, there was a direct relationship with subscapular skinfold thickness but not with any other anthropometric measurements, whereas in the white Caucasian babies, cord plasma insulin concentration was directly related to all birth measurements except the subscapular skinfold and length. Cord plasma leptin concentration was significantly related to birth weight and was higher in girls in both populations. Cord plasma insulin and leptin concentrations were related in both of the populations (Indian, r = 0.28; $P < 0.01$; white Caucasian, r = 0.57; $P < 0.001$).

TABLE 3. Correlations of cord plasma leptin and insulin concentrations with neonatal anthropometry

	Leptin		Insulin	
	Pune	London	Pune	London
No.	86	63	84	62
Birth weight (g)	0.49[b]	0.66[b]	0.21[a]	0.49[c]
Length (cm)	0.16	0.25	0.12	0.13
Head circumference (cm)	0.50[b]	0.38[b]	0.11	0.24[a]
Midarm circumference (cm)	0.51[b]	0.71[c]	0.16	0.40[a]
Abdominal circumference (cm)	0.56[b]	0.59[c]	0.19	0.43[b]
Chest circumference (cm)	0.49[b]	0.53[c]	0.08	0.35[a]
Subscapular skinfold (mm)	0.44[b]	0.37	0.26[a]	0.15
Triceps (mm)	0.04	0.49[c]	0.16	0.37[b]

Pearson correlation coefficients, adjusted for gestational age and sex of the baby and for iv glucose infusion in mothers.
[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$.

Multiple regression analysis of cord plasma insulin and leptin concentrations (independent variables: gestation, sex, maternal size, birth weight, cord glucose concentration, and country) revealed that cord plasma insulin concentrations were significantly related to cord plasma glucose concentration ($P < 0.001$) but not to gestation, sex of the baby, maternal

size, or country of residence. On the other hand, cord plasma leptin concentration was related to baby's gender (girls higher, $P < 0.001$), birth weight ($P < 0.001$), and also to country of residence (higher in India, $P < 0.01$).

Comparison of babies with similar birth weight (Table 4). When babies with birth weight between 3.0 and 3.4 kg were pair-matched, Indian babies were still smaller in most measurements compared with those in the white Caucasian babies except triceps skinfold, which was similar, and subscapular skinfold, which was larger in the Indian babies. Cord plasma glucose concentration was similar, whereas insulin and leptin concentrations were higher in Indian babies compared with those in the white Caucasian babies.

Discussion

We confirm our observation that the otherwise small Indian newborn babies preserve sc fat (skinfold thickness) compared with white Caucasian babies. Our original finding in rural Indian babies was based on literature comparison (12). In the present study, the same two observers (H.G.L. and S.S.R.) made prospective measurements in the two populations using the same instruments to test the hypothesis of higher adiposity of Indian babies. We observe that the subscapular skinfold is better preserved than the triceps skinfold, suggesting a tendency in Indians to truncal or central adiposity, even during intrauterine development. We have also extended our findings to whole body fat mass by showing that cord plasma leptin concentrations were comparable in the two groups of babies. Indian babies are particularly small in their abdominal circumference (suggesting smaller viscera) and small mid-upper arm circumference (suggesting smaller skeletal muscle mass). Thus, the Indian babies are centrally adipose but thin in muscle and viscera (protein-rich tissues). The relatively thin, centrally fat phenotype of Indian adults (9, 10) thus originates in the intrauterine life.

Indian babies were born 1.5 wk earlier than the white Caucasian babies, but anthropometric differences between the two populations persisted when adjusted for the period of gestation. The small size of Indian babies is in part a reflection of the smallness of their mothers, but the difference persisted after adjusting for the difference in maternal size. This might suggest a genetic basis for our findings. However, mean birth weight has increased by 250 g in the second generation migrant Indians in the United Kingdom (13). In a community-based study in six villages near Pune, we have shown that the mother's body size, food intake, physical activity, and circulating concentrations of nutrients and metabolites during pregnancy are important determinants of the baby's size and body composition at birth (12, 14). Thus, gene-nutrient interactions may form the basis for differences in the intrauterine growth in different populations. A comparative study between Indian babies born in India and those born in the United Kingdom will help analyze the relative influence of genetic and nutritional factors on fetal growth and body composition.

We measured leptin and other metabolic-endocrine markers in the cord blood. Cord plasma leptin concentration in Indian babies was comparable to that in the white Caucasian babies, despite the Indian babies being 700 g lighter. When adjusted for the weight difference, cord plasma leptin concentration in Indian babies was higher than that in the white Caucasian babies. Circulating leptin levels are a reflection of body fat mass (15, 16) and therefore suggest that Indian babies have higher body fat percentage than the white Caucasian babies. This was rather unexpected because Indian babies are considerably smaller in all other body measurements.

Another important finding in our study is that when adjusted for the difference in birth weight, the circulating insulin concentration in Indian babies was higher than that in white Caucasian babies and remained so after adjustment for the higher circulating glucose concentration due to iv glucose infusion to the mother during delivery. Thus, we show for the first time that the hyperinsulinemic, insulin-resistant phenotype of the Indians (6, 8–11) is present at birth, probably related to their body composition. Our results are different from those reported in babies of migrant Indians in New Zealand who had lower insulin concentrations in the cord blood compared with Europeans. The difference between Indian and European babies disappeared when corrected for birth weight. The difference in the two studies may be due to exclusion in the New Zealand study of mothers and babies more likely to be insulin resistant (17).

There are many reports of cord blood leptin concentration

TABLE 4. Comparison of Pune and London newborns pair-matched for birth weight

	Pune	London	*P*
No.	50	25	
Anthropometry			
Gestational age (wk)	39.6 (38.7–40.4)	40.0 (38.8–40.8)	0.33
Birth weight (g)	3100 (2876–3262)	3100 (2882–3250)	0.82
Birth length (cm)	49.0 (47.0–50.0)	49.7 (48.1–50.4)	0.03
Head circumference (cm)	34.0 (33.2–34.3)	34.1 (33.0–35.3)	0.26
Midarm circumference (cm)	10.2 (9.9–10.9)	10.6 (10.1–11.1)	0.02
Subscapular skinfold (mm)	4.4 (4.1–4.9)	4.1 (3.1–5.0)	0.03
Triceps skinfold (mm)	4.7 (4.1–5.1)	5.0 (4.4–5.2)	0.10
Cord plasma biochemistry			
Glucose (mmol/liter)	4.72 (3.77–63.9)	4.27 (3.60–5.21)	0.72
Insulin (pmol/liter)	55.5 (34.7–104.9)	13.9 (13.9–34.7)	0.002[a]
Leptin (ng/mliter)	10.4 (5.3–15.1)	4.6 (3.0–6.6)	0.022[a]

Data represent median (interquartile range).
[a] Adjusted for gestation, sex, and cord glucose.

in different populations. In general, they stress the association with body size and fat (16–26). Our study has expanded these observations and compared two populations with markedly different body composition and different prevalence of insulin resistance syndrome in later life. A recent study stressed that migrant Indian children are more insulin resistant compared with white Caucasian children as early as 10 yr of age (27). We report the earliest age at which adiposity and hyperinsulinemia in Indians are demonstrable, *i.e.* at birth. Our previous finding that small birth weight predisposes Indian babies to higher adiposity, central adiposity, and insulin resistance syndrome in childhood (28–30) may be explained by relative adiposity and hyperinsulinemia of these children from birth.

In summary, we confirm the characteristic thin-fat phenotype of Indians at birth and show that they are also hyperinsulinemic at birth. Elucidation of the underlying mechanisms may offer an opportunity to influence body composition of the Indian babies and therefore their susceptibility to future disease.

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