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Whole Body Magnetic Resonance Imaging of Healthy Newborn Infants Demonstrates Increased Central Adiposity in Asian Indians

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ABSTRACT: Abdominal adiposity and metabolic ill health in Asian Indians are a growing public health concern. Causal pathways are unknown. Preventive measures in adults have had limited success. The aim of this observational case-control study was to compare adipose tissue partitioning in 69 healthy full term Asian Indian and white European newborns born in Pune, India and London, UK, respectively. The main outcome measures were total and regional adipose tissue content measured by whole body magnetic resonance imaging. Although smaller in weight (95% CI for difference −0.757 to −0.385 kg, $p < 0.001$), head circumference (−2.15 to −0.9 cm, $p < 0.001$), and length (−2.9 to −1.1 cm $p < 0.001$), the Asian Indian neonates had significantly greater absolute adiposity in all three abdominal compartments, internal (visceral) (0.012–0.023 L, $p < 0.001$), deep s.c. (0.003–0.017 L, $p = 0.006$) and superficial s.c. (0.006–0.043 L, $p = 0.011$) and a significant reduction in nonabdominal superficial s.c. adipose tissue (−0.184 to −0.029 L, $p = 0.008$) in comparison to the white European babies despite similar whole body adipose tissue content (−0.175 to 0.034 L, $p = 0.2$). We conclude that differences in adipose tissue partitioning exist at birth. Investigative, screening, and preventive measures must involve maternal health, intrauterine life, and infancy. **(*Pediatr Res* 65: 584–587, 2009)**

By 2030, there will be over 80 million people with type-2 diabetes in India (1) and Asian Indians will account for approximately 40% of the global burden of cardiovascular disease (2). This prevalence will exceed that in ethnic majority populations in developed countries, but is paralleled in Indian migrants. In the United Kingdom, the age specific prevalence of type 2 diabetes in south Asian migrants is similar to that in urban India and extends from 8 to 18% in contrast to 3 to 4% in the general population (3). The determinants of this increased risk are unclear and health interventions, generally focused on obese adults, have had limited success. The adult Asian Indian phenotype is characterized by central adiposity despite a lower body mass index. In previous work, we have shown that Asian Indian newborns have elevated cord blood insulin and leptin concentrations and well preserved subscapular skin-fold thicknesses compared with white European newborns despite smaller body size (4,5). In this study, we compared anthropometric indices, and adipose tissue (AT) depots assessed by whole body magnetic resonance imaging (MRI) in Asian Indian and white European neonates.

METHODS

Full-term Asian Indian and white European infants in this study were participants in independent research projects in Pune, India and Imperial College London, respectively. The former is an observational study of nutrition in pregnancy and fetal growth in women attending the antenatal clinic of the King Edward Memorial Hospital. The London group have an ongoing program of research investigating the determinants of newborn body composition that includes the assessment of a broad range of infants by gestational age and clinical characteristics, recruited from the postnatal wards of teaching hospitals of Imperial College London. Assessment of whole body adipose tissue content has been obtained in over a hundred term and preterm infants from a range of ethnic groups. The Pune Maternal Nutrition Study is a large population based study from which only the infants reported here have undergone whole body adipose tissue imaging. The selection of infants for this comparison required the whole body MRI investigation to have been performed within 2 weeks of birth, that they were healthy full term infants delivered after uncomplicated pregnancies and that both parents were Asian Indian in the Pune group or white European in the London group.

We considered this an exploratory comparison and no *a priori* sample size calculations were performed. Written, informed parent consent was obtained in both institutions. MRI was conducted in natural sleep as previously described (6).

All MR images from UK and India were analyzed independently of the investigators by two analysts from Vardis-Group (www.vardisgroup.com) utilizing an image segmentation program as previously described (6). The coefficient of variation for these measurements was <3%. Image analysis was conducted blinded to the subject groups and in random order. Each of six AT compartments (Fig. 1) was quantified individually and then summated to derive total AT content. Abdominal adipose tissue was that contained in image slices from the sacrum to the top of the liver. The deep s.c. compartment is clearly separated from superficial s.c. AT by a fascial plane (7) (Fig. 2). The AT measurements are shown as absolute volumes (liters) (Table 1) and as Z scores expressed relative to the white European group [Z score Indian = (Individual Asian Indian value − white European mean)/white European SD] (Fig. 3). Data were analyzed using SPPS version 14.

Research ethics approval. Imaging was conducted following research ethics approval by Hammersmith Hospital NHS Trust Research Ethics Committee and King Edward Memorial Hospital and Research Centre, Pune.

RESULTS

Whole body images were compared in 30 Asian Indian (9 girls, 21 boys), and 39 white European infants (16 girls; 23 boys). The mean (SD) gestational age at birth of the Asian

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Abbreviations: AT, adipose tissue

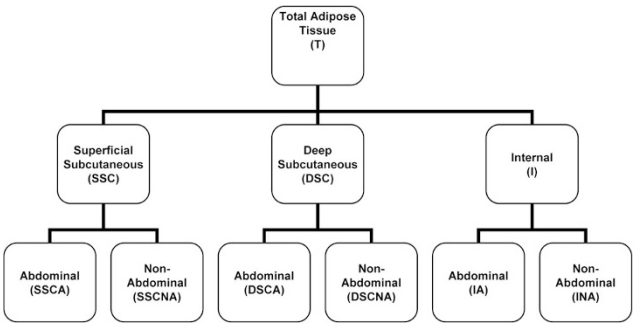

Figure 1. Adipose tissue compartments.

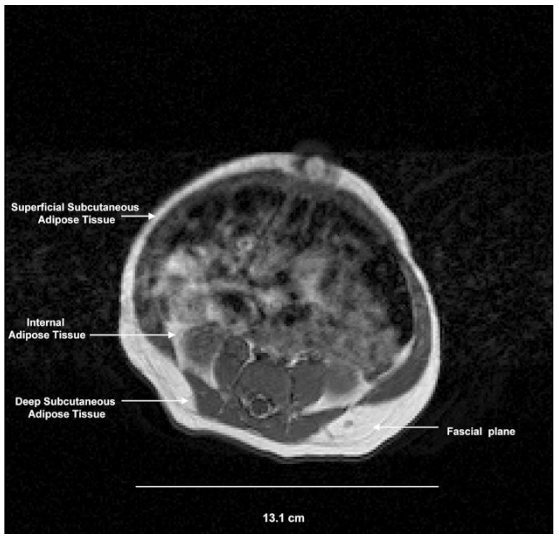

Figure 2. Abdominal MR section showing Superficial s.c., deep s.c., and internal adipose tissue compartments; magnification baby to image = ×0.305.

Indian infants was 38.9 (1.6) weeks and of the white European infants 39.7 (1.8) weeks.

Details of anthropometric measurements and adipose tissue volumes are shown in Table 1. Although the Asian Indian babies were lighter (95% CI for difference −0.757 to −0.385 kg, $p < 0.001$) and shorter (−2.9 to −1.1 cm, $p < 0.001$) with smaller head circumferences (−2.15 to −0.9 cm, $p < 0.001$), than the white European babies, absolute whole body AT content was not significantly different (−0.175 to 0.034 L, $p = 0.2$).

The Asian Indian babies had significantly increased adiposity in each of the three abdominal compartments, internal (visceral) (0.012 to 0.023 L, $p < 0.001$), deep s.c. (0.003 to 0.017 L, $p = 0.006$), and superficial s.c. (0.006 to 0.043 L, $p = 0.011$). This was most marked in the internal (visceral) compartment where it equated to a 2 SD score excess (Fig. 2). The Asian Indian babies also had a highly significant reduction in superficial s.c. nonabdominal (−0.184 to −0.029 L, $p = 0.008$) and internal nonabdominal AT (−0.022 to −0.004, $p = 0.005$) than the white European babies.

DISCUSSION

Central adiposity is an objective measure of disease risk and mortality. Preventative measures have largely focused upon lifestyle factors in adults but our data demonstrating that aberrant adipose tissue partitioning is established by birth suggest that intrauterine events are important. Evidence for this suggestion would require demonstration of tracking of central adiposity from infancy into adult life, with attenuation or amplification by lifestyle modifications. The ongoing Pune Maternal Nutrition Study will provide such information (8).

The high prevalence of central adiposity in adult Asian Indians, regardless of their geographical location, is well described (9) and represents a growing public health concern. Causal pathways are unknown but *MC4R* (melanocortin-4-receptor) involved in the regulation of energy expenditure and appetite has been suggested a possible gene candidate (10). *MC4R* is expressed widely in the CNS. Activation reduces fat stores by decreasing food intake and increasing energy expenditure. Humans with naturally occurring *MC4R* mutations have severe obesity. Although possible, we consider an effect specific to the Asian Indian genome an unlikely explanation for the aberrant adipose tissue partitioning we have demonstrated. Central adiposity is strongly correlated with insulin resistance that confers a survival advantage only under conditions of nutrient deficiency. However, the ravages of an uncertain food supply during the dawn of human evolution would have impacted upon all races and it is an improbable assumption that Asian Indians would have been more vulnerable. Recent anthropological evidence also calls into question the notion that food shortages in more recent, preindustrial history might have selected for a "thrifty genotype" (11). A much discussed alternative possibility is that of the "thrifty phenotype." Here intrauterine nutritional insults induce fetal adaptations that improve short-term survival but become maladaptive if nutrient provision improves. Support for this as an explanation for the high prevalence of central obesity and metabolic syndrome in Asian Indians would be provided if this risk were to be shown to reduce across generations following migration or improved affluence. There is, as yet, only limited evidence that this may be the case (12).

A further possibility is that of a relatively recent heritable modification of the Asian Indian epigenome or "thrifty epigenotype," induced by a suboptimal intrauterine environment (13). Animal experimentation provides evidence for intergenerational transmission of epigenetic modifications though evidence from clinical studies is more limited, as is understanding of the biochemical and molecular mechanisms responsible. Other possible mechanisms for nongenomic transgenerational effects are DNA amplification or altered telomere length (14,15). Human studies indicate that poor maternal nutrition influences not only the status of the fetus, but also that of fetal offspring (her grandchildren) (16). We have recently reported that a maternal nutritional imbalance in the two major methyl-donor vitamins, vitamin B12 and folate, is associated with offspring adiposity and insulin resistance (8), as is peri-conceptional methionine deficiency in a sheep model (17). In a rat model, maternal protein restriction results in increased visceral adiposity in offspring (18). Widespread vegetarianism coupled with the low status of Asian Indian girls and women over many generations make this a not implausible hypothesis and one that is also in keeping with the

Table 1. *Adipose tissue volumes assessed by whole body MRI: comparison of Indian and white European babies (independent samples t test)*

	Indian (n = 30), mean (SD)	White British (n = 39), mean (SD)	Mean difference (95% CI)	p
Internal-abdominal (l)	0.044 (0.01)	0.027 (0.01)	0.017 (0.012 to 0.023)	<0.001
Deep subcutaneous abdominal (l)	0.024 (0.02)	0.014 (0.04)	0.010 (0.003 to 0.017)	0.006
Superficial subcutaneous abdominal (l)	0.135 (0.04)	0.111 (0.04)	0.024 (0.006 to 0.043)	0.011
Internal nonabdominal (l)	0.046 (0.02)	0.059 (0.02)	−0.013 (−0.022 to −0.004)	0.005
Deep subcutaneous nonabdominal (l)	0.009 (0.007)	0.011 (0.004)	−0.002 (−0.005 to 0.001)	0.2
Superficial subcutaneous nonabdominal (l)	0.454 (0.16)	0.560 (0.12)	−0.107 (−0.184 to −0.029)	0.008
Total adipose tissue (l)	0.711 (0.21)	0.782 (0.22)	−0.070 (−0.175 to 0.034)	0.2

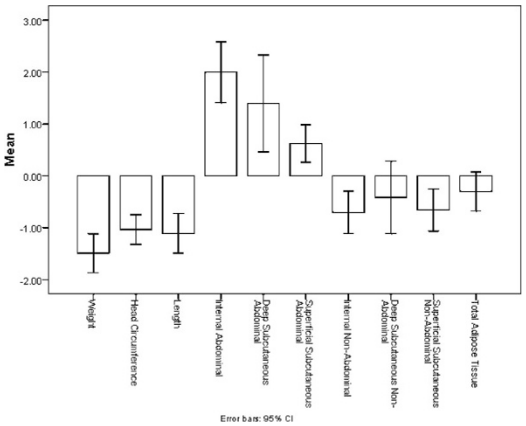

Figure 3. Anthropometry and adipose tissue compartments: Z scores (mean ± 95% CI) for Asian Indian babies with white European babies as baseline.

known association of central adiposity with socioeconomic deprivation (19).

The influence of adipose tissue compartments on metabolism is only beginning to be understood. The importance of the superficial s.c. compartment is shown by observations of insulin sensitivity in adults. In elderly women with visceral obesity, increasing s.c. adiposity is associated with greater insulin sensitivity and reduced cardiovascular risk (20,21). This suggests a direct beneficial effect of s.c. AT in addition to the adverse metabolic impact of visceral AT. Adipose tissue transplantation studies in mice also show that transplantation of s.c. AT into the intra-abdominal cavity improves metabolic parameters (22) indicating that s.c. and intra-abdominal adipocyte function is intrinsically different. Our data demonstrating not only that abdominal adipose tissue is greater but also that nonabdominal s.c. AT is significantly decreased at birth in Asian Indian than white European infants leads us to speculate that these differences in AT partitioning might contribute to their widely different susceptibilities to type 2 diabetes and cardiovascular disease. Of note, is the novel observation of an increase in the Asian Indian infants relative to the white European infants in each of the three abdominal AT compartments (superficial s.c., deep s.c., and intra-abdominal). This suggests that abdominal and nonabdominal superficial s.c. AT may be metabolically different.

Central adiposity present at birth may increase vulnerability to poor lifestyle choices at later ages. Ironically, the risk to South Asians is also likely to be exacerbated by societal attitudes and public health policies responsive to the high rate of low birth weight infants in India, that have promoted rapid weight gain in infancy. Animal studies spanning more than five decades demonstrate unequivocally that a period of relative postnatal macronutrient restriction particularly after intrauterine growth restriction, protects against adverse metabolic outcomes, including the added risks posed by a high carbohydrate, high fat diet in later life (23,24). Against this background, it would be relevant to study the effects of extended breast-feeding and avoidance of early weaning and fat-carbohydrate rich diets in infancy and childhood even in infants with intrauterine growth restriction.

In India, Britain, and around the world, public health measures to combat the rising prevalence of the metabolic syndrome are centered upon interventions in adult life. The implications of our observations are clear. The focus of investigative and preventative stratagems must extend to maternal health, intrauterine life, and infancy.

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