Lead Review Article

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The Insulin Resistance Epidemic in India: Fetal Origins, Later Lifestyle, or Both?

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In India there is a rapidly escalating epidemic of insulin resistance syndrome (diabetes and coronary heart disease). Contribution of genes and environment is under debate. Small size at birth coupled with subsequent obesity increases risk for insulin resistance syndrome in later life. The tendency of Indians to have higher body fat and central adiposity compared with other races may be programmed in utero. The adipose tissue releases not only fatty acids but also a number of proinflammatory cytokines, which increase insulin resistance and cause endothelial dysfunction. Crowding, infections, and environmental pollution in Indian cities may increase cardiovascular risk by stimulating fat cells. Prevention of diabetes and coronary heart disease in India will have to be approached throughout the life cycle.

Introduction

In recent years India and other developing countries have witnessed a rapidly escalating epidemic of diabetes and cardiovascular disease. Prevalence of type 2 diabetes increased from less than 3% in the 1970s to ~12% in the 1990s in urban Indian adults.[1] A similar number have impaired glucose tolerance. Prevalence of coronary heart disease (CHD) has also increased from less than 2% to ~10% during the last 25 years.[2] It is predicted that by 2020 India will have the highest number of diabetic patients (~60 million) in any one country and that CHD will be the leading cause of death in adult Indians.[3–4]

This phenomenal rise in diabetes and CHD has been ascribed to rapid changes in nutritional and socioeconomic factors, the so-called epidemiologic transition. The biologic basis for this has been traditionally thought to be genetic; a "thrifty gene" that helped survival in the past is proposed to have become detrimental in conditions of plentiful food and sedentary lifestyle.[5] An alternative explanation gaining momentum is the recently proposed "fetal origins" hypothesis, which ascribes the epidemic to an unfavorable intrauterine environment.[6,7] The two explanations are not necessarily mutually exclusive and may compliment each other.

Barker's fetal origins hypothesis suggests that undernutrition at critical periods in the prenatal period causes permanent changes (both structure and function) in the developing systems of the fetus (i.e., programming).[7] This may manifest as disease over a period of time. There are now many studies that show that low birth weight (or some other measure of poor fetal growth) predicts adult diabetes, hypertension, and CHD.[7] The concept of programming, though familiar to biologists, has been applied to human disease only recently. Of the many possible factors that may program the fetal systems, Barker's hypothesis favors nutrition as the most likely.

How do these new ideas apply to the situation in India? Indian mothers have been chronically malnourished and Indian babies are the smallest in the world; up to a third of Indian babies is low birth weight (birth weight <2500 g). There is therefore a strong case for maternal and fetal undernutrition to be responsible for the cardiovascular epidemic in India.

However, some observations point away from fetal undernutrition as the sole explanation for the Indian epidemic of diabetes and CHD. Low birth weight has been a problem for quite a long time, whereas the cardiovascular epidemic is a recent occurrence. Urban Indian babies are heavier (better nourished, mean weight 2900 g) than rural babies (mean weight 2650 g) and would be expected to have lower rates of diabetes and CHD. However, diabetes and CHD are 4–5 times more common in urban than in rural India. One explanation could be that the relationship between fetal growth and adult disease in India is different than the rest of the world. More likely, postnatal determinants are equally, if not more important than the antenatal determinants. There could be an interaction between the two that might be more detrimental than the effect of either alone. The mean body mass index (BMI, kg/m^2) of adult rural Indians is ~19, whereas that of the urban adults is ~24. Thus, the urban adults are larger than their rural counterparts by ~130%, whereas they were only ~110% larger at birth, highlighting the possible detrimental ef-

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fects of postnatal energy excess. In a majority of the fetal origins studies the worst sufferers are those who were born small but became big later, though this is not always discussed. The interaction between intrauterine and postnatal growth in relation to adult disease has been discussed recently.[8,9] A model based on a study in Newcastle, United Kingdom proposed that postnatal influences might contribute more to the cardiovascular risk than intrauterine events.[10] If fetal undernutrition is important, the role of postnatal nutrition and environment cannot be ignored.

This review will investigate the characteristics of Indian type 2 diabetic patients, associations of cardiovascular risk in rural Indians, and the relationship of intrauterine and postnatal growth with cardiovascular risk factors in Indian children. The author will make observations about the possible contribution of inflammatory mechanisms to the rising epidemic of insulin resistance in India.

Indian Type 2 Diabetes and Coronary Heart Disease Patients: An Example of Insulin Resistance Syndrome

Shelgikar et al.[11] studied anthropometric, biochemical-metabolic, and endocrine characteristics of different types of urban diabetic patients at diagnosis and prospectively thereafter. More than a third of urban type 2 diabetic patients in the study clinic were diagnosed below 35 years of age, were not obese according to BMI (mean BMI = 23.9), but were centrally obese (high waist-hip ratio [WHR], and high subscapular-triceps skinfold ratio).[11] They had thin limbs (smaller midarm circumference) suggestive of a small muscle mass. Contrary to the expectation that thin type 2 diabetic patients lack insulin, Indian type 2 diabetic patients were relatively hyperinsulinemic and insulin resistant. (Table 1, Figure 1)They had high circulating nonesterified fatty acid and triglyceride concentrations, which were positively related to fasting plasma insulin concentration.[13] Plasma insulin concentrations were also related to blood pressure.[14] Thus, the Indian type 2 diabetic patients represent a classic example of the insulin resistance syndrome (IRS).[15] Reports from other centers in India have highlighted similar characteristics of Indian type 2 diabetic patients.[16] Migrant Indians are usually more insulin resistant than the local populations.[17,18] In a large comparative study in the United Kingdom, migrant Indians had higher levels of IRS variables compared with local Caucasians. This difference could be largely explained by higher WHR in Indians.[19,20] Indian patients with CHD have very similar anthropometric and biochemical-metabolic characteristics to Indian type 2 diabetic patients.[21]

Rural Indian Adults: Exaggerated Cardiovascular Risk at Low BMI

Joglekar et al.[22] studied cardiovascular risk in 321 adults over the age of 40 years (84% of the eligible population) in a village ~50 km from Pune. The community consisted predominantly of farmers, and although thin (BMI 19.4 ± 2.8 in men and 19.7 ± 3.8 in women), they were physically fit. Four percent of the subjects were diabetic and 4% had impaired glucose tolerance (75 g oral glucose tolerance test, WHO 1985),[23] 14% were hypertensive (blood pressure ≥ 140/90 mm Hg), 7% had serum cholesterol > 200 mg/dL, 24% had serum high-density lipoprotein cholesterol < 35 mg/dL, and 13% had serum triglycerides > 150 mg/dL.

Despite their thinness, the cardiovascular risk in this population was related to measures of obesity. Highest BMI (quartile 4 versus lowest, mean BMI 21.1 versus 19.0) increased the risk of hyperglycemia (impaired glucose tolerance + diabetes mellitus) 3.8 times (confidence interval [CI], 0.8–16.0) and increased the risk of hypertension 6.5 times (CI, 1.5–27.0) in both men and women. Highest waist circumference similarly increased the risk of hyperglycemia 8 times (CI, 1.05–82.0) in both men and women, and

Table 1. Characteristics of Patients Without Diabetes, Patients Newly Diagnosed With Impaired Glucose Tolerance (IGT), and Patients Newly Diagnosed With Type 2 Diabetes in an Urban Diabetic Clinic in Pune, India

Patient's Characteristics	Nondiabetic (n = 133)	IGT (n = 79)	Diabetic (n = 189)
Men	57%	56%	65%
Age (years)	40	47	43
Body mass index (kg/m^2)			
Men	23.3	25.5	23.9
Women	23.6	26.6	24.9
Waist-hip ratio			
Men	0.88	0.93	0.92
Women	0.77	0.79	0.80
Blood pressure (mm Hg)	121/83	129/85	129/87
Plasma cholesterol (mg/dL)	163	180	167
Plasma triglycerides (mg/dL)	79	104	136
Plasma NEFA (mmol/L)	0.81	1.02	1.02
Fasting plasma glucose (mg/dL)	82	94	171
Fasting plasma insulin (mU/L)	7.5	11.0	16.0

Note: NEFA = nonesterified fatty acids.

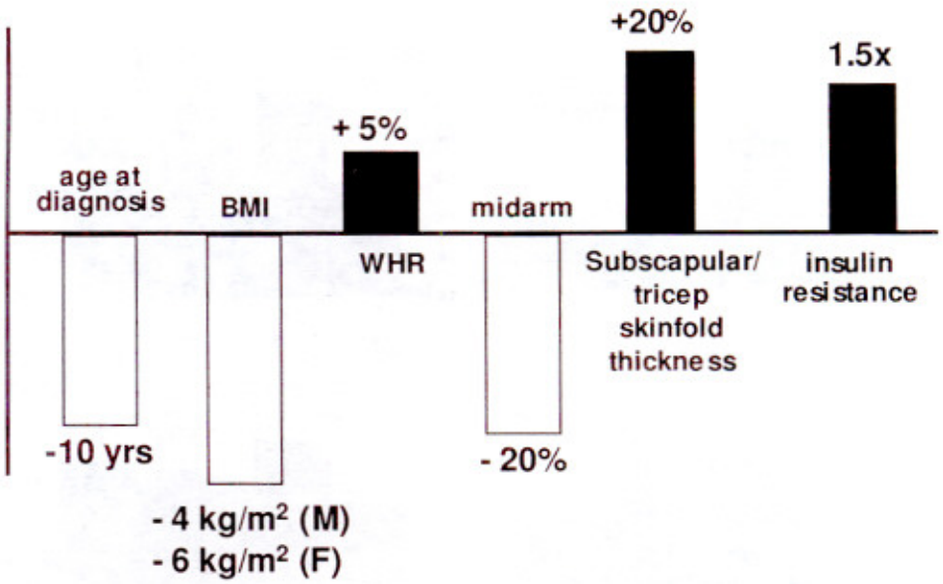

Figure 1. Comparison of characteristics of newly diagnosed Type 2 diabetic patients from India and the United Kingdom. Not drawn to scale. Bars above the line indicate higher levels in Indians. Insulin resistance was calculated from HOMA model.[12] Note: BMI = body mass index; WHR = waist-hip ratio; midarm = midarm circumference; M = male; F = female.

increased risk of hypertension 6.5 times (CI, 1.6–27.0) in men and 2.7 times (CI, 0.8–9.3) in women. Other predictors of increased cardiovascular risk included smaller head circumference and shorter height, suggesting that poor growth in early life adds to cardiovascular risk.

Cardiovascular Risk Factors in Urban Indian Children: Born Small but Grown Big Increases Cardiovascular Risk

Yajnik et al.[24] and Fall et al.[25] studied 202 4-year-old urban-born children. Birth weight was available from the labor room register. Circulating plasma glucose and insulin concentrations (30 minutes after 1.75 g/kg glucose load) and fasting insulin-like growth factor–1 (IGF-1) concentrations were strongly related to current body size (weight and skinfold thickness). When corrected for the effect of current size, glucose, insulin, and IGF-1 concentrations were inversely related to birth weight.[24,25] (Figure 2) At 8 years of age ($n = 477$, including 190 children studied at 4 years of age), levels of a number of cardiovascular risk factors (circulating triglyceride and cholesterol concentrations, insulin resistance measured as HOMA-variable, systolic blood pressure, and central obesity measured as subscapular/triceps skinfold ratio) were highest in children who were born small but had grown big.[26] (Figure 3) The "bigness" at 8 years meant not only higher weight and fat mass but also being taller. Growth velocity (between 4 and 8 years of age for height, weight, and other measurements) was also strongly related to cardiovascular risk factors. These results suggest that rapid childhood growth (probably related to positive energy balance) exaggerates cardiovascular risk in those born small; this has been referred to as ENAMAS: energy adaptation maladaptation syndrome.[27,28] It is important to note that very few of these children were obese by international standards. These findings raise important questions about the relationship between catch-up growth and cardiovascular risk. The findings have important implications for populations undergoing economic and nutritional transition in which the potential for overnutrition is substantial.

The unexpected finding in the study by Bavdekar et

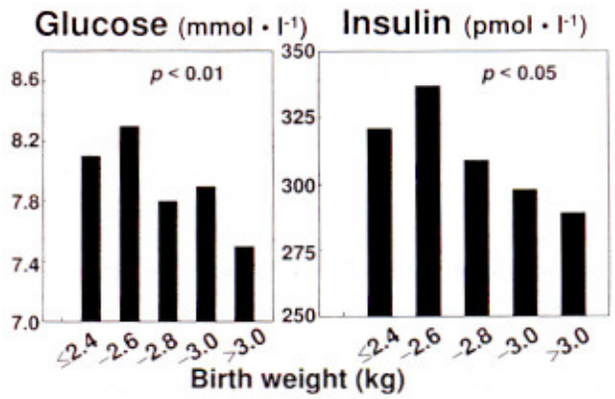

Figure 2. Plasma glucose and insulin concentrations 30 minutes after oral glucose test in 4-year-old children by categories of birth weight. Significance of the trend is corrected for age, sex, and current body weight.

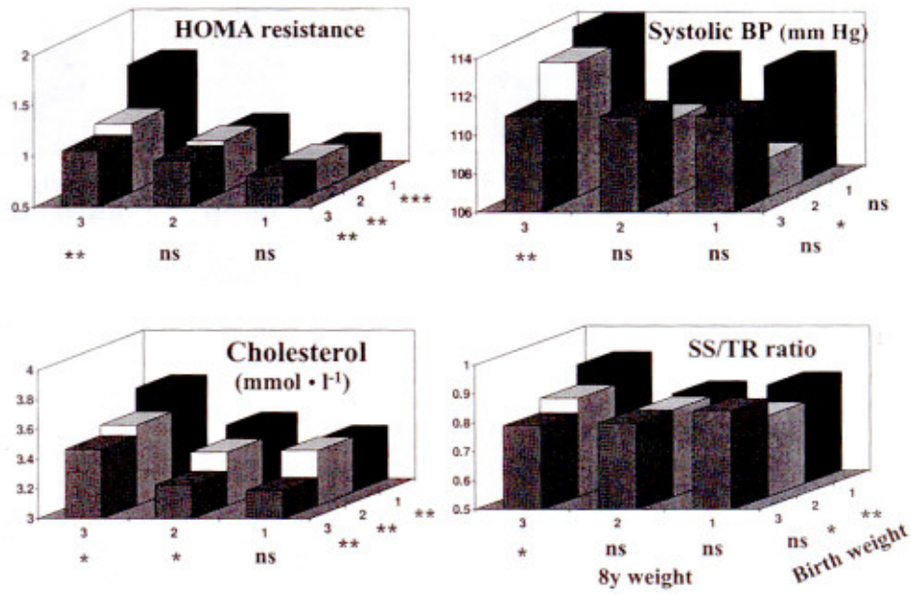

Figure 3. Display of mean levels of insulin resistance variable (HOMA), systolic blood pressure, serum cholesterol concentration, and subscapular-triceps skinfold ratio (SS/TR) at 8 years of age by tertiles (1, 2, 3) of birth weight (rows) and 8-year weight (columns). Significance level for the trend in each row and column (adjusted for age and sex) is shown at the end (ns = not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

al.[26] was the higher cardiovascular risk in taller children. Children born to shorter parents were also more insulin resistant. The risk tended to rise as the child grew taller in relation to the midparental height. (Figure 4) Thus, there seems to be an intergenerational aspect to the risks associated with catch-up growth. The authors[26] predict that these rapidly growing children may grow up as shorter adults owing to earlier fusion of the growing bones, as was reported in a French study.[29]

All of these findings in adults and children imply a predisposing role for poor intrauterine growth to later insulin resistance and other cardiovascular risk factors; this predisposition is exaggerated by rapid postnatal growth and obesity. A study of fetal growth and its determinants could shed light on the possible mechanisms of the predisposition and might suggest preventive measures. Yajnik et al.,[30] therefore, set up a prospective study of maternal nutrition and fetal growth in six villages near Pune.

The Birth of a Thrifty Phenotype: Pune Maternal Nutrition Study

Body Proportions in Newborn Indian Babies

Fall et al.[30] and Kinare et al.[31] followed more than 2500 women every month to record the date of their last menstrual period; every 3 months the authors recorded the women's detailed anthropometric measurements. Eight hundred fourteen pregnant women were enrolled in this study and 770 delivered a live baby.[30,31] Neonatal measurements were done within 3 days of birth. Mean birth weight was 2614 g and 28% of the babies were low birth weight. Birth weight measurement of 633 term babies in

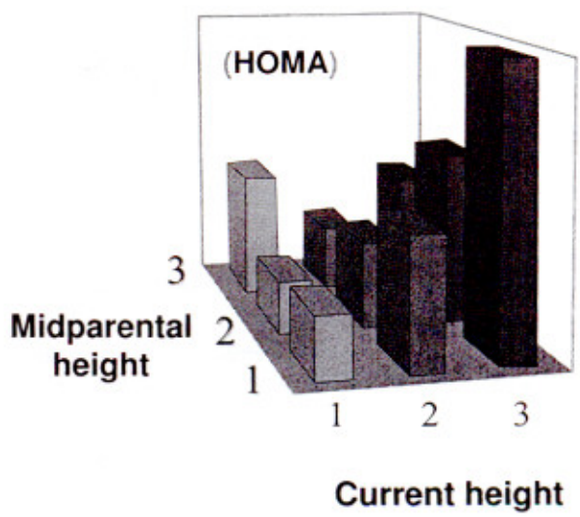

Figure 4. Display of mean levels of HOMA resistance variable at 8 years of age by tertiles (1, 2, 3) of child's height at 8 years of age (rows) and midparental height (columns). Midparental height was calculated as [average of parental heights (cm) + 7] for boys and [average of parental heights (cm) – 7] for girls.

the study by Fall et al.[30] were compared with those of 521 term babies born in Southampton, United Kingdom, who were measured using a comparable technique.[32] Indian babies were lighter (2665 g versus 3450 g), shorter (47.3 cm versus 50.2 cm), and thinner (ponderal index 24.1 versus 27.3 kg/cm^3) compared with the British babies. However, subscapular skinfold in Indian babies (4.2 mm versus 4.8 mm) was substantially preserved. (Figure 5) Thinness of the Indian babies was predominantly because of paucity of nonfat soft tissues (i.e., abdominal viscera and skeletal muscle, which can be regarded as protein-rich tissues). A thin Indian baby is therefore relatively fat. A similar finding was reported on carcass analysis.[33]

Maternal Nutrition and Fetal Growth in Indian Babies

The rural Indian mothers were considerably smaller (mean weight = 42 kg, mean height = 1.52 m, and mean BMI = 18.0) compared with the Western mothers (63 kg, 1.63 m, and 23.5 kg/m^2). Fattest babies were born to mothers who were short and fat (reflecting poor growth in early life and energy excess in later years), suggesting an influence of maternal nutritional transition on neonatal obesity.

Indian mothers ate less energy and protein compared with the Western mothers (~1800 kcal/day and 45 g protein/day compared with 2400 kcal/day and 90 g protein/day, respectively). A considerably higher proportion of the energy in the Indian diet came from carbohydrates (72% versus 50%, respectively). Of the macronutrients, only fat intake of the mother at 18 weeks gestation was related to fetal growth (i.e., the relationship was positive); intake of energy and protein was not related. Intake frequency of green leafy vegetables, fruit, and milk was a strong determinant of fetal growth as were circulating levels of folate and ascorbic acid.[34] In these rural mothers diabetes and hypertension were conspicuous in their absence but maternal fasting plasma glucose (in the normal range) and triglyceride concentrations were significant determinants of fetal size. These mothers spent a lot of energy working in the household and on the farm. Maternal physical activity was inversely related to fetal growth. Our data highlight the influence of maternal prepregnant size, nutrition during pregnancy, and metabolic milieu on fetal growth and body composition.

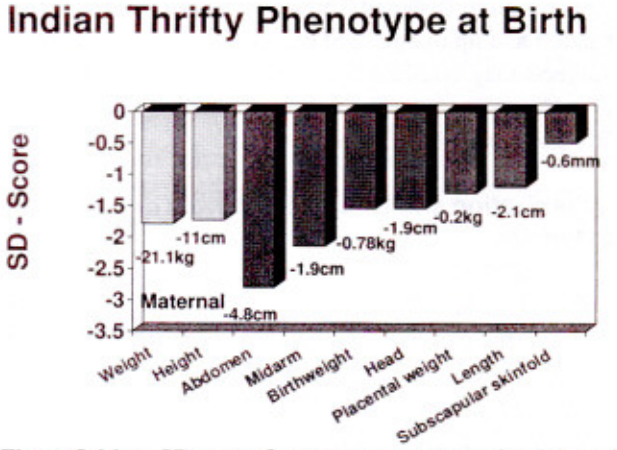

Figure 5. Mean SD scores for prepregnant maternal weight and height and birth measurements in newborn Pune babies compared with Southampton babies. The Southampton mean is represented by 0. Mean difference for each measurement is shown. All SD scores are negative, suggesting that Indian babies are smaller than the British babies. Note: abdomen, midarm, and head are circumference measurements.

Intrauterine Malnutrition and Subsequent Obesity

Babies born to Dutch mothers who were starved in early gestation during the "winter hunger" showed an increased risk of obesity as young adults.[35] The association between poor intrauterine growth and obesity in later life (i.e., BMI) has been reviewed.[36,37] In the study by Bavdekar et al.[26] of 8-year-old urban children the authors noticed a significant relationship between low birth weight and high subscapular-triceps skinfold ratio (STR), which is thought to be a better indicator of central fat deposition in children than the WHR. Low birth weight has been shown to be associated with higher WHR[38] and higher STR[39] in adults, and with higher STR in children[40] and adolescents.[41] In summary, it appears that individuals who were malnourished in utero have a tendency to be obese in later life, and preferentially deposit fat in the truncal region.

Relationship of Birth Size to Diabetes and CHD in Indians: Mysore Study

There are many difficulties in testing Barker's hypothesis in a country like India. Hospital records are poorly preserved and tracing individuals after many years is difficult. In an admirable effort, Dr. Caroline Fall and her colleagues[42,43] studied people born in a hospital in Mysore (South India). Birth measurements were available from birth records. Five hundred seventeen people (mean age 45 years) living near to the hospital and who could be matched with birth records were studied. Prevalence of CHD (angina + major q-waves on resting electrocardiogram) was significantly higher in people who were born small (lower birth weight, shorter height, and smaller head circumference). These individuals were born to lighter mothers.[42] As adults these people were normal weight (i.e., they had achieved catch-up growth). On the other hand, glucose intolerance (impaired glucose tolerance and diabetes mellitus) was not related to birth weight, but was predicted by shorter length and higher ponderal index (fatness) at birth; these babies were born to mothers who were heavier. Insulin resistance was predicted by low birth weight in men but not in women. Insulin "increment" was inversely related to ponderal index at birth in both men and women.[43]

Thus, the only Indian study in adults has produced

somewhat conflicting results. Unlike the reports from Caucasian populations on which the fetal origins hypothesis is based, the predictors of diabetes and CHD are almost opposite. The findings point toward a U-shaped relationship between birth size and diabetes and cardiovascular risk in later life. This has important implications for planning public health measures to reduce diabetes and CHD in communities.

Adult Indian Phenotype

Higher Fat for a Given BMI and Centrally Obese

The exaggerated risk of insulin resistance syndrome in Indians at a relatively lower BMI may be due to excess total body fat and a tendency toward central adiposity. Studies of migrant Indians compared with Caucasians in Sweden[44] and compared with black Africans in the United States[45] (Table 2, Figure 6) showed higher percent body fat in Indians. A comparative study of South Asians and Caucasians in the United Kingdom showed that truncal skinfold thickness in South Asian men was significantly greater, despite similar skinfold thickness on the limbs, at comparable BMI.[19] (Table 3) A recent study in the United States by Chandalia et al.[46] confirmed that Indians have a higher percent body fat, higher central visceral fat, and higher posterior subcutaneous abdominal fat than Caucasians, and that this was associated with higher insulin resistance in Indians.[46] Studies in neonates suggest that the tendency of Indians toward adiposity originates in utero.[30] Measurement of skinfold thickness and body fat at birth may provide important clues in the fetal origins investigation.

Adipose Tissue: More Than a Mere Bag of Triglycerides?

Adipose Signals for Insulin Resistance and Vascular Disease

Traditionally, the risk of excess body fat is ascribed to liberation of excess amounts of nonesterified fatty acids (NEFA), which cause metabolic problems (e.g., through the glucose fatty acid cycle).[47] NEFA are also vasculotoxic.[48] Visceral fat is thought to be more problematic because it pours NEFA into the portal system, bathing the liver and altering its metabolic settings, causing widespread effects on metabolic pathways.[49] These include insulin action, lipid synthesis, and coagulation mechanisms among others. Recent demonstration that adipose tissue is involved in synthesis and release of cytokines and like molecules (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], and leptin) offers new explanations for the role of adipose tissue in the pathogenesis of cardiovascular risk.[50]

Table 2. Comparative Body Composition of Asian Indians and Other Groups in the United States

	Asian-Indian	African-American	Caucasian
Number	20	32	146
Age range (years)	27–63	35–64	40–59
BMI (kg/m²)	24.5	26.3	26.4
Body fat (%)	33.0	26.7	26.9
Muscle volume (L)	28.0	35.1	–
Body fat (%) BMI	1.34	1.02	1.01
Total fat/muscle volume	0.76	0.53	–

Note: BMI = body mass index.

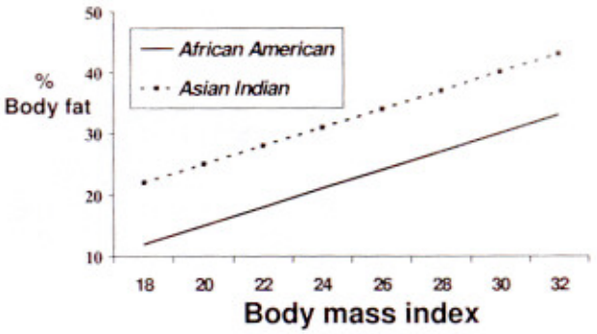

Figure 6. Regression lines between body mass index (BMI, kg/m²) and percent body fat in Asian Indians and African Americans in the United States. Asian Indians have higher percent body fat at each BMI.

In a study of residents of London, Yudkin and his colleagues[51] showed that both insulin resistance syndrome variables and markers of endothelial damage are related to circulating concentrations of the acute-phase reactant C-reactive protein and the proinflammatory cytokines, TNF-α and IL-6. The concentrations of cytokines were related to the measures of global obesity (BMI $r = 0.3, p < 0.001$) and particularly to central obesity (WHR $r = 0.5$, $p < 0.0001$). Both IL-6 and TNF-α are expressed in adipose tissue[52] and up to one third of circulating IL-6 in healthy subjects may originate from adipose tissue,[53] potentially providing a novel mechanism of association between obesity and metabolic and vascular risk.

Urbanization and Circulating Levels of Cytokines in Indians

In a preliminary study, we measured circulating levels of leptin, IL-6, and TNF-α in three geographic locations in and near the city of Pune. The circulating levels of leptin and cytokines in the rural subjects were low but were elevated in the urban subjects, and were highest in the urban slum dwellers.[54] (Table 4) These findings suggest an exciting possibility for the epidemic increase in diabetes and CHD in urban Indians. Adipose tissue–derived cytokines may make an important contribution, possibly stimulated by the infected and polluted environment in the cities and the overcrowded slums.

Table 3. Comparison of Anthropometric Measurements in Europeans and South Asians in the United Kingdom[a]

	Men		Women	
	European (n = 1515)	South Asian (n = 1421)	European (n = 246)	South Asian (n = 291)
BMI (kg/m^2)	25.9	25.7	25.2	27.0
WHR	0.94	0.98	0.76	0.85
Skinfolds (mm)				
Triceps	10.0	10.0	24.0	29.0
Subscapular	18.0	22.0	23.0	32.0
Suprailiac	21.0	24.0	23.0	36.0
SS/TR	1.65	2.01	0.88	1.08
SS/anterior thigh	1.42	1.72	0.57	0.78

[a] Values are age-adjusted means.
Note: BMI = body mass index; WHR = waist-hip ratio; SS/TR = subscapular/triceps ratio; SS/anterior thigh = subscapular/anterior thigh ratio.

Table 4. Proinflammatory Cytokines, Leptin, and Obesity in Three Indian Populations

	Urban Middle Class (n = 40)	Urban Slum Dwellers (n = 28)	Rural (n = 43)
Interleukin-6[a] (pg.ml^{-1})	7.52 (2.51)	13.6 (2.34)	3.50 (3.31)
Tumor necrosis factor-α[a] (pg.ml^{-1})	17.9 (2.74)	21.3 (2.44)	2.54 (2.84)
Leptin (ng.ml^{-1})	7.10 (2.28)	8.11 (2.12)	2.20 (2.09)
Body mass index (kg.m^{-2})	23.5 (3.9)	22.2 (3.1)	18.9 (2.4)
Waist-hip ratio	0.85 (0.08)	0.85 (0.10)	0.83 (0.07)

[a] Values are shown as geometric mean (SD); all other values are shown as mean (SD).

Origins of Insulin Resistance Syndrome in Indians (Figure 7)

In a study by Fall et al.[30] a pattern of intrauterine growth in Indian babies was defined that suggests visceral and muscle depletion but central fat preservation. The causes and mechanisms responsible for this pattern of growth may be partly genetic and partly nutritional. The well recognized fundamental biologic drive in a developing fetus is to preserve the brain (head) growth. This is achieved by preferential diversion of blood flow to the head;[55] this process is presumably helped by rendering other tissues insensitive to action of insulin and related growth hormones, allowing diversion of nutrients from the peripheral tissues to the brain. Hediger et al.[56] demonstrated this fat-preserving tendency in growth-retarded fetuses even in well-fed U.S. populations. It is speculated that the endocrine and metabolic adaptations that allow the best use of available nutrients for survival in utero influence nutrient utilization in later life. In situations of positive energy balance, the tendency toward fat deposition is exaggerated, especially in central depots. An urban environment not only provides opportunities for positive energy balance and qualitatively inappropriate nutrients, but also a backdrop of a polluted and infective environment. Body fat (especially central adiposity) increases and adipocytes are stimulated to secrete metabolically deleterious mol-

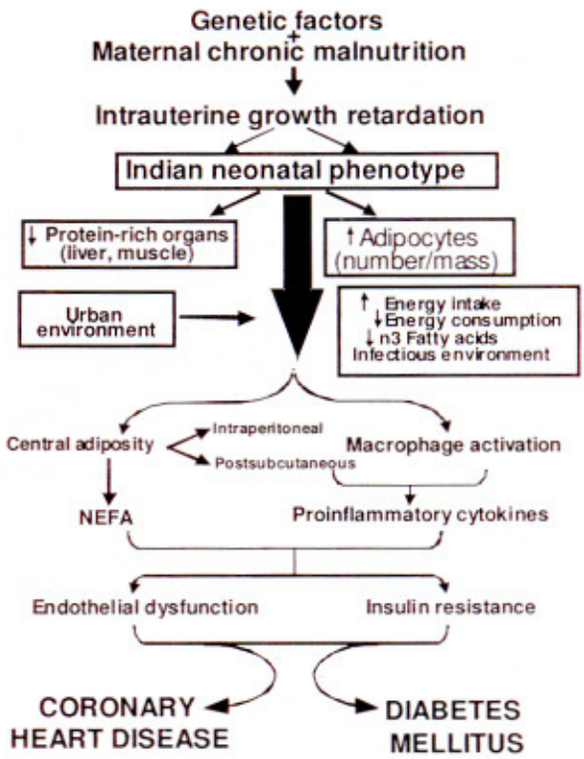

Figure 7. A proposed model to explain rapidly rising incidence of diabetes mellitus and coronary heart disease in urban Indians. Note: NEFA = nonesterified fatty acids.

ecules. This promotes insulin resistance and endothelial dysfunction leading to type 2 diabetes and CHD. Gene-environment interactions will determine the outcome at a number of points in this sequence of events. Some clues are provided by the recently described associations between different genetic markers and fetal growth.[57–60]

If the above postulate is true, prevention of type 2 diabetes and CHD in Indians will depend on improving fetal growth, reducing overnutrition in later life, and controlling environmental factors that stimulate adipocytes. On a practical level, improving the nutrition and growth of a female child, avoiding obesity in children and adults, and controlling atmospheric pollution should be given high priority. Curtailing urbanization would achieve many of these goals but is practically impossible.

The rapid growth of socioeconomic status in developing countries suggests some inevitability to the epidemic of insulin resistance syndrome. Gandhiji's vision of self-dependent rural India, a human-oriented development rather than one based on the Western "auto" model (let alone the "atomic" model) may be the most appropriate solution to stem the insulin resistance epidemic in India and other developing countries.

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