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The Obesity–Diabetes Association: What Is Different in Indians?

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Abstract

There is a growing epidemic of obesity and type 2 diabetes in the world, more than 75% of the patients are in the developing countries. India is facing a twin burden of under-nutrition and over-nutrition: it figures prominently both in the hunger map of the world as well as being the world's capital of diabetes. Indians are susceptible to diabetes at a younger age and at a relatively lower BMI compared to the white Caucasians. This is partly explained by the fact that the thin-looking Indians are quite adipose (higher body fat percent). Intrauterine epigenetic regulation could explain the thin-fat Indian body composition. A combination of maternal one carbon metabolism derangement (influenced by vitamin B12 and Folate nutrition) and hyperglycemia appear to be major drivers. Persistent micronutrient abnormalities and rapid economic development seem to contribute to the intergenerational amplification of the diabetes-adiposity epidemic in Indians. Effective curtailment of the growing epidemic may lie in the realm of maternal and child health and nutrition.

Keywords:

Diabetes epidemic, India, Fetal programming, Gestational Hyperglycemia, One Carbon Metabolism.

There is a growing epidemic of obesity and type 2 diabetes in the world.[1] What is surprising is that more than 75% of the patients are in developing countries. The poor and the young appear to be increasingly affected, which suggests that diabetes is no longer a disease of the affluent and the old. Indian statistics make compelling reading and provide an insight into the causes of this growing pandemic. Toward the beginning of the 20th century, diabetes in India was compared to gout in Britain, affecting only the rich and the royal.[2] Within a 100 years, India has become the world's capital of diabetes. India is a very paradoxical case: on one hand, it belongs to the elite group of G-13 countries (with an estimated annual income of more than US$1 trillion), whereas on the other, almost half of its population lives below the poverty line (daily income of less than $1). India figures prominently in the world map of diabetes while occupying a major position in the world hunger map. Obesity is rising among urban affluent children, at the same time when India contributes the largest number to the world's low-birth-weight babies. The paradoxes go on and suggest an intriguing link between poverty and undernutrition and also rapid transition and obesity-diabetes. Diabetes seems to affect those who were historically poor and undernourished but in a postmodern context are now nouveaux riche and overnourished. The complexities of the link between nutrition and diabetes have confused many. The expert committee of WHO wrote in 1965, "The evidence that malnutrition protects adult populations from diabetes seems unassailable."[3] In 1980, they wrote, "In some societies, malnutrition is probably a major determinant of diabetes"[4]

With the evolution of the diabetes epidemic over the past 50 years, the prevalence has rapidly risen in Indian urban slums and among the rural poor, and the age at diagnosis of type 2 diabetes has fallen by many years. Clinical observations showed that Indians get diabetes at a lower basal metabolic index (BMI) compared with Europeans,[5] and what is more, central obesity was more predictive of diabetes than generalized obesity.[6] A prospective follow-up of urban normal glucose tolerance showed that risk of incident hyperglycemia increased by a factor of more than 2 beyond the BMI of 23 kg/m^2, a level considered healthy among Europeans.[7] This finding was supported by the cross-sectional study in South India.[8] Even more surprisingly, we found in a different study that incident diabetes was predicted by BMI of as low as 19 kg/m^2 in young rural women.[9] Moreover, the National Urban Diabetes Survey showed a high rate of IGT in the young.[10] Thus, Indians are susceptible to diabetes at a young age and at a relatively low BMI; finding an answer to this could provide an insight into the etiology of diabetes.

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An important clue came from comparison with Europeans: Indians are short and have a smaller body frame, and therefore, appear thin. However, the relationship between BMI and body fat percentage (adiposity) is steeper in Indians compared with Europeans, and at each BMI, Indians have higher body fat percentage compared with Europeans.[11,12] Body fat is the major culprit for the risk of diabetes as it increases inflammation and insulin resistance. Thus, thin-looking Indians are quite adipose, and this finding led to the description of the "thin-fat Indian."[13] In a recent study, we found that a third of rural middle-aged men were adipose despite having a low average BMI of 19 kg/m^2, and this result was reflected in their metabolic profile too.[14]

These observations led to further investigations; it was suggested to us that these observations must reflect genetic factors. Every biological characteristic has a genetic basis; however, environmental influences regulate gene expression and therefore the phenotype. This characteristic forms the basis of epigenetics. We demonstrated that the well-known diabetes genes (*TCF7L2*, *FTO*) are indeed associated with type 2 diabetes in Indians[15,16]; however, there might be subtle differences in comparison with Europeans. In Europeans, the *FTO* gene influences the risk of diabetes through its effect on obesity. We found that the *FTO* gene is strongly associated with type 2 diabetes in Indians, but the effect is independent of obesity. It would be informative to study if the environmental nutritional regulation of this gene is different in Indians.

The most influential environment that regulates gene function and influences phenotype is the intrauterine environment. The blueprint of the structure and the function of fetal systems are heavily influenced by maternal nutrition and the mother's metabolism. Many of these effects are permanent and influence the behavior of the systems in future life, contributing to the differences in responses of different individuals to the same environment. This permanent change is called fetal programming, and epigenetics is the major pathway for this programming. The current understanding is that methylation of DNA (influenced by folate and vitamin B12), acetylation of histones, and certain species of RNA (iRNA) are involved in epigenetic regulation of genes. Thus, individuals with the same genetic composition (base pair sequence of DNA) may have different phenotypes because of different epigenetic modifications. Epigenetic regulation could explain fetal programming of the thin-fat Indian body composition.

We demonstrated that newborn Indian babies, who are almost 700 g lighter than European babies, have a higher body fat percentage, higher levels of intra-abdominal fat, and higher concentrations of insulin and leptin in cord blood; these findings support a role for intrauterine programming in the thin-fat story.[17-19] Moreover, maternal vitamin B12 deficiency and high folate status program offspring adiposity and insulin resistance.[20]

In addition to nutrition, maternal hyperglycemia in Indian women has a potent influence on fetal programming of adiposity and type 2 diabetes.[21] In this study, there was an intriguing association between maternal vitamin B12 deficiency, obesity, and gestational diabetes.[22] A combination of maternal one carbon (1-C, methyl) metabolism (influenced by vitamin B12 and folate) and hyperglycemia appear to be major drivers of the intergenerational amplification of the diabetes epidemic in Indians.[23]

One more interesting phenomenon that adds to the risk of obesity and diabetes is the postnatal growth of small babies. Growth-retarded babies tend to catch up after birth, and both parents and doctors feel rewarded when they become "normal" children. There is increasing evidence illustrating that rapid childhood growth contributes to adiposity, insulin resistance, and risk of diabetes.[24] The most important period after birth influencing the "windows of opportunity" is under debate.[25]

In summary, effective curtailment of the growing epidemic of diabetes in Indians may lie entirely out of the busy diabetic clinics; rather, it may lie in the realm of maternal and child health and nutrition.

Declaration of Conflicting Interests

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References

1. International Diabetes Federation (IDF). *Diabetes Atlas*. 4th ed. Brussels, Belgium: IDF; 2009.
2. Bose RKC. Diabetes in the tropics. *BMJ.* 1907;2:1053-1056.
3. World Health Organization Expert Committee on Diabetes Mellitus. *Second WHO Technical Report, Series 310*. Geneva, Switzerland: World Health Organization; 1965. Page 17.
4. WHO Expert Committee Report on Diabetes Mellitus. *Second Report*. Geneva, Switzerland: World Health Organization; 1980. WHO Technical Report series no. 646. Page 7.
5. Yagnik CS. The insulin resistance epidemic in India: fetal origins, later lifestyle, or both? *Nutr Rev.* 2001;59(1, pt 1):1-9.
6. Shelgikar KM, Hockaday TD, Yajnik CS. Central rather than generalized obesity is related to hyperglycaemia in Asian Indian subjects. *Diabet Med.* 1991;8:712-717.
7. Yajnik CS, Shelgikar KM, Naik SS, et al. Impairment of glucose tolerance over 10 years in middle-aged normal glucose tolerant Indians. *Diabetes Care*. 2003;26:2212-2213.
8. Snehalatha C, Viswanathan V, Ramachandran A. Cutoff values for normal anthropometric variables in Asian Indian adults. *Diabetes Care*. 2003;26:1380-1384.

9. Kulkarni SR, Fall CH, Joshi NV, et al. Determinants of incident hyperglycemia 6 years after delivery in young rural Indian mothers: the Pune Maternal Nutrition Study (PMNS). *Diabetes Care*. 2007;30:2542-2547.
10. Ramachandran A, Snehalatha C, Kapur A, et al; Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia.* 2001;44:1094-1101.
11. Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab*. 1999;84: 137-144.
12. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev.* 2002;3:141.
13. Yajnik CS, Yudkin JS. The Y-Y paradox. *Lancet.* 2004; 363:163.
14. Yajnik CS, Joglekar CV, Lubree HG, et al. Adiposity, inflammation and hyperglycaemia in rural and urban Indian men: Coronary Risk of Insulin Sensitivity in Indian Subjects (CRISIS) Study. *Diabetologia.* 2008;51:39-46.
15. Chandak GR, Janipalli CS, Bhaskar S, et al. Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. *Diabetologia.* 2007;50:63-67.
16. Yajnik CS, Janipalli CS, Bhaskar S, et al. FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia.* 2009;52:247-252.
17. Yajnik CS, Fall CH, Coyaji KJ, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. *Int J Obes Relat Metab Disord*. 2003;27:173-180.
18. Yajnik CS, Lubree HG, Rege SS, et al. Adiposity and hyperinsulinemia in Indians are present at birth. *J Clin Endocrinol Metab.* 2002;87:5575-5580.
19. Modi N, Thomas EL, Uthaya SN, Umranikar S, Bell JD, Yajnik C. Whole body magnetic resonance imaging of healthy newborn infants demonstrates increased central adiposity in Asian Indians. *Pediatr Res.* 2009;65:584-587.
20. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. *Diabetologia.* 2008;51:29-38.
21. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH. Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care*. 2010;33:402-404.
22. Krishnaveni GV, Hill JC, Veena SR, et al. Low plasma vitamin B12 in pregnancy is associated with gestational "diabesity" and later diabetes. *Diabetologia.* 2009;52: 2350-2358.
23. Yajnik CS. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. *Int J Gynaecol Obstet*. 2009;104(suppl 1): S27-S31.
24. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body mass index to impaired glucose tolerance in young adulthood. *N Engl J Med.* 2004;350: 865-875.
25. Gluckman PD, Hanson MA. Developmental plasticity and human disease: research directions. *J Intern Med.* 2007;261: 461-471.