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REVIEW

Developmental origins of diabetes—an Indian perspective

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The developmental origins of health disease (DOHaD) hypothesis proposes that altered environmental influences (nutrition, metabolism, pollutants, stress and so on) during critical stages of fetal growth predisposes individuals to diabetes and other non-communicable disease in later life. This phenomenon is thought to reflect permanent effects ('programming') of unbalanced fetal development on physiological systems. Intrauterine programming may underlie the characteristic Indian 'thin–fat' phenotype and the current unprecedented epidemic of diabetes on the backdrop of multigenerational maternal undernutrition in the country. India has been at the forefront of the DOHaD research for over two decades. Both retrospective and prospective birth cohorts in India provide evidence for the role of impaired early-life nutrition on the later diabetes risk. These studies show that in a transitioning country such as India, maternal undernutrition (of micronutrients) and overnutrition (gestational diabetes) co-exist, and expose the offspring to disease risk through multiple pathways. Currently, the Indian scientists are embarking on complex mechanistic and intervention studies to find solutions for the diabetes susceptibility of this population. However, a few unresolved issues in this context warrant continued research and a cautious approach.

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DEVELOPMENTAL ORIGINS OF ADULT DISEASE—LINK TO DIABETES EPIDEMIC IN INDIA?

There is a global epidemic of diabetes in recent times. Particularly disturbing trends are witnessed in India and other south-east Asian countries that are undergoing rapid economic transition. According to the recent International Diabetic Federation estimations, India currently has ~69 million adults with diabetes, predicted to rise to ~125 million by 2040. Urgent measures are warranted to understand the underlying causes of these worrying trends to help prevention.

Generally considered a disease of adults and obese, diabetes occurs at a younger age and lower body mass index (BMI) in Indians compared with Europeans. This has been traditionally attributed to genes. James Neel hypothesized the presence of a 'thrifty genotype', which enabled storage of surplus energy as fat during the plentiful periods and gave survival advantage during famines.[1] These genes become detrimental in the modern environment of continuous energy supply. Though this could be a plausible explanation for the current Indian situation, these genes have not yet been identified.

Indian adults are shorter and have a higher body fat and lower lean mass for a given BMI than Caucasian adults.[2,3] They have tendency towards abdominal (central) obesity. This 'muscle-thin but adipose' or 'thin–fat' phenotype, may partly explain their high rates of diabetes. A pioneering study in Pune demonstrated that the 'thin–fat' phenotype was present at birth and, therefore, not solely a consequence of adult lifestyle as had been thought generally.[4] This evidence at once changes the strategy for prevention of diabetes.

In this context, David Barker's 'fetal origins' hypothesis provides the most promising lead.[5] He suggested that altered nutrition during critical stages of fetal growth has permanent effects on structure and function of the body systems ('fetal programming'), including that of pancreas, liver and skeletal muscles. Reduced cell number (for example, pancreatic beta cells), altered structure (for example, muscle cell thickness) or function (for example, reduced glucose clearance or neuroendocrine function) are some of the suggested effects. The resulting 'thrifty phenotype' was suggested to preserve brain growth and maximize immediate survival. It is suggested that growth-compromised organs 'fail' when exposed to 'excess' nutrition in later life leading to diabetes and other non-communicable disease (NCD). This hypothesis was based on findings in the UK that the prevalence of type 2 diabetes and impaired glucose tolerance was higher in adults with lower birth weights.[6] Subsequently, the hypothesis was expanded to include maternal overnutrition and postnatal growth and environment, and is now called the 'developmental (or early) origins of health and disease' hypothesis (DOHaD).

India has a high prevalence of maternal undernutrition and low birth weight babies, and a continuing trend of childhood malnutrition. On the other hand, the country has witnessed a dramatic rise in diabetes and coronary heart disease prevalence within a single generation. Archeological and historical evidence suggests a failure to gain in height over several generations among Indians, possibly triggered from a long-term nutritional disruption.[7] The Indian 'thin–fat' phenotype, thus, may have resulted from generations of maternal undernutrition and consequent intrauterine programming. The developmental origins concept suggests that individuals exposed to a mismatch between the intrauterine nutrient-constrained environment and the postnatal, energy-rich environment develop obesity, insulin resistance and subsequent diabetes. The recent socio-economic transition has resulted in such a mismatch on the backdrop of a multigenerational fetal undernutrition in India. Among the growth-impaired Indians, even a small degree of 'mismatch' is likely to have huge adverse implications on NCD development.

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BIRTH WEIGHT, EARLY GROWTH AND DIABETES

India has been at the forefront of the DOHaD research in collaboration with the MRC Lifecourse Epidemiology Unit in Southampton, UK since 1991. The Pune Children's Study confirmed an association between lower birth weight and higher glucose and insulin concentrations in 4-year-old children for the first time in the country.[8] These children developed greater central fat (subscapular-to-triceps skinfold ratio) and higher insulin resistance (HOMA) at 8 years of age.[9] The children of lowest birth weight but the highest current weight had highest levels of many cardiovascular risk factors. Follow-up of this cohort at 21 years of age showed that the above risk factors tracked into adulthood and predicted adult disease risks.[10,11]

Birth weight and serial childhood growth data were available in the Delhi and Vellore cohorts. They showed that higher diabetes risk in young adulthood was predicted by lower birth weight, slower infant growth and rapid childhood weight gain (Figure 1).[12,13] In the New Delhi Birth Cohort, adults with diabetes or impaired glucose tolerance had a low BMI up to 2 years, followed by an accelerated BMI increase until adulthood, but most rapidly between 2 and 12 years of age.[12] However, these children were not obese in absolute terms. This led to the concept that growing bigger in relation to one's earlier size predisposed to diabetes though the actual size was still within the 'normal' range.

In contrast, in Mysore Birth Records Study, the prevalence of diabetes was higher in 40–60-year-old adults who were short but heavy (higher ponderal index) at birth (Figure 1).[14] The prevalence also increased with maternal size. The Mysore researchers speculated that these heavier mothers had gestational glucose intolerance and that this could explain the high risk of diabetes in their offspring in late middle age. This study suggested an epidemiological shift in the diabetes causation in urban India. Another study of neonates in north India also observed higher glucose–insulin concentrations and insulin resistance in association with low as well as high birth weight.[15]

EVIDENCE FROM PROSPECTIVE STUDIES

As birth size is an indirect marker for fetal nutrition, prospective cohorts were started in Pune and Mysore to investigate determinants of fetal growth and birth size. They were designed to study associations of maternal nutrition and metabolic status on offspring disease risk on long-term follow-up.

Undernutrition

The Pune Maternal Nutrition Study (PMNS) contributed significantly to the understanding of fetal programming by maternal undernutrition in India.[16] The young PMNS rural mothers (mean age: 21 years) were generally undernourished with a mean BMI of 18.1 kg/m^2 before pregnancy and 20.5 kg/m^2 at 28 weeks of pregnancy (Figure 2), and low intake of calories and proteins. Nearly 70% had vitamin B12 (B12) concentrations < 150 pmol/l during pregnancy. The newborns were small, short and thin but had comparable skinfold thickness with white Caucasian babies ('thin–fat' phenotype).[4] Higher maternal intake of green leafy vegetables, milk and fruits during pregnancy was associated with higher offspring birth weight but total energy and protein intake had no effect. This highlighted the importance of micronutrients for fetal growth in this undernourished population. Their lifestyle was characterized by low dietary intake and high physical activity, even during pregnancy.

The children have been followed up for growth and cardiometabolic risk factors. Higher maternal folate concentrations during pregnancy predicted higher adiposity and insulin resistance in their 6-year-old offspring.[17] The highest insulin resistance was observed in children born to mothers with lowest B12 but highest folate concentrations. Lower B12 was associated with higher maternal homocysteine, which predicted lower birth weight.[18] These findings are of particular significance on the backdrop of a widespread B12 deficiency among Indians and adequate folate status due to dietary intake and medical supplementation. These findings were indicative of 'nutrient-mediated teratogenesis', where intrauterine micronutrient imbalances program long-term disease susceptibility.[19] Animal studies conducted at the National Institute of Nutrition in Hyderabad corroborated these findings. Offspring of rat mothers fed on a B12-restricted diet had higher visceral adiposity, lower fat-free mass and altered lipid and glucose–insulin metabolism in the postnatal life.[20,21] These changes were corrected on rehabilitation from conception.

Overnutrition

Fetal overnutrition due to maternal obesity and hyperglycemia also programs the offspring for NCDs. Maternal gestational diabetes (GDM) results in over-supply of glucose, lipids and amino acids to the fetus. These fuels stimulate the secretion of growth promoting insulin and insulin-like growth factors resulting in 'macrosomia'. Freinkel postulated that this will have long-lasting effects on the structure and metabolic functions of the fetus, and may cause obesity and diabetes in later life ('fuel mediated teratogenesis').[22]

The Mysore Parthenon Study examined the long-term effects of GDM on the offspring in an urban setting. Unlike the PMNS women, pregnant women in Mysore were relatively overweight (mean BMI 23.4 kg/m^2), and the incidence of GDM was 6.2% using

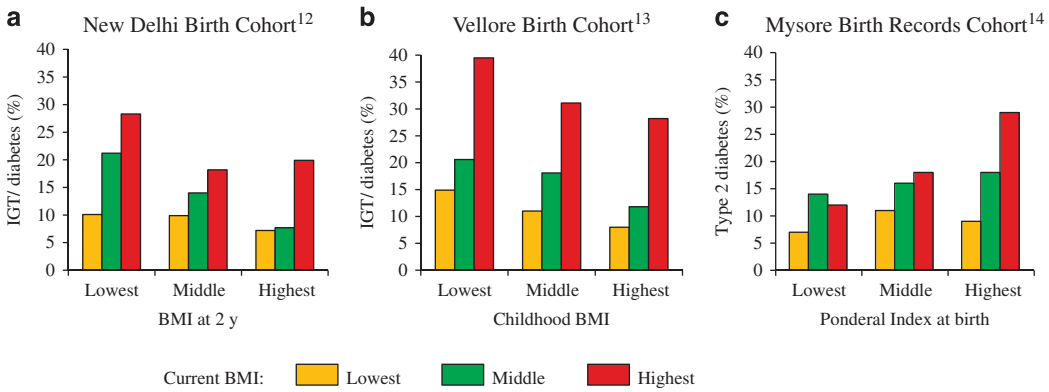

Figure 1. Risk of diabetes according to early-life and adult body size in Indian retrospective birth cohorts. In (**a**) New Delhi and (**b**) Vellore cohorts, higher prevalence of IGT/diabetes was in those adults with lowest early-life BMI (infancy and childhood respectively) and highest current BMI; whereas in (**c**) Mysore older adults higher prevalence of diabetes was in adults with higher ponderal index at birth and highest current BMI suggesting a role of intrauterine overnutrition.

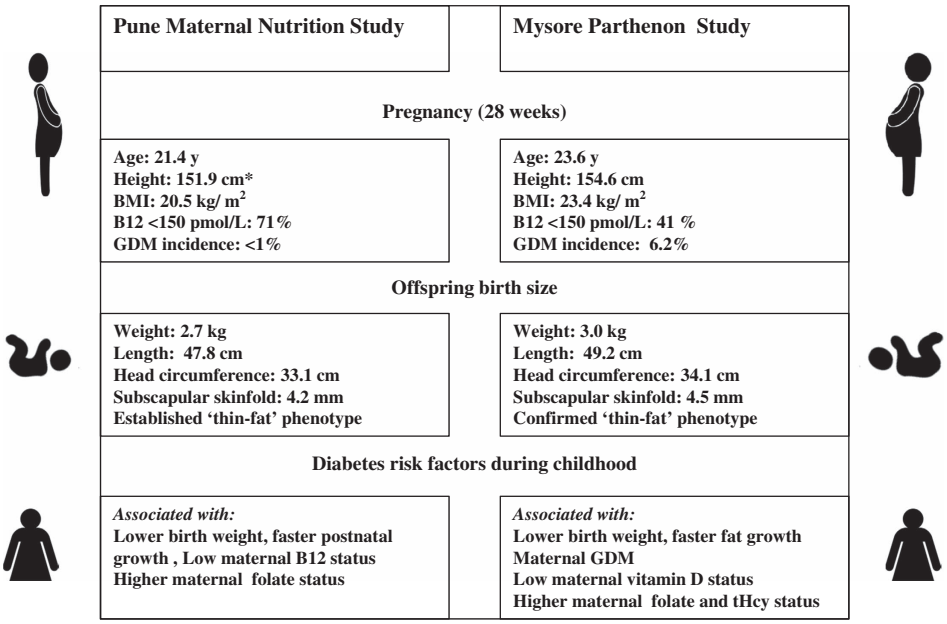

Figure 2. Similarities and contrasts in DOHaD-related characteristics between the Pune Maternal Nutrition Study and the Mysore Parthenon Study. This figure depicts that both undernourished Pune rural mothers and relatively overweight urban mothers in the transitioning Mysore gave birth to 'thin–fat' babies, who exhibited cardiometabolic risk factors later in life. *Pre-pregnant height. BMI, body mass index; B12, vitamin B12; GDM, gestational diabetes mellitus; tHcy, total homocysteine.

the Carpenter and Coustan criteria (Figure 2).[23] The offspring of GDM had higher subcutaneous adiposity at birth compared with those of non-GDM mothers. There was a clustering of higher adiposity, insulin resistance and blood pressure in offspring of GDM during childhood.[24] Though ~40% of the mothers had low B12 concentrations, it was not associated with offspring diabetes risk as in Pune, but higher maternal folate status was related to higher insulin resistance during childhood and adolescence.[25]

In both the PMNS and the Parthenon study, there were continuous associations of glucose concentrations in normoglycemic mothers with newborn size including weight and ponderal index (Mysore).[23,26] The PMNS also showed associations between maternal total cholesterol and triglyceride concentrations even in normoglycemic, undernourished pregnant women and offspring birth size.

Thus, Indian cohort studies show that in rapidly transitioning populations, maternal undernutrition and overnutrition co-exist (Figure 2). The Parthenon study showed that micronutrient deficiencies (B12) and GDM may co-exist in pregnancy, thereby exposing the fetus to multiple programming pathways.[27]

PROPOSED MECHANISMS

Several mechanisms proposed for early-life origins of diabetes based on Barker's initial hypothesis may be extended to the Indian situation. Yajnik *et al.*[28] demonstrated that growth-compromised neonates in Pune tended to be shorter, have markedly lower muscle (mid-arm circumference) and visceral mass (abdominal circumference) than white Caucasian neonates, but higher cord blood insulin relative to birth weight. Sophisticated magnetic resonance imaging studies showed that these neonates also have relatively greater subcutaneous, abdominal and visceral adiposity.[29] Wells *et al.*[7] applied a 'capacity-load' model to explain Indian diabetes susceptibility in this context. They suggested that ability to maintain glucose homeostasis depends on a balance between individuals' 'metabolic capacity' determined by lean mass and pancreatic function, and 'metabolic load' determined by adiposity and positive energy balance. The Indian babies are born with low metabolic capacity but high metabolic load related to adiposity, which is made worse by excess nutrition and physical inactivity postnatally.

Altered neuroendocrine activity is another proposed mechanism. It is suggested that impaired fetal nutrition alters neuroendocrine structure and function, and impaired hypothalamic–pituitary–adrenal axis feedback systems through glucocorticoid receptors, and influence stress reactivity.[30,31] Studies in Mysore adults and children showed that increased hypothalamic–pituitary–adrenal axis activity, measured using fasting plasma cortisol concentration, was associated with higher glucose and triglyceride concentrations, insulin resistance, insulin secretion and higher blood pressure.[32,33] It was suggested that high hypothalamic–pituitary–adrenal axis activity and maintenance of high cortisol levels in the face of higher adiposity may increase NCD risk in Indians. The Parthenon children's study also observed associations between lower birth weight and higher corticosteroid binding globulin.[33] Using a dynamic stress test module, this study also showed that offspring of GDM exhibited exaggerated cardiovascular stress responses.[34] This research area needs further exploration.

The current understanding that epigenetic processes mediate differential phenotypic expression of a genotype provides a likely explanation for fetal programming phenomenon. Epigenetic changes are mitotically heritable changes in gene expression without altering DNA sequence, and occur as a part of normal development and differentiation or externally induced.[35] They are established early during fetal growth and are sensitive to environmental influences like maternal nutrition and metabolic milieu. Epigenetic modifications induced by adverse environmental exposure provide a basis for phenotypic changes, which underlie the development of complex diseases including diabetes. Epigenetic regulations are mediated by mechanisms such as DNA methylation, histone modification and micro RNAs, though DNA methylation is the most studied pathway.[35] Studies in animals and humans have shown that altered fetal nutrition modifies DNA methylation pattern resulting in long-term phenotypic changes.[36,37] Nutrients related to one-carbon metabolism such as B12, folate, choline and betaine are the important methyl donors. An imbalance in these nutrients may therefore alter

normal epigenetic processes. As described above, B12 and folate appear to have an important role in the programming of adiposity and diabetes risk in Indians. Epigenetic exploration related to DOHaD hypothesis is still at its infancy in India. However, a trial of preconceptional micronutrient-rich food supplements in Mumbai, and an ongoing B12 trial in Pune are examining epigenetic pathways of fetal programming.

LEADING THE WAY FOR INTERVENTIONS

Over two decades of DOHaD research in India provides enough evidence to make a case for early-life interventions to prevent long-term diabetes risk. Particular emphasis is being placed on preconceptional nutritional supplementation to target gametogenesis and early pregnancy processes such as fertilization, implantation, placentation and organogenesis when even a small environmental insult could have a large effect on the phenotype. The epigenetic 'reprogramming' which happens soon after fertilization will be influenced by preconceptional intervention.

The Mumbai Maternal Nutrition Project in India is probably the first preconceptional trial aimed to test the DOHaD hypothesis.[38] In the Mumbai Maternal Nutrition Project, married, non-pregnant women were randomized to receive either a snack enriched with green leafy vegetables, milk powder and dried fruit or a snack made from low-micronutrient vegetables. The study showed that preconceptional supplementation increased offspring birth weight by ~48 g, and reduced the incidence of low birth weight babies, compared with controls. The effect on birth weight was larger in mothers of higher BMI. This led to the speculation that a maternal macronutrient reserve is essential to utilize micronutrient supplements or partition them effectively to the fetus. Indeed, Barker had proposed that mother's lifetime nutrition is equally important as her current diet for fetal growth.[39] The Mumbai Maternal Nutrition Project researchers suggested that other nutritional deficiencies may limit the benefits of nutritional interventions in populations where multinutrient deficiencies are common during pregnancy. The ongoing follow-up of the offspring may elucidate mechanisms and suggest solutions for the developmental origins issues.

The Pune Rural Intervention in Young Adolescents is a community-based randomized control trial of preconceptional micronutrient supplementation in the PMNS offspring. Adolescent girls and boys are supplemented with vitamin B12, and micronutrients (UNIMAPP) and milk powder from before they are married and continued till the delivery of the first child. The trial is ongoing.

IMPLICATIONS FOR FUTURE RESEARCH AND POLICIES

India has come a long way in understanding the developmental basis for the current diabetes explosion and has made important contributions. Indian researchers established the Society for the Natal Effects of Health in Adults in 1994, which is one of the pioneering consortiums of DoHAD scientists. This collaboration was instrumental in organizing the first world congress on fetal origins of adult disease in Mumbai in 2001 that set the stage for further DOHaD congresses. Currently, these scientists are embarking on complex mechanistic and intervention studies that are aimed to find definitive solutions for the NCD susceptibility of this population, though a few unresolved issues in this context warrant cautious approach.

It is essential that ongoing intervention studies explore the differential effect on neonatal body composition in addition to birth weight. Specifically, identifying ways to prevent the thin–fat phenotype at birth could go a long way in preventing the cascading phenotypic changes that cause diabetes. It has been suggested that specific nutritional deficiencies with or without macronutrient excess will interfere with fetal lean mass deposition, leading to energy being deposited as fat.[40] Fetal nutritional disruption may be caused by maternal nutritional imbalances as well as placental insufficiency. Maternal stress and exposure to environmental pollution, including smoking and indoor pollution may be other causes. Thin–fat phenotype may also be inherited due to genetic and epigenetic mechanisms. Advanced techniques to measure neonatal body composition, cutting-edge genetic and epigenetic studies to identify causal pathways and complex statistical methods to tease out distinct exposures that underlie different body composition patterns may shed some light in this direction. Finally, follow-up of the children born during trials will inform whether interventions have long-term functional and health effects.

Although prenatal interventions may offer a sustainable means for reducing disease risk, we cannot ignore the fact that more than one billion people in India alone have already missed this opportunity. There is an urgent need to identify critical periods in postnatal life where the preventive measures will still have impact on disease development. Infancy and adolescence have been currently recognized as effective windows of opportunity. Statistical techniques using conditional variables to examine the separate effects of linear growth and fat mass and lean tissue gain on risk factors in Mysore children suggested that factors that increase fat growth, but not linear and lean growth during later childhood predict adverse cardiometabolic profile.[41] Identifying ways to promote lean mass, simultaneously preventing the fat accrual remains a challenge.

Recent knowledge that epigenetic changes are dynamic and reversible has given new hope for the preventive strategy of NCDs. Epigenetic modulators have been shown to be of therapeutic value in certain cancers.[42] Researchers suggest that epigenetic mechanisms hold key to identify persons 'at risk' based on their early environmental exposure and develop targeted interventions.[43] Existing as well as future studies in India should invest more in exploring these novel putative mechanisms.

Finally, there is a need to understand the social implications of the DoHAD paradigm, especially in traditional societies such as in India where specific gender roles may place increased responsibilities on mothers and young women for the health of their offspring. Richardson *et al.*[44] suggest that selective DOHaD research findings may be oversimplified by the society to particularly blame the mothers. This necessitates sensitivity in interpreting and presenting research findings in this context.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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