Maternal malnutrition and anaemia in India: dysregulations leading to the ‘thin-fat’ phenotype in newborns

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Abstract
Maternal and child malnutrition and anaemia remain the leading factors for health loss in India. Low birth weight (LBW) offspring of women suffering from chronic malnutrition and anaemia often exhibit insulin resistance and infantile stunting and wasting, together with increased risk of developing cardiometabolic disorders in adulthood. The resulting self-perpetuating and highly multifactorial disease burden cannot be remedied through uniform dietary recommendations alone. To inform approaches likely to alleviate this disease burden, we implemented a systems-analytical approach that had already proven its efficacy in multiple published studies. We utilised previously published qualitative and quantitative analytical results of rural and urban field studies addressing maternal and infantile metabolic and nutritional parameters to precisely define the range of pathological phenotypes encountered and their individual biological characteristics. These characteristics were then integrated, via extensive literature searches, into metabolic and physiological mechanisms to identify the maternal and foetal metabolic dysregulations most likely to underpin the ‘thin-fat’ phenotype in LBW infants and its associated pathological consequences. Our analyses reveal hitherto poorly understood maternal nutrition-dependent mechanisms most likely to promote and sustain the self-perpetuating high disease burden, especially in the Indian population. This work suggests that it most probably is the metabolic consequence of ‘ill-nutrition’ – the recent and rapid dietary shifts to high salt, high saturated fats and high sugar but low micronutrient diets – over an adaptation to ‘thrifty metabolism’ which must be addressed in interventions aiming to significantly alleviate the leading risk factors for health deterioration in India.

Key words: Anaemia: Low birth weight: Malnutrition: Pathological mechanisms: Physiological programming

Introduction
India is home to almost one-fifth of the world’s population. People living in each of its twenty-nine states and seven union territories differ in ethnic origins, cultures, religions and socio-economic means, which are exposed to a wide variety of often difficult climatic and ecological conditions as well as to numerous other factors affecting their health¹². A recent survey³ shows that the overall disease burden per person varies considerably between states, the burden rate due to the major diseases ranging five to ten times amongst states. However, contrarily to the all too often repeated view presenting India as the ‘diabetes capital of the world’⁴⁵, it is maternal and child malnutrition and anaemia which are the leading risk factors for the burden of health problems in India³. The primary consequences of these are insulin resistance and infantile stunting and wasting, diabetes and obesity

Abbreviations: 5-mTHF, 5-methyltetrahydrofolate; BAT, brown adipocyte tissue; EAA, essential amino acids; FA, fatty acid; GSH, glutathione; Hcy, homocysteine; LBW, low birth weight; PE, phosphatidylethanolamine; SAM, S-adenosyl methionine; TG, triacylglycerol; WAT, white adipocyte tissue

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appearing as low prevalence secondary consequences and certainly not as primary causes for the disease burden\(^3\). Dietary behaviours, including foods preferentially consumed, meal frequency and timing, are heavily influenced by the ecology, demography, regions, religions, traditions, seasons, cultural specificities, economic burden and psychosocial beliefs\(^6\). Such beliefs around food choices are extremely deep-rooted and are mostly practised by women especially during pregnancy and lactation\(^7\). These practices determine what they eat, how much, why and when. Consequences of such beliefs are seen in health of women of childbearing age, in newborn babies and in infants and adolescents\(^8\).

Across India, dietary intakes of children and adults in rural and urban areas show gross inadequacy of all nutrients and poor quality of protein\(^9\). Maternal and child malnutrition is characterised by low energy intake (eating less often and small portions) and low dietary diversification. The usual diets are low in proteins, vitamins and micronutrients but rich in carbohydrates and saturated fats. Concurrently, hygiene conditions can vary from very poor to excellent not only between rural areas but within urban centres as well\(^10\). A suboptimal prenatal environment, in particular global nutrient restriction during the periods of placental and embryonic development, is increasingly being recognised as programming physiology, enhancing predisposition for metabolic diseases in adult life\(^11,12\).

Low birth weight (LBW) offspring of women suffering from malnutrition, clinical anaemia and chronic micronutrient shortages, including vitamins, are characterised by elevated subcutaneous adiposity but very low visceral adiposity (thin-fat phenotype)\(^11,14\). They also exhibit insulin resistance and infantile stunting and wasting, together with increased risk of developing cardiometabolic disorders in adulthood, hence promoting a self-perpetuating, highly multifactorial disease burden which cannot be remedied through uniform dietary recommendations\(^15\). To propose coherent modes of interventions likely to alleviate this multifactorial disease burden, it appears necessary to first understand the physiological roots of the pathological phenotypes encountered within affected populations and communities. To this effect, we implemented a previously described\(^16,17\) systems-analytical approach (Computer-Assisted Deductive Integration (CADI)) that had already proven its efficacy in multiple biological contexts\(^18–21\). We utilised the results of previously published field studies\(^22–27\), undertaken in rural as well as urban populations, addressing qualitative phenotypic biomarkers together with the corresponding maternal and infantile metabolic and nutritional parameters (glucose tolerance, circulating levels of individual amino acids, haematocrit, haemoglobin levels, morphological indices and inflammatory parameters) to precisely define the range of pathological phenotypes encountered and their individual biological characteristics. These characteristics were then integrated, via extensive literature searches, into metabolic and physiological mechanisms to identify the dysregulations most likely to underpin the ‘thin-fat’ phenotype and its associated self-perpetuating high disease burden.

Our studies reveal hitherto poorly understood maternal nutrition-dependent mechanisms most likely to promote and sustain this self-perpetuating situation, suggesting clear avenues for interventions likely to significantly alleviate the leading risk factors for health deterioration in India.

**Maternal characteristics in the populations studied**

The data used in this analysis was obtained from Indian population, and all women who participated in the previously published field studies\(^22–27\), whether pregnant or not, were characterised by low body weight, elevated subcutaneous adiposity (thin-fat phenotype), significant anaemia, malnutrition, insulin resistance, low micronutrients and vitamin B12 levels together with low circulating glutathione (GSH), high homocysteine (Hcy), triacylglycerols (TGs) and 5-methyltetrahydrofolate (5-mTHF) levels.

However, in this context, since B12-dependent physiological processes such as odd carbon chain-length fatty acid (FAs) metabolism, serine-glycine interconversion (see later) and nucleic acids synthesis are clearly functional, low vitamin B12 circulating levels, while certainly indicative of vitamin intake deficiency\(^28\), may be representative of high cellular uptake for metabolic purposes rather than low availability\(^29\). Furthermore, it seems highly unlikely that deficiency in vitamin intake could address B12 only. It appears more likely that all essential vitamins would be similarly affected, in particular vitamins A, B1, B2 B6, B8, B9 and C\(^30\). Circulating levels of non-essential and essential amino acids (NEAA and EAA, respectively) were generally low, with the notable exception, most particularly in pregnant women, of aspartic acid which was extremely elevated, followed by elevated serine, threonine and histidine (in descending order, respectively, Table 1).

**Integration**

**Micronutrient deficits and their effects**

Micronutrients, and in particular zinc and selenium, act as key regulators of metabolic and immune functions\(^31,32\). Zinc deficiency in human subjects is now known to be an important malnutrition problem worldwide. It is more prevalent in areas of high cereal and low animal food consumption not because the diet could be low in zinc and selenium but because phytic acid is the main known inhibitor of zinc absorption\(^33\), while selenocysteine, the organic form of selenium most easily absorbed by human subjects, dominates in products of animal origin\(^32\). Compared to adults, infants, children, adolescents, pregnant and lactating women have increased requirements for zinc and selenium and are at increased risk of deficiencies. Zinc deficiency results in growth failure, while epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems are the organs clinically most affected by zinc and selenium deficiencies\(^34,35\).

Hence, in a context characterised by significant maternal malnutrition, micronutrient deficiency during the periconceptional period, and in particular zinc and selenium deficiencies, is likely to result in widespread, low level but persistent maternal as well as foetal metabolic dysregulations with deleterious consequences upon placentation and embryogenesis,
A large group of proteins \(^{41,42}\) Selenoproteins W and N (SELENOW and SELENON) are both required for muscle growth, differentiation and regeneration, as well as satellite cell maintenance in skeletal muscle \(^{43-46}\). Selenoprotein S (SELENOS) is involved in the degradation process of misfolded endoplasmic reticulum (ER) luminal proteins \(^{47}\), while selenoprotein T (SELENOT) is involved in the control of glucose tolerance by contributing to prolonged adenylyl cyclase-activating polypeptide 1 (ADCYAP1/PACAP)-induced insulin secretion \(^{48}\) while also contributing to increased quantitative insulin sensitivity \(^{49}\). Growth retardation, poor appetite and mental lethargy are some of the manifestations of chronically zinc-deficient human subjects \(^{50}\).

Furthermore, low serum zinc has been reported as a major predictor of anaemia, mediating the effects of low selenium upon oxidative stress-dependent haemoglobin denaturation and erythrocytes osmotic fragility \(^{51}\), whereas vitamin B12 and folate deficiencies were found not to be associated with anaemia \(^{52}\). Table 2 lists the selected key enzymes that are either zinc-/selenium-dependent or the activities of which are controlled by zinc/selenium and are of prime relevance in the context of maternal malnutrition.

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### Table 2. List of the key enzymes that are either zinc-/selenium-dependent or the activities of which are controlled by zinc/selenium and are of prime relevance in the context of maternal malnutrition

| Zn-dependent enzymes | Physiological roles | References |
|----------------------|---------------------|------------|
| Aminolevulinic acid dehydrase (ALAD) | Catalyses the second step in the synthesis of the haem portion of haemoglobin, thus playing a key role in haemtopoiesis. | (53–55) |
| Methionine synthase (MTR, also B12-dependent) and homocysteine S-methyltransferase (BHMT) Glyoxalase I (GOI) | Both MTR and BHMT play key roles in the transmethylation-tetrahydrofolate cycle (THF), the attenuation of which leads to Hcy and 5-mTHF accumulation. Involved in metabolic detoxification, is active in erythrocytes, and requires GSH as a cofactor. | (36,56,57) |
| Placental alkaline phosphatase (ALPP) Protein tyrosine phosphatase 1B (PTP1B) | Plays key roles in placental development and nutrients transfer. Inhibited by Zn, PTP1B dephosphorylates insulin receptor and insulin receptor substrates 1 and 2, thereby inhibiting insulin signalling & promoting insulin resistance. | (60,61) |
| Superoxide dismutase (SOD1) | Cytoplasmic enzymes; converts naturally occurring superoxide radicals to molecular oxygen and hydrogen peroxide. Zn binding promotes dimerisation and stabilises the native form. | (64,65) |
| Leucyl and cystinyl aminopeptidase (LNPEP) | In response to insulin redistributes with GLUT4 to the cell surface in fat and muscle tissues. Cleaves peptide hormones (vasopressin, oxytocin, lys-bradykinin, met-enkephalin and dynorphin A). | (66–68) |
| Se-dependent enzymes | | |
| Glutathione peroxidases (GPX) 1-4 | Play key limiting roles in H₂O₂ accumulation and are negatively associated with heart diseases. | (69,70) |
| Thioredoxin reductases (TXNRD) 1/2 | The major H₂O₂ scavenger providing a primary defence against ROS produced by the mitochondrial respiratory chain, regulate mitochondrial integrity. | (71,72) |
| Thyroxine deiodinase type I (DIO1) | Catalyse, in the liver, the conversion of the prohormone thyroxine (T₄) to the bioactive thyroid hormone (T₃) by outer ring 5'-de-iodination and is negatively associated with growth retardation. Expression is Zn-dependent | (41,73–75) |
| Thyroxine deiodinase type II (DIO2) | Catalyse in situ conversion of thyroxine (T₄) to the bioactive hormone (T₃) in central nervous system (CNS), brown adipose tissue & muscle, the metabolic functions of which depend on T₃. | (76,77) |
| Thyroxine deiodinase type III (DIO3) | Highly expressed in placenta, regulates circulating foetal thyroid hormone concentrations throughout gestation. Essential for the regulation of thyroid hormone inactivation during development | (78,79) |

In selenium deficiency, there is a strict hierarchy of selenium supply to specific tissues and also to different selenoenzymes within a tissue. Concentrations of selenium and selenoenzymes are greatly decreased in liver, kidney and muscle, whereas those in the brain and endocrine organs such as the thyroid gland are less affected. Within different organs, specific selenoproteins are retained at the expense of others, presumably to preserve the most important aspects of metabolism in selenium deficiency. For example, in the selenium-deficient rat, DIO1 is better retained than cytoplasmic glutathione peroxidase in thyroid, liver and kidney, presumably in order to preserve thyroid function and iodothyronine de-iodination and to limit changes in plasma T₄, T₃ and TSH(76). Many of the beneficial effects of selenium are attributable to its presence as selenocysteine in the selenoenzymes, a small but vital group of proteins[41,42]. Selenoproteins W and N (SELENOW and SELENON) are both required for muscle growth, differentiation and regeneration, as well as satellite cell maintenance in skeletal muscle[43–46]. Selenoprotein S (SELENOS) is involved in the degradation process of misfolded endoplasmic reticulum luminal proteins[47–49], while selenoprotein T (SELENOT) is involved in the control of glucose tolerance by contributing to prolonged adenylate cyclase-activating polypeptide 1 (ADCYAP1/PACAP)-induced insulin secretion[50] while also contributing to increased quantitative insulin sensitivity[51].

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### Maternal metabolic skewing and its consequences

**Transmethylation cycle (one-carbon metabolism) alterations.** Maternal dietary methyl donor intake (methionine, folate and choline) and cofactor (zinc and vitamins B2, B6 and B12) play crucial roles in one-carbon metabolism and DNA methylation in the foetus and placenta, impacting foetal growth and lifelong health outcomes. However, in a context characterised by significant maternal malnutrition, not only such dietary intakes will be highly restricted, but the deficiencies in cofactors intake apparently promote down-regulation of the THF-transmethylation cycle. The resulting elevation in Hcy and 5mTHF concurrently with low GSH circulating levels observed in the populations studied probably does not arise from low vitamin B12 availability but from attenuation of zinc-dependent methionine synthase and betaine–homocysteine S-methyltransferase enzymatic activity. Here, high Hcy circulating levels lead to GSH depletion through uncoupling of the activities of NOX (NADPH-dependent) from those of XO [S-adenosylhomocysteine (SAH)-dependent] and NOS (BH4-dependent), both of which are:

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negatively affected by dysregulation of the transmethylation pathway. This dysregulation, resulting in S-adenosyl methionine (SAM) deficiency, besides reducing methylation potential, also has an effect upon choline biosynthesis from phosphatidylethanolamine (PE), each step of which requires methyl groups donated by SAM (Fig. 1). In pregnancy, increased maternal Hcy levels are associated with increased risk of adverse pregnancy outcomes such as intrauterine growth restriction leading to small size for gestational age at birth and LBW (58). Dietary protein restriction in animals and marginal protein intake in human subjects cause characteristic changes in one-carbon metabolism that are further exacerbated by micronutrient deficiency, negatively impacting the health of the mother, impairing growth and reprogramming metabolism of the foetus, and causing long-term morbidity in the offspring (82,86).

Amino acid metabolism alterations. Four amino acids (aspartic acid, serine, threonine and histidine) show elevated serum levels in malnourished pregnant women, and in particular aspartic acid is extremely elevated (see Table 1). Under protein deficiency, the NEAA aspartate becomes a significant metabolic hub, a major product of the oxidative glutaminolysis pathway and a required substrate for other anabolic pathways, including the synthesis of purines and pyrimidines (87). Besides playing a key role in the urea cycle as well as in pyrimidine synthesis, aspartate carries reducing equivalents in the malate-aspartate shuttle, which utilises the ready interconversion of aspartate and oxaloacetate in order to maintain mitochondrial oxidative phosphorylation (Fig. 2). Hence, extremely elevated serum aspartate levels could be a consequence of high biosynthesis and interconversion rates. Aspartate can be synthesised by the transamination of α-keto acids using either alanine or glutamine, yielding aspartate and an α-keto acid (88–90). Interestingly, in malnourished pregnant women alanine, and even more so glutamine, show low circulating levels, possibly comforting hypothetically increased aspartate de novo synthesis and interconversion levels.

However, such mechanisms would be at the expense of amino acid supply and cannot be sustained indefinitely. Furthermore, glutamate dehydrogenase, which, in this scheme, catalyses the oxidative deamination of glutamate to α-ketoglutarate and ammonia, is zinc-dependent and its activity would be down-regulated by zinc deficiency. This could be alleviated by increased FA oxidative catatolism, provided that sufficient L-carnitine is available. Since diets low in meat and dairy products lead to low L-carnitine uptake, this could be compensated by de novo L-carnitine biosynthesis, which takes place mainly in skeletal muscle, kidney and liver, using L-lysine, an EAA, as primary substrate (81) (Fig. 3). In malnourished pregnant women, serum lysine and methionine levels are lower than those of most other EAA:s, indicative of active de novo L-carnitine biosynthesis. However, this methylation-dependent mechanism implicates SAM as methyl group donor (82), hence placing further demands on the transmethylation cycle.

In malnourished pregnant women, serum serine levels also are elevated, while glycine levels are not, suggesting down-modulated activity in serine hydroxymethyltransferase-mediated interconversion to glycine (synthesis of 5,10-methylene tetrahydrofolate from tetrahydrofolate) for the cytoplasmic synthesis of thymidylate, purines and methionine regeneration (94–96). Furthermore, high circulating levels of serine might also be indicative of down-regulated PE biosynthesis (97) which, together with SAM deficiency, could lead to low phosphatidylcholine synthesis. This may take particular importance in a context where the availability of choline-rich food items such as fish, crustaceans, meat and eggs are highly limited, since, in pregnancy, choline deficiency could worsen placental dysfunctions while promoting foetal slow growth as gestation progresses.

In human subjects, choline and phosphatidylcholine are synthesised de novo via the PE N-methyltransferase (PEMT) pathway (98) but biosynthesis is not enough to meet physiological requirements (99). In the hepatic PEMT pathway, 3-phosphoglycerate (3PG) receives two acyl groups from acyl-CoA forming a phosphaticid acid. It reacts with cystidine triphosphate to form cystidine diphosphate-diacylglycerol. Its hydroxyl group reacts with serine to form phosphatidylserine which decarboxylates to ethanolamine and PE forms. A PEMT enzyme moves three methyl groups from three SAM donors to the ethanolamine group of the PE to form choline in the form of a phosphatidylcholine. Three SAHs are formed as a by-product (99). Most of the physiological requirements for phosphatidylcholine are met by channelling dietary choline through the CDP pathway which utilises adenosine triphosphate (ATP), cystidine triphosphate (CTP) and diacylglycerol to generate phosphatidylcholine (Fig. 4).

In a context dominated by maternal malnutrition, low protein diet will lead to inhibition of mammalian target of rapamycin complex 1 (mTORC1), thereby promoting autophagy as a mechanism maintaining EAA availability for protein synthesis and protective mechanisms (see later) while supplying ketogenic and glucogenic precursors, such as glutamine and alanine, for ATP generating pathways (101–103). These effects would be amplified during pregnancy, triggering the placentation mammalian amino acid response pathway and thereby programming the growth capacity of offspring not only in utero but also long after gestational protein restriction (104,105). Elevated plasma threonine, a member of the EAA group, could reflect zinc and/or vitamin B6 deficiencies, since the initial step in threonine catabolism to Kreb’s cycle precursors requires vitamin B6, the activation of which, via pyridoxal kinase, is zinc-dependent (106,107). However, this would also suggest sufficient dietary supply in EAA:s which, in the context addressed here, is highly improbable. Hence, it appears more likely that elevated plasma threonine, arising from maternal autophagy, could supply the developing foetus with an immunostimulant which promotes thymus growth while concurrently promoting maternal innate immune defence functions (108). Elevated plasma histidine, another member of the EAA group, might also play significant protective roles benefiting both the mother and the foetus, particularly in a context dominated by chronic anaemia. Histidine is essential in globin synthesis and erythropoiesis and has also been implicated in the enhancement of iron absorption from human
diets. Histidine-deficient diets predispose healthy subjects to anaemia and accentuate anaemia in chronic uraemic patients\(^{109}\). Furthermore, histidine plays key roles in the detoxification of cytotoxic oxidative stress metabolites such as reactive carbonyls\(^ {110}\).

**FA metabolism alterations.** Under conditions characterised by deficit in methyl donors and increased homocysteine levels, β-oxidation becomes deficient and hypertriglyceridaemia ensues\(^ {111}\) as reflected by high circulating TGs in anaemic Indian women (see earlier). Low amino acid availability, and in particular lysine, may further contribute to high circulating TG levels. Low lysine levels would lead to low L-carnitine de novo synthesis, while diets low in meat and dairy products would lead to low L-carnitine uptake\(^ {112}\). This, in turn, would further impede mitochondrial β-oxidation of FAs without affecting cytoplasmic FA synthesis from excess carbohydrates intake\(^ {113}\). Under these conditions, mitochondrial β-oxidation of medium-chain FA, including odd medium-chain FA, the catabolism of which requires the activity of B12-dependent methylmalonyl-CoA mutase, an enzyme indispensable in human metabolism\(^ {114}\), would remain functional. However, both microsomal α-oxidation, which requires Fe\(^{2+}\), vitamin C/GSH and thiamine (vitamin B1) as cofactors\(^ {115,116}\), as well as ω-oxidation, which requires haem iron protein such as microsomal or mitochondrial cytochrome P-450\(^ {117}\) together with zinc-dependent alcohol dehydrogenase, are also likely to be impeded. Hence, peroxisome-mediated β-oxidation of dietary long- and very long-chain FA and α-oxidation of dietary branched-chain FA stand to be favoured. However, this process would also increase oxidative stress since the first step in peroxisome-mediated β-oxidation results in the generation of H\(_2\)O\(_2\) and subsequent increase in Fe\(^{2+}\)-dependent catalase activity\(^ {118}\). Here, the activity of the main ROS-controlling enzymes (SODs, GLO1, GPXs and TXNRDs) will be attenuated through zinc and selenium deficiencies, while GSH will be subjected to Hcy-mediated depletion. These phenomena stand to exert negative impacts upon placental functions.

**Functional placental alterations.** During pregnancy, the characteristics of maternal blood biochemistry will necessarily constitute the nutritional supply provided to the developing foetus. Maternal hypertriglyceridaemia during pregnancy is correlated with foetalplacental endothelial dysfunction\(^ {119}\). This can be expected to result in constitutive mild placental (and consequently foetal) hypoxia and subsequent ER stress, which would then affect metabolic control via ATF4 and ATF6\(^ {120}\). This would stand to further worsen the direct
effects of maternal anaemia. Additionally, most of the serological maternal characteristics will also be transferred to the foetus via the foetoplacental endothelial system. Hence, in a context dominated by maternal malnutrition, the developing foetus will be constitutively supplied with low vitamins, micronutrients, unbalanced amino acid supply, high TGs and Hcy. Furthermore, due to maternal selenium deficiency, the foetus will also experience a drastically reduced supply of thyroid hormones and in particular low bioactive T3 supply. Furthermore, maternal deficiencies in protein intake will trigger the placental mammalian amino acid response pathway, thereby programming the growth capacity of offspring not only in utero but also long after gestational protein restriction (104, 105).

Foetal developmental dysregulations leading to the LBW ‘thin-fat’ phenotype

The cord blood of LBW infants is characterised by low adiponectin levels which correlate with hyperinsulinaemia and differential distribution of fat depots giving rise to the newborn’s thin-fat phenotype characterised by insulin resistance and increased subcutaneous fat but decreased intra-abdominal fat. Given the marked differences in metabolic and pathophysiological characteristics which differentiate subcutaneous and visceral fat depots (121, 122), this situation is radically different from that observed in normal-weight obese individuals of Asian and Indian descent (123, 124), characterised by high visceral adiposity and disproportionately lower subcutaneous adiposity (124, 125). The fat overflow hypothesis invoked to explain this phenotype (126) does not correlate with the anatomical and pathological consequences observed in association with the ‘thin-fat’ phenotype of these LBW infants studied here.

Indeed, the lipid overflow/ectopic fat model states that excess visceral fat accumulation, while causally related to the features of insulin resistance, might also be a marker of a dysfunctional adipose tissue being unable to appropriately store the excess calories. According to this model, the body’s ability to cope with the surplus of energy (resulting from excess caloric consumption, a sedentary lifestyle or a combination of
both factors) might ultimately lead to metabolic syndrome presentation. There is evidence suggesting that if the extra energy is channelled into insulin-sensitive subcutaneous adipose tissue, the individual, although in positive energy balance, will be protected against the development of metabolic syndrome. However, in cases in which adipose tissue is absent, deficient or insulin-resistant with a limited ability to store the energy excess, the triacylglycerol surplus will be deposited at undesirable sites such as the liver, the heart, the skeletal muscle, and visceral adipose tissue, a phenomenon described as ectopic fat deposition. The resulting metabolic consequences include visceral obesity, insulin resistance, atherogenic dyslipidaemia and a pro-thrombotic, inflammatory profile. This clearly cannot be invoked to explain the thin-fat phenotype addressed here, characterised by elevated subcutaneous adiposity but very low visceral adiposity (thin-fat phenotype), exhibiting infantile insulin resistance, stunting and wasting, together with increased risk of developing cardiometabolic disorders in adulthood.

**Roles of adipokines in the inception of the LBW ‘thin-fat’ phenotype**

Adiponectin is an adipocyte-derived plasma protein with insulin-sensitizing and anti-atherosclerotic properties. There is no correlation between cord adiponectin levels and maternal body mass index, cord leptin or insulin levels, and there is no correlation between cord and maternal adiponectin levels. However, high cord blood adiponectin levels, compared with serum levels in children and adults, positively correlate with
foetal birth weights. Taking fat mass-related parameters such as the birth weight/birth length ratio into consideration, plasma adiponectin concentrations exhibit a significant inverse correlation with insulin concentrations. The high adiponectin levels in newborns may be due to lack of negative feedback on adiponectin production resulting from lack of adipocyte hypertrophy, low percentage of body fat or a different distribution of fat depots in the newborns as compared to children and adults (128–131). This indicates that adiponectin in cord blood is derived from foetal and not from placental or maternal tissues.

During pregnancy, leptin and adiponectin seem to act in an autocrine/paracrine fashion on the placenta and adipose tissue, playing a role in the maternal–foetal interface and contributing to glucose metabolism and foetal development (132). Hence, the low cord blood adiponectin levels observed in LBW births and its correlation with hyperinsulinaemia and differential distribution of fat depots giving rise to the newborn’s thin-fat phenotype clearly suggest that the metabolic skewing resulting from maternal malnutrition and anaemia induce significant changes in foetal metabolism.

Cumulative effects of maternal malnutrition and placental alterations in the development of the LBW ‘thin-fat’ phenotype

Maternal nutrition, particularly micronutrients, vitamins and omega-3 FAs play a role in modulating the activity of peroxisome proliferator-activated receptors (PPARs) during placentation and angiogenesis, which affects placental and foetal growth (133). In placental angiogenesis, PPARγ signalling causes increased vascular endothelial growth factor receptor 2 (VEGFR2) expression. VEGF binding to VEGFR2 then mediates angiogenic signalling involving increases in NOS activity (134,135). Hcy suppresses PPARγ signalling and expression (136) while impeding NO production. Hence, during pregnancy, the multiple methylation network dysregulations resulting from micronutrient and vitamin deficiencies are likely to primarily result in placental vascularisation defects, while endothelial ER-stress resulting from chronically elevated Hcy levels (137) is in turn likely to result in elevated placental leptin production. These factors, together with the low circulating levels of vitamins, micronutrients and amino acids together with high TGs, are now likely to have serious consequences upon foetal development, predisposing the newborn to insulin resistance, dyslipidaemia (138) and preferential subcutaneous adipocyte patterning, whereas imbalance in the availability of amino acids and low T3 hormone production, resulting from selenium deficiency, will promote growth retardation (73).

Differential adipocyte patterning and dyslipidaemia mechanisms in the development of the LBW ‘thin-fat’ phenotype

In mammals, individual white and brown adipocyte tissues (WAT and BAT, respectively) depots appear at different times in development and have unique functional characteristics. The distinction between subcutaneous and visceral fat may be oversimplified because evidence suggests that metabolic properties vary between some visceral fat depots, while heterogeneity exists even within a single fat depot (139). Furthermore, metabolic and environmental challenges highlight the extraordinary plasticity of the mammalian adipose organ. Two distinct subtypes of preadipocytes have been characterised in human fat (Myf5+ and
Myf5), the proportions of which vary among depot locations\(^{146,141}\). Despite the heterogeneity in the adipocyte precursor cell compartment, it appears that the Myf5\(^{-}\) lineage may selectively differentiate in the BAT, subcutaneous and retroperitoneal WAT (sWAT and rWAT, respectively), while Myf5\(^{-}\) lineages selectively give rise to most adipocytes in the inguinal and visceral WAT (ingWAT and vWAT, respectively)\(^{142}\). Up-regulation of the PI3K-Akt-mTORC1 pathway (PTEN silencing) dramatically redistributes body fat such that interscapular WAT (iWAT), sWAT and rWAT (the Myf5\(^{-}\) lineage depots) expand, while the ingWAT and vWAT (the Myf5\(^{-}\) lineage depots) disappear\(^{142}\). In other words, the adipocytes of Myf5\(^{-}\) lineage expand (causing lipohypertrophy of BAT, sWATs and rWAT) at the expense of Myf5\(^{-}\) lineage (i.e. inguinal and visceral WAT).

Hence, the thin-fat phenotype of LBW infants, characterised by increased subcutaneous fat but decreased intra-abdominal fat, is clearly indicative of metabolic skewing towards AKT-mediated mTORC1 up-regulation, probably as a result of elevated Hcy and insulin supply, concurrently with foetal hypoxia and oxidative stress, as a result of placental dysfunctions(143). As a direct consequence, adipogenesis (lineage commitment, clonal expansion and terminal differentiation of preadipocytes) and lipogenesis in adipose tissue will be promoted, while \(\beta\)-oxidation and ketogenesis will be attenuated, leading to dyslipidaemia and insulin resistance\(^{144}\), a situation which shall remain dominant after birth. Should the affected individual be then exposed to chronic malnutrition, these developmental phenomena will then have predisposing effects towards stunting/wasting and the development of cardiovascular diseases later in life.

**Post-birth nutrition and stunting/wasting in 'thin-fat' phenotype individuals**

Following weaning, LBW infants are subjected to the same restrictive dietary conditions experienced by their parents, namely malnutrition characterised by diets low in proteins, vitamins and micronutrients but rich in carbohydrates and saturated fats, leading to metabolic dysfunctions, including significant anaemia, which will be considerably worsened by increased consumption of low-quality processed products rich in saturated fats, salt and sugars and low in vitamins and micronutrients (ill-nutrition, or so-called junk food). In this context, the deficiencies in micronutrients and metabolic cofactors, and in particular selenium and vitamins, appear to play a key role. Recurrent nightly leg muscle cramps, muscle weakness and fatigue, are indicative of significant L-carnitine deficiency\(^{145}\) and subsequent dysregulation of FA metabolism (see earlier), non-ketotic hypoglycaemia and muscle wasting\(^{146}\). The latter effect stands to be further reinforced by selenium deficiency. Selenium bioavailability, which, in muscles, plays a key role in oxidative stress defence and calcium transport control, and the development of nutritional muscular dystrophies affecting cardiac and skeletal muscles have long been established both in human subjects and livestock. Skeletal muscle degeneration leads to muscle weakness or stiffness, postural instability or walking disability, while cardiac muscle degeneration is associated with respiratory distress, cardiogenic shock, enlarged heart, cardiac arrhythmias, congestive heart failure and ultimately sudden death\(^{147}\). Concurrently, selenium deficiency will also result in deficient thyroid hormone supply\(^{73}\) which, conjunctly with malnutrition, will promote stunting.

It is important to note that the results of malnutrition, such as deficiencies in amino acids, vitamins and micronutrients together with an oversupply of saturated fats, do not lead to the full inhibition or full activation of metabolic reactions or pathways. These deficiencies and/or oversupplies are not absolute but only relative and act as ‘rheostats’, slowing down or facilitating particular metabolic reactions or pathways. These will in turn have discrete metabolic skewing effects, the cumulative result of which will swing development in a particular direction while opening the door to predisposing effects towards context-dependent pathologies over longer period.

**Conclusion**

According to the earlier analysis, significant maternal malnutrition leads to deficiencies in amino acids, vitamins and micronutrients together with an oversupply of saturated fats. These deficiencies result in alterations affecting key maternal metabolic processes, and in particular the amino acid interconversion, transmethylation, FA oxidation and redox control pathways. These alterations, together with the deficiencies in micronutrients, result in high maternal anaemia, exacerbated during pregnancy and placental dysfunctions. The ensuing alterations in oxygen and nutrients supply to the embryo give rise to in utero foetal metabolic alterations. This results in LBW children characterised by high subcutaneous but low abdominal adipocyte deposits and already existing insulin resistance (Figure 5). Being raised in the same environment as their parents promote significant anaemia, accompanied by stunting and wasting in late childhood, repeating the same cycle as in their parents. Should these individuals shift, during mid to late childhood, to a food environment which primarily consists of processed foods low in proteins, vitamins and micronutrients but rich in saturated fats, salt and sugar (so-called junk food), their condition stands to be worsened by the appearance of significantly increased insulin resistance and the pathogenesis of cardiovascular and metabolic disorders. These individuals, after reaching sexual maturity, are now likely to perpetuate this deleterious cycle via their own children.

However, attempts to remedy this situation must take into consideration the history of Indian diets. This history demonstrates gradual transitions over the centuries from a low energy diet of large quantities of indigestible fibre carbohydrate, small amounts of digestible carbohydrate, moderate fat and moderate protein, to an increasing intake of low fibre and refined carbohydrates associated with increased fat and decreasing intake of animal proteins interspersed with variable periods of starvation. There were fourteen recorded famines in India between the 11th and 17th centuries, while those that took place over the course of the 18th, 19th and early 20th centuries
resulted in more than 60 million deaths\textsuperscript{(148)}. Currently, food intake patterns show that most Indians are vegetarians consuming poor and monotonous cereals-based diets and that food items rich in micronutrients (pulses, other vegetables, fruits, nuts, oils and animal foods) are generally consumed less frequently\textsuperscript{(149)}. However, from 1947 onwards there has been an increase in the frequency of intake and quantities of low fibre and refined carbohydrates, with protein intake improving only marginally while intakes of industrially processed foods containing high salt, high saturated fats and high sugar but low micronutrients kept increasing\textsuperscript{(148,150,151)}. Hence, Indian populations are most probably genetically as well as epigenetically adapted to forms of ‘chronic malnutrition’ characterised by low energy, low refined carbohydrates, low protein and moderate fat intake with seasonal variation in micronutrient intake (thrift metabolism). Hence, it most probably is the metabolic consequences of the recent and rapid dietary shifts over an adaptation to ‘thrift metabolism’ which must be addressed.

The task is made more challenging by the complexity of political, economic, climatic, social and cultural factors twined together. The resolution of malnutrition-associated problems will require a product well suited to the cultures addressed and developed in light of the actual needs as depicted by the biological evidence. To alleviate the consequences of malnutrition, improvement in affordability, accessibility, delivery to end-users, knowledge and awareness of social and cultural constrains and, most importantly, in the convergence between demand and supply must also be addressed. The solution therefore cannot merely consist in providing a ‘one size fits all’ supplement but in the use of a well-designed supplement which suits the nutritional requirements along with a social and behaviour change approach, training the beneficiaries in the basics of nutrition based on what is locally available and accessible.

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