Metabolic Syndrome: Is It Nutritionally Programmed?

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Abstract: This review considers the metabolic and neuroendocrine responses that occur when there is an alteration in fetal substrate supply and highlight those specific responses that appear to have immediate adaptive benefit, which result in a permanent alteration of the developmental pattern of cellular proliferation and differentiation in key tissue and organ systems to result in pathological consequences in adult life.

Introduction

Metabolic syndrome (MetS), previously named syndrome X is a contemporary disease, characterized by a set of metabolic and cardiac risk factors, which together exacerbate cardiovascular and renal risks [1]. The syndrome was first described in 1998 by a consultation group tasked with defining diabetes for the World Health Organization [2]. It has been defined in several ways by different organizations, but the common criteria adopted by all the investigators include the concomitant presence of systemic hypertension (SH), abdominal or central obesity, dyslipidemia and changes in glucose homeostasis or basal increase of blood glucose levels [3]. The positive diagnosis of the syndrome was established when at least three of the following were present: 1) fasting plasma glucose ≥100 mg/dL (or history of doctor diagnosed diabetes), 2) systolic (and / or

diastolic) blood pressure ≥130 (85) mmHg or treated hypertension, 3) serum triglycerides ≥150 mg/dL, 4) serum high-density lipoproteins (HDL) cholesterol ,<40 mg/dL in men and ,<50 mg/dL in women and 5) waist circumference of >80 cm in women and >94 cm in men [4]. India is in the midst of a rapidly escalating "epidemic" of type 2 diabetes and coronary heart disease (CHD). Indians, as an ethnic group are particularly at high risk for insulin resistance (syndrome X) and central obesity; both are fore runners of diabetes, CHD and other life style disorders [5].

Prevalence of metabolic syndrome

The prevalence of MetS varies substantially across populations and settings, both as a result of background differences in the distribution of its components across populations, but also of the diversity of criteria for defining the condition. There have been recent efforts to harmonize the clinical definition of MetS by accounting for ethnic differences in the cutoff values of key components such as central obesity and atherogenic dyslipidemia [2, 6]. It is estimated that the incidence of MetS varies between 12.4% to 28.5% of men and 10.7% to 40.5% of women, not surprising considering increasing lifestyle factors in recent decades [7]. NCEP:ATP III (National Cholesterol Education Program, Adult Treatment Panel III) shows a prevalence with a similar increase among men and women about 24% but increases dramatically with age, about 7% among people in their 20's-about 40% in people older than 60. Racial and ethnic trait heterogeneity gives rise to substantial variation in the prevalence of syndrome itself. 50% of hypertensive is IR (Insulin resistance), 60 % of IGT (Impaired glucose tolerance) subjects and 90% of diabetics are IR, and 25% of normal subjects are also having IR [8].

Complications of Metabolic Syndrome

The presence of metabolic syndrome is strongly associated with the development of diabetes [9], hypertension [10], cardiovascular disease [11], and all-cause mortality [12]. Metabolic syndrome also is both associated with and a risk for the development of chronic kidney disease (CKD) (defined as GFR _60 ml/min) and micro albuminuria, and the risk increased progressively with the number of criteria constituting the syndrome [13].

What is the cause of this increase in young generation?

The recent discovery states that people who develop chronic diseases grow differently from other people during fetal life and childhood has led to a new 'developmental' model, these groups of disease including coronary heart disease, stroke, high blood pressure and type II diabetes. Nutrition is the major intraenvironmental factor that alters the expression of the foetal genome and may have lifelong consequences. Pioneering work by David Barker has produced a wealth of data in this field [14]. This phenomenon termed 'fetal programming' has led to recent theory of 'Foetal Origin of Adulthood Disease' (FOAD) or the 'early origin hypothesis of Barker', 'Thrifty Phenotype hypothesis' [15].

Foetal Origin Hypothesis

The "foetal origin" hypothesis or 'thrifty phenotype hypothesis' states that foetal responses to the adverse intrauterine conditions, viz adaptations in endocrine, metabolic, vascular functions or other structural changes, are firmly imprinted in the individual (foetal programming) and can cause chronic diseases in the individual in his later life. Maternal derived abnormalities relate to lifestyle, environment and nutrition and while some of these directly affect embryonic development, there is also growing evidence that some effects are more subtle and relate to later life health events. Fetal malnutrition has two main causes, poor maternal nutrition and placental insufficiency. The element of this theory was that it is the poor foetal nutrition that predisposes the individual to develop diseases during adult life

How does fetal responses to under nutrition lead to metabolic syndrome in later life?

The components of metabolic syndrome are hypothesized to develop through plasticity.

Developmental Plasticity

It is well appreciated that these chronic diseases may have their origin in the mother's womb [16]. During development, there are sensitive periods when the organs and the systems of the body are plastic and show greater degree of sensitivity to the

environment and usually for most of the organs and systems, this period occur in utero [17]. Developmental plasticity is defined as the ability of an organism to develop in various ways, depending on the particular environment or setting. Nutrition serves as informational molecules that interact with the genome and trigger or facilitate developmental programmes.

The genesis of this illness springs from the complex interplay between maternal nutrition, genetic susceptibility and environmental factor.

Interaction of nutrients and developmental biology

Deficiency or excess of particular nutrients at a critical time will impair specific genetically programmed developmental processes. Plasticity enables the babies to adjust to their environment. Any adverse environment exposure is likely to exert a fundamental effect on the metabolic capacity and may have lifelong consequences [17]. Therefore, the risk of these impairments is associated with a specific developmental period or "critical window" underlying the programming of adult disease.

Critical windows and initiating mechanism (Table 1)

CRITICAL WINDOWS OF DEVELOPMENTAL PLASTICITY	PROGRAMMING MECHANISMS
Primordial germ cell Mature germ cell Ovulation Fertilization :Zygote Blastocyst: Inner cell mass and Trophoectoderm Differentiation	Epigenetic regulation of gene expression

Similarly a range of endocrine signals have been implicated as key mediators for the impact of prenatal nutrition on subsequent development, whereby the concentrations of hormones and hormone analogs present during critical windows of development can permanently alter the hormonal responses to specific stimuli and / or tissue sensitivity to specific hormones [18].

The most important factor allegedly contributing to the magnitude of the problem in India is maternal malnutrition.

1) Maternal malnutrition

Exposure to under-nutrition in utero results in structural and functional changes in various organs in a manner beneficial to survive in conditions of poor nutrition later as well. Allocation of adequate energy to the growth of an essential trait, like brain development, reduces its allocation to growth and development of other organs like the kidneys, pancreas and muscle.

a) Insulin Resistance

Insulin resistance is a condition wherein the target cells like liver, muscle and fat cells of the body become resistant to effects of insulin i.e., the peripheral uptake of glucose to a given amount of insulin is decreased and hence the body tries to compensate for this by increasing its insulin secretion resulting in hyperinsulinaemia. Islet development occurs mainly during the second trimester, although remodeling may occur throughout late gestation and early childhood. Thrifty phenotype hypothesis explains that poor nutrition in fetal and early infantile life affects the function and development of beta cells and insulin sensitive tissues, leading to, decreased fetal growth, insulin resistance and obesity-induced IGT in later childhood and adolescence [19-21]. Maternal malnutrition inhibits the normal development of endocrine pancreas and the rate of beta cell apoptosis also gets accelerated, which may result in impaired insulin secretion and hyperglycemia in adult life.

- Development of fetal islet cells has been shown to be dependent on the availability of glucose and amino acids. Amino acids appear to be more important than glucose during post natal and most part of gestation. Islet development may be altered by both which results in decrease of cells [19].
- Reduction in total calorie intake during pregnancy also affects development of fetal endocrine pancreas. Maternal under nutrition and restriction of glucose reduces the fetal beta cell mass and increases the alpha to beta cell ratio in developing pancreas [20].
- Gross protein-energy malnutrition or deficiency of specific nutrients like vitamin B12, Folic Acid or Methionine during critical periods of pregnancy has shown [22] to induce insulin resistance.

The hypothalamic-pituitary-adrenal axis: a target and mediator in the developmental origins of adult diseases

- Programming of the endocrine axis has been postulated to occur during critical phases of fetal developmental and is affected by IUGR. Barker et al [23] pointed out that while IUGR of symmetric type attributable to maternal nutrition deprivation in mid-

pregnancy is associated with vulnerability to insulin resistance syndrome whereas the IUGR of the asymmetric type attributable to nutritional deprivation during late pregnancy is associated with increased risk of coronary heart diseases in adult life. Glucocorticoids have also been implicated in this pathogenesis. Increase in circulating glucocorticoids may play a role in early programming which results in impaired renal development, hypertension, glucose intolerance, and insulin resistance in the offspring [24-28]. Glucocorticoids inhibit the development of endocrine pancreas by repressing the expression of transcriptional factors involved in beta cell differentiation. Outcomes following glucocorticoid exposure are dependent on programmed changes in GR and 11 -β HSD1 and 2 within different target tissues. There is also evidence that there may be programming of the HPA axis itself during critical windows of development such that the set point of the axis changes resulting in altered basal and / or stress induced glucocorticoid responses in postnatal life [29].

- Altered maternal behavior such as reduced grooming and licking, can affect glucocorticoid-receptor gene expression in the hippocampus of the offspring's [30]. This neuroendocrine programming could in turn contribute to the association between low birth weight and cardiovascular and metabolic disease in later life.

Foetal exposure to maternal diabetes can result in maldevelopment of beta cells. Severe diabetes or prolonged maternal hyperglycemia causes a decrease in the insulin content and leads to degranulation of beta cells and beta cell exhaustion. They have low circulating insulin levels and a reduced beta cells response to exogenous glucose [31-33].

b) **Hypertension**: It has been hypothesized that the intra-renal rennin angiotensin system is critical for normal nephrongenesis and can get altered by maternal malnutrition [34] which may lead to permanent structural alterations within the kidneys that contribute to a propensity for adult cardio renal disease.

Hypertension is related to changes in renal and arterial development. In the kidneys, reduced nephron mass may result in enhanced blood flow through each nephron and this may subsequently lead to premature nephron death and rise in blood pressure [35, 36]. Brenner and colleagues [37, 38] originally proposed the theory that essential

hypertension, including that associated with intrauterine growth restriction, is a consequence of a reduced total number of nephrons, leading to sodium retention.

This theory was developed further by the proposal that reduction of nephron number is followed by increasing single-nephron GFR and where increased pressure within single nephrons is sustained, focal glomerulosclerosis occurs, resulting in nephron loss. The individual therefore enters a cycle in which mean arterial pressure continues to rise to maintain hemodynamic function with progressive and irreversible renal injury [39, 40] and [41] (Figure 1). In the human, nephrogenesis is completed within 32–34 wk, and therefore, a nephron deficit present at birth would persist through life. Reduced activity of anti-apoptotic homebox gene Product Paired Box-2 (Pax -2) [42] as well as oxidative stress resulting in altered regulation of sodium transport [43] has also been implicated in pathogenesis.

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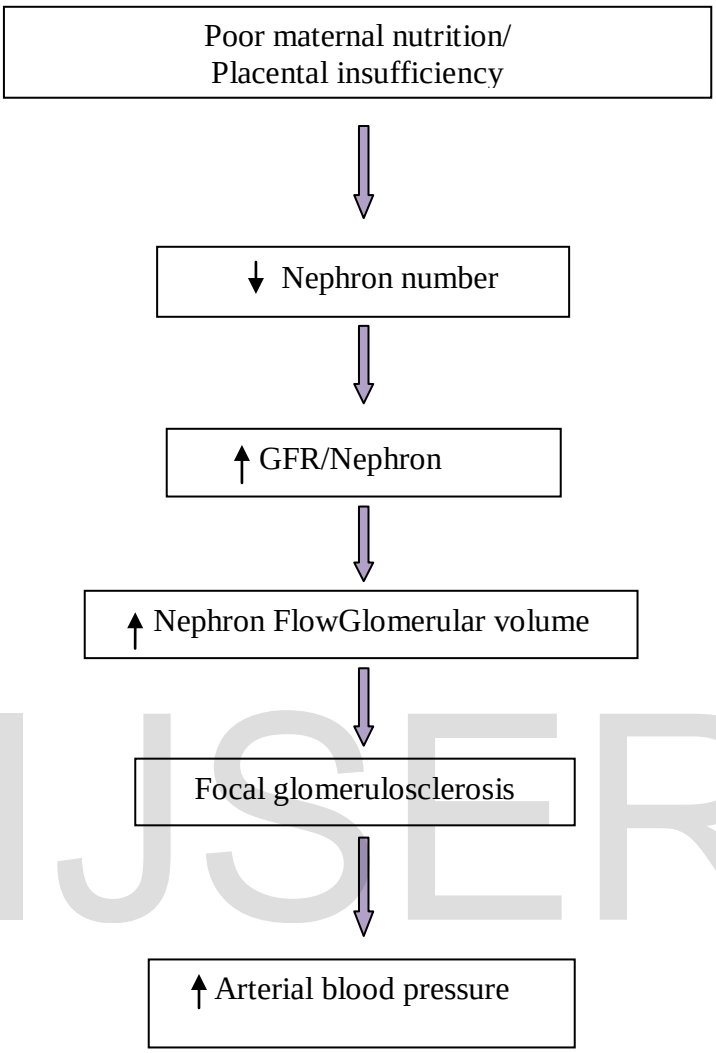

A diagrammatic summary of how decreased nephrogenesis in early life may result in adult hypertension (Figure 1)

2) Genetic predisposition

The genome encompasses the complete set of genetic material (i.e., DNA) that determines the development of an organism and all its traits and characteristics (i.e., the phenotype). Changes (i.e., mutations) in the DNA can lead to the development of various diseases, including AUDs. In comparison, the epigenome, as first defined by Waddington

(1942) refers to chemical modifications that occur within a genome without changing the DNA sequence [44].

Epigenetic alterations include the direct addition of methyl groups to (i.e., methylation of) DNA and the chemical modification of the proteins around which the DNA is wrapped (i.e., histone proteins) to form the chromosomes. Both of these mechanisms work in concert to remodel the structure of the protein–DNA complex (i.e., the chromatin) and regulate gene expression [45-47].

Epigenetic mechanisms are also involved in the process of developmental plasticity. Epigenetic alterations in early embryos allow durable, lifelong changes in gene expression.

The best-characterized epigenetic modification of DNA is the methylation of cytosine residues within CpG dinucleotides [48] and histone acetylation or methylation, in the absence of any change in the gene DNA sequence. Such changes are mitotically transmitted and can be passed on to subsequent generation. Paternally expressed genes can enhance fetal growth while maternally expressed genes can suppress this [49].

Studies of in vitro embryo culture have shown that the methylation status of genomically imprinted genes, including *IGF2, H19, IGF2R*, etc., can be altered with consequences for subsequent organ growth and function [50], [51]. Recent studies have also demonstrated that retrotranspons are elements within the genome that may also be epigenetically labile to early nutrition [48, 52].

3) Environmental Factors

The environment is another etiopathogenic culprit. In India, a nutritional and lifestyle transition results in high fat intakes [53], linked to the consumption of refined foods, and foods of animal origin with an increased fat content [54], coupled with a low physical activity [55] would result in an increased total body fat mass and obesity which is linked to lowered insulin sensitivity [56] and the risk of diabetes (Figure 2) and heart disease [57].

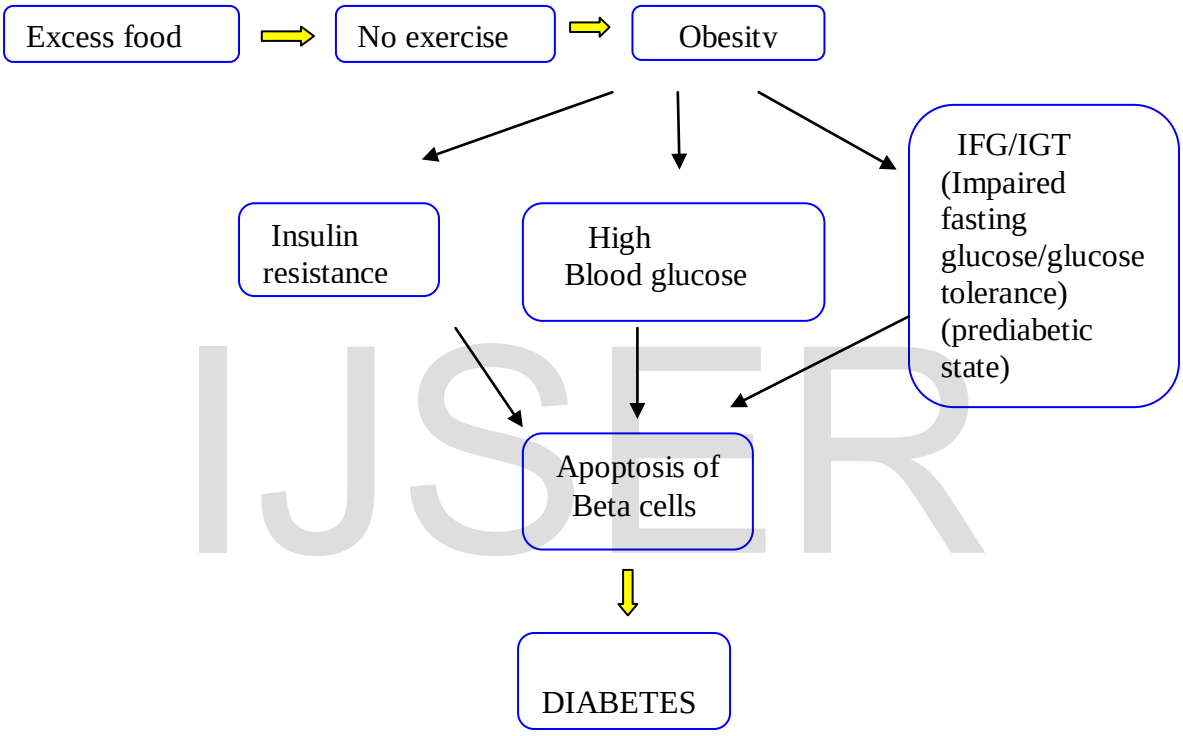

Figure 2

Association of Birth weight and obesity

During the past two decades there has been a marked increase in the global prevalence of adult and childhood obesity. An increase in the prevalence of obesity (BMI >30 kg/m^2) is associated with an increase in a range of co-morbidities including type 2 diabetes, high blood pressure, and ischemic heart disease [58-60].

a. High birth weight and adult obesity

The relation between birth weight and fatness, measured in childhood or adulthood, is generally positive, although a number of studies have reported that there is a J-shaped or U-shaped relationship between birth weight and adult fat mass, with a higher prevalence of obesity occurring at both low and high birth weights [61, 62]. It has been suggested that the influence of maternal weight on the relationship between birth weight and subsequent BMI may operate through an impact of high maternal and hence fetal nutrient supply.

b. Low birth weight and central obesity in later life

Central or truncal obesity is associated with the clustering of pathologies which defines the insulin resistance or metabolic syndrome (hypertension, dyslipidemia, hyperinsulinism, impaired glucose tolerance or frank diabetes) [63]. Whereas people who were small babies tend to have a lower BMI in adult life than people who were larger at birth, these individuals tend to have a more abdominal distribution of obesity, a significantly reduced muscle mass, and a high body fat content in adolescent and adult life despite their lower BMI [64, 65].The common cause of insulin resistance, is associated with a decreased number of receptors and with post receptor failure to activate tyrosine kinase. Obesity leads to an increase in the fetal pancreatic insulin content, improved insulin secretion in response to glucose and greater proliferation of the islet cells [31]. Insulin resistance and atherogenic lipid profile (Dyslipidemia) include: High triglyceride, Low HDL-c level, Elevated apo-B level and Increase of small LDL particles.

Availability of nutrients in the maternal circulation is determined by maternal metabolism and body composition and by the amount and balance of macronutrients and micronutrients in the diet. The ability of a woman to nourish her foetus, depends on her nutrition and growth throughout her life, including her foetal life, as well as her nutritional state at conception and her nutrient intake during pregnancy.

These adaptations become permanent or ‘programmed’ as they occur during critical periods of early development. Hence it follows that an adequate or excessive nutrition post-natally or during childhood may result in accumulation of several cardio-

metabolic risk factors predisposing the individual to develop disease in later life. Thus India proves to be a fertile soil to prove Barker hypothesis.

Nutritional supplementation of mothers during late pregnancy only makes the babies fat without improving their brain or bone growth. Neonatal survival may improve by such short-sighted supplementation programme but in the long run can lead to increased cardio vascular risk. So the preventative treatment should be aimed at female nutrition throughout their life or even before they are born, by way of improved nutrition.

Now it is clearly known that sub optimal intrauterine and neonatal environment play key role in programming the individual to develop metabolic syndrome in the adult hood. With the epidemic of this metabolic syndrome in the young spreading to even rural areas in our country it has become a national problem. Our health authorities should concentrate at all levels to create awareness among the general public about this major health problem and try to evolve a national consensus to thwart this menace as early as possible.

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