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Developmental Origins of Obesity: Programmed Adipogenesis

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Abstract

The metabolic syndrome epidemic, including a marked increase in the prevalence of obesity and gestational diabetes mellitus (GDM) among pregnant women, represents a significant public health problem. There is increasing recognition that the risk of adult obesity is clearly influenced by prenatal and infant environmental exposures, particularly nutrition. This tenet is the fundamental basis of developmental programming. Low birth weight, together with infant catch-up growth, is associated with a significant risk of adult obesity. Exposure to maternal obesity, with or without GDM, or having a high birth weight also represents an increased risk for childhood and adult obesity. Animal models have replicated human epidemiologic findings and elucidated potential programming mechanisms that include altered organ development, cellular signaling responses, and epigenetic modifications. Prenatal care has made great strides in optimizing maternal, fetal, and neonatal health, and now has the opportunity to begin interventions which prevent or reduce childhood/adult obesity. Guidelines that integrate optimal pregnancy nutrition and weight gain, management of GDM, and newborn feeding strategies with long-term consequences on adult obesity, remain to be elucidated.

Keywords

Maternal obesity; gestation diabetes mellitus; birth weight; catch-up growth; developmental origins of obesity; programmed adipogenesis

Introduction

It is difficult to overestimate the significance of the steadily developing epidemic of global obesity, the resultant pathologies that develop, and their collective impact on health, well-being, and quality of life. Obesity and its related diseases are the leading cause of death in western society. Currently, 65% of adults in the United States are overweight and more than one third are obese [1], representing a modern health crisis. Worse, epidemiologic data indicate that obesity continues to increase relentlessly, particularly among blacks and Hispanics. In parallel the rates of type 2 diabetes mellitus (DM) is increasing in the United States and worldwide [2]. Of concern to obstetricians, there is a marked and continuing

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increase in the prevalence of obesity and gestational DM (GDM) among pregnant women (~30%) [3,4], a factor associated with both high birth weight newborns and a known risk factor for childhood obesity [5,6]. As childhood obesity is a major risk factor for adult obesity [7], the 20% incidence of childhood obesity [8] portends a further increase in the prevalence of adult obesity and DM.

Obesity is often attributed to a Western style, high-fat diet combined with decreased activity levels. While there is little doubt that these factors are strong determinants of obesity, the long-term sustainability of dieting combined with exercise have largely proved unsuccessful. In recent years, there is compelling data from our laboratory and others which support the concept that origins of obesity begin *in utero*. As the developing fetus is dependent upon the maternal nutritional, hormonal and metabolic environments, any perturbation which "programs" organ structure, cellular composition, gene expression and/or the epigenome may ultimately alter metabolism and function. Importantly, interactions with the postnatal environment and neonatal growth further modulate susceptibility to obesity. This review focuses on the influence of prenatal/neonatal growth and adipogenesis in developmental origins of obesity.

Nutrition and Growth

Growth of tissues and organs during development involves proliferation, differentiation and migration of cells into organized structures. In humans, as in other mammalian species, the major part of the developmental process pertaining to cell division occurs during intrauterine life, emphasizing the need for optimal *in utero* environment. Unquestionably, therefore, nutrition is one of the cornerstones of growth, development and health. The merit of nutritional supplementation especially during pregnancy is obvious, as demonstrated with iodine and folate supplementation in preventing iodine deficiency-induced cretinism and spina bifida, respectively. The field of developmental origins of adult disease has incorporated this phenomenon and portends that sub-optimal maternal nutrition impacts fetal growth leading to adult diseases. In addition to nutritional influences, factors including GDM, maternal stress, preterm delivery and maternal glucocorticoid therapy, among others, may significantly impact adult health and disease. Evidence for the concept of programming health and disease is provided by both human studies and animal models that have used birth weight as a proximate measure for *in utero* growth and development.

Maternal Influence on Birth Weight

Beyond fetal genetic potential, maternal nutrition, oxygenation and placental perfusion have predominant effects on birth weight. Animal models using maternal nutrient restriction, placental uterine artery ligation or glucocorticoid exposure, have effectively replicated findings associated with low birth weight (LBW) [9-12]. Conversely, maternal overnutrition, resulting from obesity, high fat diet, or excess weight gain during pregnancy, has reported variable effects on birth weight. However, the adult offspring consistently exhibit obesity and metabolic abnormalities [13-15], evidence of in utero programming. Offspring of women with GDM are consistently larger than normal controls, with birth weight proportional to the mean glucose levels [16].

Whether the programming effects of GDM-associated macrosomia differ from that of maternal obesity alone, is unknown at present.

Association between Birth Weight and Obesity

Epidemiological studies and animal models link birth weight to risk of adult obesity and metabolic syndrome, including insulin resistance. Notably in humans, both low and high

birth weights lead to increased risk for childhood and adult obesity, suggesting increased risk of obesity at both ends of the birth weight spectrum [17,18].

High Birth Weight

Obesity in pregnancy has not only adverse effects on maternal health and pregnancy outcome but also on the developing fetus. Specifically, maternal obesity before and during pregnancy, including increased weight gain in pregnancy, has been associated with higher birth weight [16,19] as well as lower birth weight newborns, the later a result in part of the increased risk of preterm delivery [20]. The 25–36% increase in maternal BMI over the last decade has translated to an approximately 25% increase in the incidence of high birth weight babies [21]. This is of particular importance, as high birth weight newborns show increased adipose tissue mass and an increased risk of obesity and diabetes risk in later life (review [22]). However, both human and animal studies indicate that increased maternal prepregnancy BMI and excessive maternal weight gain during pregnancy are greater predictors of offspring obesity than high newborn birthweight [5,23,24]. As the majority of GDM women have accompanying obesity, the independent programming effects of GDM are uncertain.

Low Birth weight

Early epidemiologic studies initially demonstrated that the LBW infants with rapid catch-up growth have higher risk of obesity and metabolic syndrome. The prevalence of metabolic syndrome increased progressively in both men and women, from those who had the highest to those who had the lowest birth weights. Of 64-year-old men whose birth weights were 6.5 pounds or less, 22% had metabolic syndrome. Those with the lowest birth weight were 10 times more likely to have metabolic syndrome as compared to those who were heaviest at birth [25,26]. The reduced rate of obesity amongst the heavier infants (born from 1935-1943), further suggests that maternal obesity and pregnancy diet/weight gain have greater effect on programming of offspring obesity than birthweight alone. Numerous epidemiologic studies from diverse populations confirm this relationship [17].

U-Shaped Curve

Epidemiologic studies confirm that the relationship between human birth weight and adult obesity, hypertension, and/or insulin resistance is a “U-shaped curve” [27-30]. Perhaps most importantly, the relation of fetal growth to offspring obesity and metabolic syndrome is a continuum [25], rather than a threshold response. There may well be an optimal newborn weight (potentially specific to an individual mother) at which the programming of obesity potential is minimized. However, within ranges of lower or higher birth weights in comparison to mean values, studies indicate a gradation of propensity to programming sequelae. Thus, deviations from “optimal” *in utero* growth, be it from limited or excess nutrition, increase the relative risk of adult metabolic syndrome (Figure 1).

Additive Risk of Postnatal Catch-up Growth

Although the long term effects of LBW are linked to adult obesity, several studies have demonstrated detrimental effects of newborn or childhood catch-up growth among the LBW infants (Figure 1). Those infants that are born small, and remain small exhibit a lower risk of obesity and metabolic syndrome, then those born small who catch up and exceed normal weights through infancy or early adolescence [31,32]. Importantly, LBW or preterm infants with catch-up growth during early life have less lean body mass and higher body fat that shows predominant abdominal distribution [33,34]. A similar phenomenon is seen in normal birth weight newborns that exhibit accelerated weight gain in first two years of life [35].

These findings have been successfully replicated in animal models using prenatal nutrient restriction to produce LBW newborns, followed by normal nursing to promote catch-up growth. As adults, the LBW offspring not only have higher body weights and body fat [36-39] but show greater susceptibility to high fat diets [40]. Conversely, prevention of catch-up growth in LBW newborns prevents an obese adult phenotype [37]. These results suggest that the degree of newborn nutrient enhancement and timing of newborn catch-up growth may determine the programming of offspring obesity [37,41]. A fundamental question that arises is what mechanism regulates preferential catch-up of fat [42] in these offspring. Again, animal models have provided initial insight that prenatal factors result in programming of hyperphagia, reduced energy expenditure and/or enhanced adipogenesis, which result in a propensity for fat accrual in the offspring [43-46].

Catch-up Growth and Fat Accrual

Adipocytes are highly specialized cells that maintain whole body energy homeostasis by regulating glucose and lipid metabolism [47]. More recently, adipocytes are recognized for their role in inflammation and immune response [48]. Adipose tissue contains functionally distinct cellular subtypes with white adipocytes serving as energy storage depots whereas brown adipocytes dissipate energy through thermogenesis. Fat storage is facilitated by insulin which stimulates adipocyte glucose uptake and lipogenesis. Alteration in either adipose tissue mass, increased circulating free fatty acids, and/or fuel partitioning into adipocytes may result in dyslipidemia, obesity, insulin resistance and DM.

Increase in fat mass or adipogenesis occurs primarily during the prenatal and postnatal development, though some adipogenesis continues throughout adulthood [49]. The process of adipogenesis involves differentiation of preadipocytes to mature adipocytes that can store fat. The differentiation pathway is tightly regulated by a cascade of transcription factors that are salient within the preadipocytes and are sequentially expressed in response to stimuli (nutrient, hormones) probably under the influence of epigenetic mechanism (Figure 2). Obesogens, including environmental factors, have the potential to alter key adipogenic pathways, including adipogenic transcription factors, via epigenetic modifications of promoters or histones [50].

Regulation of Adipogenesis and Lipogenesis

The induction of adipocyte differentiation is driven by transcription factors PPAR (peroxisome proliferator-activated receptor) and C/EBP (CCAAT-enhancer-binding proteins) [51-53]. Of these, the principal adipogenic transcription factor, PPAR $_{2\gamma}$ induces lipogenic transcription factor SREBP1 (sterol regulatory element binding protein) thereby initiating both adipocyte differentiation and lipogenesis [54-56]. SREBP1 can also activate PPARγ, by both stimulating the production of an endogenous ligand [57], as well as by inducing PPAR promoter activity [54,57]. These data are suggestive of a feed-forward mechanism, in which PPAR activates SREBP1 and vice-versa, and which is aimed at promoting adipogenesis and lipogenesis [55]. SREBP1 facilitates lipogenesis by induction of extracellular lipolytic enzyme (lipoprotein lipase) and lipogenic enzyme (fatty acid synthase) that in turn, lead to an increase in fatty acid uptake and synthesis, promoting lipid accumulation within the adipocyte [58,59]. The release of free fatty acid from adipocytes is facilitated by an intracellular lipolytic enzyme, hormone-sensitive lipase [60].

Synthesis of fatty acids (via *de novo* lipogenesis) and triglycerides are important factors in fat accumulation. Triglycerides destined for fat storage in adipose tissue are composed of fatty acids from dietary sources and from *de novo* synthesis. *De novo* synthesized fatty acids can undergo modification through creation of double bonds via desaturation, and/or further lengthening via chain elongation. While *de novo* synthesis and chain elongation promote

energy storage, breakdown of fatty acids by chain shortening and β-oxidation promote energy release. Since triglycerides become incorporated into adipose tissue for storage, an increase in the monounsaturated to saturated fatty acid ratio, therefore, increases propensity for fat storage [61].

Perturbation of the metabolic network may shift the energy balance toward increased energy release, or, as in obesity, increased energy storage. Animal studies provide some insight into underlying mechanistic basis for programmed enhanced adipogenesis/lipogenesis or alteration in function/response of adipocytes.

Effects of Increased Adipogenesis on DM in offspring

Increased fat accumulation, especially visceral fat, has been shown to cause impaired glucose and lipid metabolism, leading to insulin resistance and DM [62]. The underlying mechanistic basis involves perturbation in the production of adipose-derived 'adipocytokines' that modulate insulin sensitivity. In the obese state, adipose tissue secretes proportionally more adipokines that cause insulin resistance (e.g., TNFα, IL-6, leptin) and fewer that promote insulin sensitivity(e.g., adiponectin) [63-65]. Indeed, numerous human studies have confirmed that increased plasma TNFα, IL-6 and leptin, and decreased plasma adiponectin levels are associated with obesity/insulin resistance [66-69] This relationship has recently been demonstrated in childhood obesity, suggesting that adipocytokines may serve as early markers of development of DM [68,70].

LBW Offspring

LBW rat newborns, either as a result of maternal nutrient restriction in pregnancy or uteroplacental insufficiency, which demonstrate subsequent postnatal catch-up growth exhibit an altered adipocyte phenotype and function. Early studies of offspring exposed to maternal protein restriction during pregnancy show that obese adult offspring have increased expression of insulin receptor, hypertrophic adipocytes and upregulation of genes involved in adipocyte differentiation [71-73]. Recent studies, including those from our laboratory, have specifically investigated proximate mechanisms that predispose LBW offspring to fat accrual. These include demonstration of altered adipocyte gene expression, morphologic variations, and differential response to modulators at birth and at end of nursing period (prior to onset of obesity). For example, growth restricted LBW newborns have an upregulated adipogenic signaling cascade, specifically increased adipose tissue expression of PPAR [44,74] with increased *de novo* fatty acid synthesis [75]. *Ex-vivo* cultures indicate that newborns have higher rates of preadipocyte proliferation at birth [76], and early induction of adipocyte differentiation together with increased PPAR expression [77]. At the end of the nursing period, LBW rats exhibit elevated plasma leptin levels, hypertrophic adipocytes and increased expression of PPARγ, SREBP1 and lipid enzymes that influence adipocyte lipid synthesis, storage and release. Cell culture studies indicate a continued higher preadipocyte proliferation rate [78] with higher *de novo* fatty acid synthesis, greater glucose utilization for fatty acid synthesis and lipid accumulation in adipocytes of LBW offspring [37,38,44,74,79-81]. Collectively, these findings indicate increased susceptibility to retain fat in adipocytes of LBW offspring, and thus an increased propensity for adiposity. Furthermore, increased lipid accumulation is likely to alter adipocyte endocrine function with resultant impact on insulin sensitivity and inflammation.

As these changes are evident early in life, it suggests a programmed pathway of increased adipocyte differentiation and lipogenesis which likely promotes the development of obesity and DM in LBW offspring (Figure 2).

Maternal Obesity/High Fat Diet Offspring

Programming of adipose tissue as a result of *in utero* overnutrition likely involves an interplay of effects: preexisting maternal obesity, maternal weight gain during pregnancy, high fat Western diet, and varying degrees of maternal glucose intolerance. Adipogenesis programming may occur in the presence of absence of increased newborn birth weight. Limited mechanistic studies on programmed adipogenesis due to maternal obesity or high fat diet show remarkably similar phenotype as LBW offspring. This includes increased expression of PPAR in fetal and newborn adipose tissue [82,83] as well as increased expression of enzymes mediating fatty acid biosynthesis [84].

Clinical Implications and Conclusions

A major public health challenge in the 21st century is to devise an effective policy and practice to combat the epidemic of obesity across all spectrums of age groups. Prevention of childhood obesity remains a high priority for many health professionals. There is irrefutable evidence that departures from optimal growth *in utero*, whether from limited or excess nutrition, increase the relative risk of adult obesity and metabolic syndrome. This predisposition is especially paramount within a postnatal environment that facilitates neonatal catch-up growth as well as access to energy-intense childhood and adult diets. Collectively, these findings have great significance for neonatal and childhood care. For example, a major goal of treatment for premature, LBW newborn infants is the achievement of a weight satisfactory for hospital discharge. Contrary to existing practice, it may be advisable to limit the rapid weight gain in the neonatal period. Fortunately, the recent enthusiasm for exclusive breastfeeding may provide one approach to prevention of offspring obesity [85] and the accompanying insulin resistance, perhaps due to favorable nutrient and hormone composition and the natural limitation which avoids excessive feeding. Although macro- and micronutrient guidelines for nutrition in pregnancy continue to evolve, there is critical need for additional research as to how these guidelines may influence offspring long-term sequelae, particularly among obese or gestationally diabetic pregnant women.

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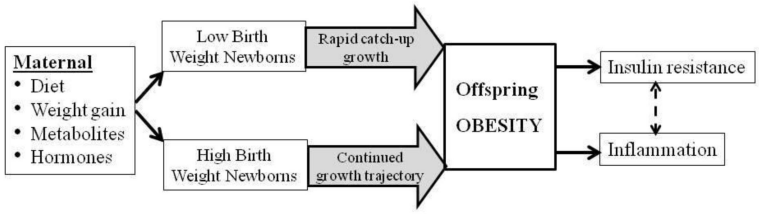

Figure 1. Developmental Programming of Obesity

Altered maternal nutrition, hormonal or metabolite milieu impacts fetal growth resulting in low or high birth weight newborns. As a result of this growth deviation *in utero* combined with accelerated/similar postnatal growth causes enhanced adipogenesis, resulting in childhood and adult obesity. Obesity in turn leads to insulin resistance and inflammation.

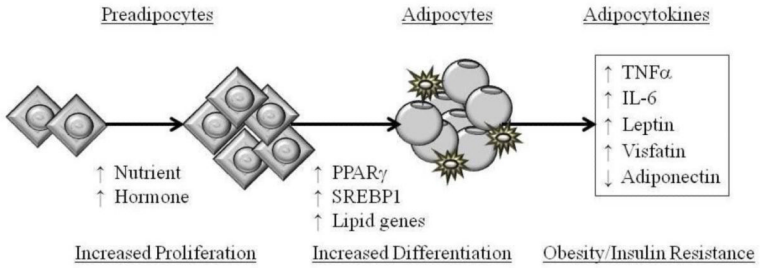

Figure 2. Increased Adipogenesis Mediated Diabetes Mellitus

Adipogenesis is a process of cell differentiation by which preadipocytes become adipocytes. Increased nutrient supply or elevated hormonal levels (e.g., insulin, corticosterone, IGF1) stimulate cell proliferation and differentiation. Induction of adipocyte differentiation is facilitated by adipogenic transcription factor (PPARg) and fat storage by lipogenic transcription factor (SREBP1). Increased adipogenesis is associated with increased macrophage infiltration and increased secretion of pro-diabetic (TNFα, IL-6, leptin, visfatin) with decreased secretion of anti-diabetic (adiponectin) adipocytokines.