The Relationship of Insulin-Like Growth Factor 2 to Fetal Growth and Adiposity

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Abstract

Insulin-like growth factor 2 (IGF-2) is necessary for adequate human growth. Overexpression of the *IGF2* gene is associated with fetal overgrowth and may play a role in the intrauterine programming of adipose tissue. As obesity in children is a major public health problem associated with early onset of comorbid metabolic diseases, identifying early life markers of obesity may serve as useful tool for counseling and implementation of preventive efforts before obesity develops. The relationship between IGF-2 and body composition is an emerging field of study and existing data are conflicting. In this review, we discuss the *IGF2* gene and its function, highlight the proposed mechanisms for the effects of IGF-2 on adiposity, and examine the current literature studying the relationships between IGF-2 levels, changes within the *IGF2* gene, weight, and adiposity. With additional study, IGF-2 may emerge as a useful marker of future obesity risk in infants.

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Introduction

Obesity is a major public health problem in the United States, with a current estimated prevalence of 17% or 12.5 million children aged 2–19 [1]. Obesity risk begins early in life – infants who are born large for gestational age (LGA) have been shown to weigh more as adolescents [2]. In addition, childhood obesity is a strong predictor of obesity in adulthood [3–5]. Metabolic diseases once considered to be adult-onset such as type 2 diabetes mellitus, hypertension, and fatty liver disease are occurring in children at younger ages as a result of the obesity epidemic.

The etiology of nonsyndromic obesity is multifactorial and its prevention requires a multidisciplinary approach. Researchers have previously identified biomarkers that are known to correlate with obesity and adiposity such as leptin and insulin or its surrogate, c-peptide [6, 7]. Identifying the presence of such biomarkers early in life can serve as a platform for earlier implementation of targeted preventive efforts before obesity develops. In contrast, there are a number of inheritable genetic obesity syndromes that cause severe obesity and are difficult to manage. Many of these syndromes are accompanied by hyperphagia, dysmorphic features, developmental delay, and/or other associated organ dysfunction. The onset of obesity is during infancy or early childhood and persists into adulthood [8].

Insulin-like growth factors (IGFs) are important for adequate intrauterine and postnatal growth. Researchers

have explored the role that IGFs play in excessive growth and adiposity of neonates; however, the literature that exists is conflicting. In this review, we aim to specifically examine the relationship of IGF-2 with weight and adiposity in infants.

Growth Hormone and Body Composition

Growth hormone has long been known to affect body composition by increasing lipolysis within adipocytes and promoting development of lean muscle mass. This relationship is illustrated by the clinical example of Laron syndrome, a condition of growth hormone resistance in which growth hormone function is impaired. The lack of growth hormone's lipolytic effects leads to the phenotype of increased fat mass, decreased lean mass, and short stature [9]. A model of growth hormone receptor null mice (GHR^{-/-}) has been used to study the impact of growth hormone on body composition. These mice are all dwarf and obese. In GHR^{-/-} mice followed twice monthly from 2 to 16 weeks and monthly from 16 weeks to 2 years, it was found that the body composition of GHR^{-/-} mice consisted of significantly higher percent fat mass compared to wild-type mice [10]. A separate mouse model in which the growth hormone receptor was selectively mutated in adipose tissue also demonstrated that these mice were noted to have increased body fat without alteration in glucose homeostasis suggesting that other organs are more important on growth hormone's regulation of glucose [11]. While growth hormone itself can impact adipose tissue, its downstream peptides IGF-1 and IGF-2 may also contribute to body composition.

Insulin-Like Growth Factors and Intrauterine Growth

IGF-1 and IGF-2 are peptides primarily secreted by the liver. Postnatally, IGF-1 is produced in response to growth hormone. Murine and human studies have emphasized the important role of IGFs in intrauterine growth. Disruption of *IGF1* and *IGF2* genes in knockout mice studies led to reductions in birth weight. Mice heterozygous for an *IGF1* gene deletion had a birth weight 10–20% less than wild-type mice, while a homozygous deletion led to birth weights 40% less than wild-type mice along with underdeveloped muscles and lungs and high perinatal mortality [12]. Heterozygous loss of the *IGF2* gene led to a 60% reduction in birth weight compared to wild-type mice, suggesting that IGF-2 is a larger contributor to in-

trauterine growth [13]. Reinforcing this theory is a study that previously showed that human cord blood IGF-2 concentrations are more than 6 times higher than IGF-1 concentrations [14]. When thinking about protein-receptor interactions, higher protein levels may translate to greater signal transduction but may also represent resistance at the receptor level, meaning that higher protein levels are needed to achieve the desired effect.

In humans, even partial *IGF1* deletions have been associated with intrauterine growth restriction (IUGR). Reported human cases of *IGF1* gene abnormalities leading to reduction in IGF-1 production or activity demonstrate a phenotype of severe IUGR, extreme postnatal growth failure, and developmental delay [15–18]. All described cases occurred in children born to consanguineous parents and three of four also had sensorineural hearing loss [15, 16, 18]. In one instance, an adult male was diagnosed with a homozygous missense mutation of the *IGF1* gene at the age of 55. When genetic analysis was performed in 24 relatives, carriers of the mutation had significantly shorter adult heights and birth weights than noncarriers [18]. Interestingly, there are no reported human cases of *IGF2* gene deletions, suggesting that *IGF2* gene expression is needed for survival.

As deletion of the *IGF2* gene in mouse models appears to have a greater reduction of birth weight than deletion of *IGF1*, it is plausible that higher circulating levels of IGF-2 are present during fetal development. IGF-2 is more abundant during fetal life than IGF-1 in both human and sheep fetuses with IGF-2 concentrations declining throughout gestation in sheep [19, 20]. In humans, IGF-1 levels rise greater than IGF-2 postnatally due to increased growth hormone-regulated production of IGF-1 [21].

In addition to directly affecting fetal growth, IGF-2 also contributes to placental size and nutrient delivery, which indirectly impact fetal size [22]. Deletion of a promoter of *IGF2* expression in the mouse placenta reduced placental growth and passive nutrient delivery, subsequently leading to fetal growth restriction [23]. Even with adequate placental *IGF2* gene expression, downstream effects of blocked processing of pro-IGF-2 to active IGF-2 are associated with IUGR [24].

IGF-2

IGF-2 is a widely expressed polypeptide hormone, primarily secreted by the liver but also in utero by the placenta. The *IGF2* gene is a maternally imprinted gene lo-

Fig. 1. IGF-2 and its receptors.

cated on chromosome 11p15 near a paternally imprinted noncoding gene, *H19*. These two genes share enhancer regions that can affect either gene depending on parent of origin. Each gene also has promoter regions that are differentially methylated and thus differentially expressed depending on parental origin. Just upstream of the *H19* promoter is the imprinting control region (ICR). When ICR is methylated, as occurs on the paternal chromosome, the gene enhancers cannot act at that location and instead are available to act upstream on the *IGF2* promoter leading to *IGF2* expression. On the maternal chromosome, ICR is unmethylated allowing for *H19* expression and *IGF2* repression [25, 26].

The interaction of IGF-2 with its receptors is schematically depicted in figure 1. IGF-2 signal transduction occurs through binding at the type 1 IGF receptor (IGF-1R) and insulin receptors. The IGF-1R has a higher affinity for IGF-2 than the insulin receptors. The IGF-1R and insulin receptors have similar homology. Both are heterotetramers with two membrane-spanning alpha subunits linked by disulfide bonds and two intracellular beta subunits. The intracellular beta subunits consist of a transmembrane domain, an ATP-binding domain, and a tyrosine kinase domain that is responsible for signal transduction [27].

When binding occurs, the receptor tyrosine kinase phosphorylates insulin receptor substrate 1. The Ras/Raf/MAP kinase and PI3-kinase/Akt pathways are then activated, leading to proliferation and/or differentiation of cells [26].

In contrast to the IGF-1R, the type 2 IGF receptor (IGF-2R) is a monomeric receptor consisting of an extra-

cellular domain, a transmembrane domain and a small cytoplasmic domain. There is no signal transduction mechanism within the IGF-2R. Instead, IGF-2 binding to IGF-2R targets IGF-2 for degradation [27]. Interestingly, while the *IGF2* gene is paternally expressed, the *IGF2R* gene is maternally expressed demonstrating the opposing parental effects of growth promotion and growth restriction [25]. Mice studies in which a mutant-imprinted IGF-2R is inherited from the mother demonstrated birth weights 130–140% of normal, presumably by lack of IGF-2 degradation leading to increased IGF-2 bioavailability. The mothers were phenotypically normal because the mutant allele they carried was inherited paternally and thus not expressed [28, 29].

IGF-2 and Growth

Much of what is known about IGF-2 and growth stems from the clinical conditions of Beckwith-Wiedemann syndrome (BWS) and Russell-Silver syndrome (RSS). In BWS, there is a gain of methylation at the maternal ICR leading to biallelic *IGF2* gene expression and fetal overgrowth. In contrast, RSS fetuses have a phenotype of growth restriction, caused by a loss of methylation on the paternal ICR leading to biallelic loss of *IGF2* expression. Newborns with BWS are LGA and newborns with RSS are small for gestational age (SGA) [30, 31]. These two conditions represent extremes of fetal growth patterns and emphasize the important role of IGF-2 in fetal growth.

Fig. 2. Insulin action on adipose tissue. TG = Triglycerides; FFA = free fatty acids; LPL = lipoprotein lipase; HSL = hormone-sensitive lipase.

IGF-2 can bind to insulin receptors during fetal development, which may mediate the effects of IGF-2 on adipose tissue. Typically, as shown in figure 2, insulin stimulation of the insulin receptors leads to fat accumulation by stimulating the differentiation of preadipocytes to adipocytes, increasing uptake of fatty acids from circulating lipoproteins via the action of lipoprotein lipase, inhibiting fat breakdown in adipose tissue, and facilitating glucose entry into adipocytes. Once glucose enters the adipocyte, a portion of it is converted to glycerol and combines with free fatty acids to make triglycerides [32].

Recent studies have suggested that the affinity of the insulin receptor type A (IR-A) for IGF-2 approaches that of its affinity for insulin [33]. If IGF-2 is present in abundance, IGF-2-mediated IR-A activation may also occur more freely. In humans, IR-A is traditionally expressed in the central nervous system and hematopoietic cells, while IR-B is more abundantly expressed in adipose tissue, liver, and muscle. However, the study of fetal brain, muscle, liver, kidney, and fibroblast tissues has demonstrated a predominance of IR-A. There is not yet an understanding of whether IR-A in fetal adipose tissue is also more robustly expressed than IR-B as proven in other tissues. Pre-adipocytes and adipocytes do express IR-A which, when potentially stimulated by IGF-2 in utero, could lead to adipocyte growth prenatally and increased adiposity at birth. In pigs, a quantitative trait locus associated with fat deposition mapped to the *IGF2* gene. Greater expression of the *IGF2* gene led to higher intramuscular fat content [34, 35]. Perhaps this is mediated by preferential activation of IR-A.

Studies Examining IGF-2, Weight, and Adiposity

The Relationship between IGF-2 and Birth Weight

Most studies of IGF-2 in early life have been performed in infants at birth and may not truly represent the concentration or effects of IGF-2 at various points throughout the intrauterine course. Data examining IGF-2 early in gestation is sparse. In a study of 260 pregnancies in which chorionic villus sampling (CVS) was performed at 11–13 weeks to evaluate for chromosomal defects, quantitative expression analysis of *IGF2* PCR in the CVS tissues was also performed. All 260 pregnancies subsequently led to normal term births. The authors found that increased expression of the *IGF2* gene in CVS tissue was significantly associated with higher birth weight, highlighting the in utero role of IGF-2 on growth. Furthermore, 19% of infants in this study were classified as SGA and had reduced expression of *IGF2* compared to appropriate for gestational age (AGA) infants [36].

The comparison of cord blood IGF-2 levels and birth weight yield conflicting results. AGA infants have been found to have higher cord serum IGF-2 levels than IUGR infants; however, no difference in IGF-2 levels was identified when comparing AGA and LGA infants [37, 38]. In another study of 36 infants born after 32 weeks' gestation, IGF-2 cord blood concentrations were again lower in fetal growth-restricted infants compared to controls [39]. When comparing AGA and LGA full-term infants born to healthy, nondiabetic mothers, se-

rum IGF-2 levels at birth were significantly higher than IGF-1, though there was no definite correlation between IGF-2 and birth weight [40].

In contrast, studies in two different American cohorts of full-term infants found that IGF-1 levels but not IGF-2 levels were associated with larger birth weight [41, 42]. This pattern was also present in a Chilean study of 28 full-term healthy newborns in which IGF-1 was positively correlated with birth weight, ponderal index, and placental weight [43].

It is notable that all of these studies provide only a snapshot of IGF-1 and IGF-2 levels at birth and do not provide information on the trajectory of IGF-1 and IGF-2 throughout gestation. As IGF-2 levels are dynamic throughout fetal development, perhaps IGF-2 levels at birth do not always correlate with its action during gestation, leading to these conflicting results. Furthermore, when examining obesity risk in humans, it is important to distinguish birth weight and adiposity. While birth weight is correlated with body fat, it is important to note that birth weight is comprised of both adipose and lean tissue so increases in birth weight do not always accurately solely reflect an increase in fat content [44].

Ponderal index, a ratio of birth weight to length, has been used as a marker of leanness or fatness in newborns. Ponderal index is defined as $[\text{weight (kg)}]/[\text{length (cm)}]^3$ while body mass index (BMI) is $[\text{weight (kg)}]/[\text{length (cm)}]^2$. In lieu of birth weight alone, both ponderal index and BMI account for infant's length. Neither are ideal measures of adiposity in neonates as a given ponderal index or BMI accounts for a large range of body fat percentages; however, when taken together, both ponderal index and BMI can provide complementary information [45].

Pregnant women with diabetes are well known to be at increased risk of delivering an LGA fetus. Studies looking at IGF-1 and IGF-2 levels in small numbers of diabetic pregnancies compared to nondiabetic pregnancies have also been conflicting with regards to IGF-2. One study showed that IGF-2 levels were higher in cord serum of offspring of diabetic mothers but did not correlate with birth weight [46]. Another showed that cord blood IGF-2 levels did not vary between mothers with and without diabetes but that IGF-2 was weakly correlated with birth weight and placental weight [47]. Both studies found a positive relationship between IGF-1 and birth weight and that infants of diabetic mothers had greater IGF-1 levels [46, 47].

The Relationship between IGF-2 and Postnatal Adiposity

Researchers have identified an association of IGF-2 with fat mass and ponderal index. The AVON Longitudinal Study of Parents and Children (ALSPAC) studied growth factor levels, weight, and adiposity over the first 5 years of a child's life. IGF-2 levels at birth were related to serum IGF-2 levels at age 5, which in turn was related to fat mass at age 5. On the other hand, IGF-1 level at age 5 correlated with fat-free mass. These results suggest that cord blood IGF-2 may be a useful marker of later adiposity [48].

The ALSPAC cohort has also associated IGF-2 with ponderal index, specifically that elevations in the molar ratio of IGF-2/soluble IGF-2 receptor were associated with higher birth weight and ponderal index [49]. The soluble IGF-2 receptor results from proteolytic cleavage of the intact IGF-2 receptor. Binding of IGF-2 to the soluble IGF-2 receptor leads to degradation of IGF-2 and inhibition of its effects. Thus, elevations in the IGF-2/soluble IGF-2 receptor ratio lead to higher bioavailability of IGF-2 and presumed greater impact on growth.

The IGF2 Gene and Weight

Changes within the *IGF2* gene and its related genes have also been related to weight, likely by altering *IGF2* expression. Single nucleotide polymorphisms located in the *IGF2*, *IGF2R*, and *H19* genes that may modify gene expression have been significantly associated with birth weight in a group of full-term infants born to healthy mothers [50].

The presence of particular *IGF2* gene alleles may change one's weight or obesity risk. Individuals homozygous (GG) for the *IGF2* gene *Apal* allele had higher body weights and risk of higher BMIs than other genotypes [51]. Another study showed that individuals homozygous (GG) for the *Apal* allele had higher adult BMIs when their birth weight was >3.5 kg [52]. This finding is intriguing as it suggests that the presence of a homozygous genotype in an overweight infant may program the infant for future obesity. Genotype was also examined in a large British cohort of adult men and women. While there was no significant relationship between genotype and weight, there was a trend towards higher birth weights in both sexes and adult weight in men in the presence of the GG genotype [53]. In contrast, a Baltimore cohort of adult men and women failed to show a relationship between the GG genotype and BMI, fat mass, or IGF-2 levels [54]. As the studies that evaluated birth data were retrospective in nature, birth

weight was the main measure of neonatal size; neonatal adiposity data were not available.

Epigenetics is a newer field of study that looks at modifications to DNA that can alter gene expression independent of gene sequence. These changes can be heritable or modified by the intrauterine environment. Given that the *IGF2* gene is paternally expressed, epigenetic changes in paternal *IGF2* could be transmitted to the offspring and serve as a predictor of childhood obesity. This relationship was examined as part of the Newborn Epigenetics Study (NEST), a prospective study aimed at determining how the in utero environment affects childhood epigenetics and phenotype. The *IGF2* differentially methylated region (DMR) in umbilical cord DNA of 67 newborns was evaluated. Paternal obesity was associated with hypomethylation of the *IGF2* DMR in newborns and thus potential *IGF2* overexpression [55]. This relationship persisted even when controlling for birth weight.

Another aspect of the NEST study examined breastfeeding status in the first year of life and methylation patterns of the *IGF2* gene. Higher methylation at birth was noted at the *H19* DMR in overweight/obese infants compared to normal weight. Higher methylation at the *H19* DMR translates to increased *IGF2* transcriptional activity. Interestingly, this relationship was more pronounced in overweight/obese children who were never breastfed, suggesting that infant feeding practice may be a modifiable factor to reduce obesity risk [56].

Conclusion

The study of IGF-2 levels or alterations in *IGF2* gene expression in relation to fetal and childhood obesity is an emerging area of obesity research. Studies of *IGF2* gene alleles and modifications to the *IGF2* gene seem promising in explaining the contribution of the gene to adiposity. Given that IGF-2 levels vary throughout gestation, understanding changes to the *IGF2* gene that may alter its expression might give us a better understanding of growth-related events occurring in utero. Increasing IGF-2 levels may enhance downstream effects of binding at IGF and insulin receptors as well as impacting placental size and passive fetal nutrient delivery. Collectively, these effects may contribute to overgrowth. As the current data on IGF-2 and obesity is both limited and conflicting, further study is warranted with particular attention to IGF-2 levels throughout gestation, heritable or environmentally mediated changes within the *IGF2* gene, fetal body composition, and markers of childhood obesity such as BMI. A better understanding of these relationships could allow for IGF-2 or changes in the *IGF2* gene to be used as a predictive marker of obesity in children, allowing for earlier counseling and implementation of preventive efforts in those at risk.

Disclosure Statement

The authors have nothing to disclose.

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