Indian Journal of Pediatrics (December 2021) 88(12):1235–1240
https://doi.org/10.1007/s12098-021-03897-0

REVIEW ARTICLE

The Auxological and Metabolic Consequences for Children Born Small for Gestational Age

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Received: 19 May 2021 / Accepted: 12 July 2021 / Published online: 17 August 2021

Abstract

'Small for gestational age' (SGA) is an auxological and not an etiological definition that characterizes children born small based upon low-birth-weight and/or birth-length criteria [≥2 standard deviations (SD) below the mean for gestational age]. Most SGA children exhibit catch-up growth into the normal range within 6 mo of age. Overall SGA children are 4 cm shorter than expected based upon midparental height and being born SGA is a common cause of adult short stature. Recombinant human growth hormone (rhGH) has been shown to improve adult height by 0.9 SDs and is a safe treatment. Surprisingly, a higher rhGH dose (67 µgm/kg/d) did not lead to a greater adult height than a conventional dose (33 µgm/kg/d). At least 85% of SGA children treated through childhood with rhGH achieve a height within the normal adult range. Other long-term consequences for children born SGA include insulin resistance, abdominal adiposity, dyslipidemia, type 2 diabetes mellitus, and metabolic syndrome. Cross-sectional studies have found reduced insulin sensitivity in the neonatal, childhood, and young adult periods. Increased abdominal fat has been shown in preschool SGA children and is more evident in young adults. Increased adiposity markedly accentuates reduction in insulin sensitivity. Many SGA children have suffered from in utero nutritional restriction that leads to long-term growth restriction and adverse metabolic sequelae.

Keywords SGA · Stature · Growth hormone · Metabolism

Definition

For nearly 20 y small for gestational age (SGA) has become the preferred term to describe children born at the lower end of the birth weight spectrum [1]. SGA categorizes infants based upon size at birth using auxological parameters from the growth charts of healthy newborns. SGA is often used as a diagnostic label; however it is simply a descriptive term and does not identify the cause of small birth size.

Historically, small newborns were referred to as having intrauterine growth retardation (IUGR), which implies that the fetus suffered from growth restriction in utero. However, IUGR was commonly misused to describe a small newborn of unknown etiology. In essence, IUGR is a subgroup of small for gestational age, with up to 20% of SGA infants thought to have had some degree of IUGR [2, 3].

Both SGA and IUGR have been defined by a range of auxological birth weight for gestational age criteria, from less than the 10th percentile to −2 standard deviations (SD) below the mean [4, 5]. This renders comparisons across study populations difficult when examining the long-term consequences of infants born SGA.

In 2003, an international SGA consensus group addressed SGA auxological definitions to standardize terminology. Sensibly the SGA definition included birth weight (SGA_W) and length (SGA_L) and also both birth weight and length (SGA_{WL}), set at ≤ −2 SD below the mean for gestational age [1]. One of the main reasons for selecting the more marked end of the birth weight spectrum was to identify a group at significant risk for later long-term short stature and poor growth.

The use of arbitrary auxological cutoff to define a group of children creates the illusion that those above the cutoff do not develop any long-term sequelae. There is abundant evidence to show that as children deviate below from an

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optimal birth size there is an increasing risk of sequelae, notably metabolic sequelae such as insulin resistance as discussed later.

Whatever definition of SGA is used, there will be some children categorized as above the SGA threshold who have suffered in utero nutritional constraint and in contrast up to 22% of SGA children are "constitutionally small" when maternal characteristics are taken into account [6].

There are many diverse causes of an infant born SGA that broadly include maternal, placental, and genetic factors. A constitutionally small infant born to a small mother and/or father is the commonest cause of SGA. The commonest pathological cause of SGA is considered to be placental dysfunction leading to suboptimal in utero nutrition.

Gene mutations in growth or metabolic regulation are very uncommon causes of SGA and typically include a have distinctive phenotype. More common gene polymorphisms such as in the *IGF-I* gene do not occur more frequently in SGA children [7]. Children with Silver–Russell syndrome have a characteristic phenotype and often have an epigenetic mutation involving 11p15 hypomethylation (40%) or maternal uniparental disomy of chromosome 7 (10%) [8, 9]. However, it appears that 11p15 epigenetic mutations are rare in SGA children who do not have Silver–Russell syndrome [10].

Auxology

Short stature in childhood is the most well-studied sequelae of SGA children. Ultimately up to 14% of SGA children become short adults who were more likely to be SGA_L than SGA_W [2, 4].

Rapid linear growth in early infancy is normally seen in SGA infants, with that more than 80% attaining a length in the normal range by 6 mo, further increasing to > 85% by 12 mo of age [2, 5]. Rarely is further catch-up growth seen later in childhood [2].

Conversely, in short SGA children there is lack of early catch-up growth with subsequent short stature in childhood progressing into adulthood [2, 3, 5].

Parents' height reflects genetic height potential which is the most important biological determinant of childhood growth in SGA [2]. SGA is one of the commonest disorders causing short stature in adults. However, across the normal childhood height range SGA children have a height SDS that falls four centimetres below their midparental height SDS [11]. In early childhood shorter birth length is the main influence on SGA catch-up growth. Conversely, throughout the rest of childhood genetic height potential has the greatest influence on growth. Thus, SGA children with taller parents display the highest degree of catch-up growth [12].

A large portion of SGA children are also preterm [13]. In contrast to term SGA children, preterm SGA children commonly exhibit a more delayed pattern of catch-up growth into the normal range [13]. More severe prematurity can extend catch-up growth until 6 y of age with a greater likelihood of short adult stature [14].

Growth Hormone and IGF-I Axis

There are changes that occur in the GH-IGF-I and insulin axes in SGA children that begin in early infancy and evolve into adult life. At birth changes in these axes are thought to be due to reduced nutrition in late fetal life. As typically seen in childhood malnutrition, these changes are consistent with transient GH resistance with elevated serum GH together with diminished IGF-I, IGF-II, and IGFBP-3 levels [15, 16]. The status of these axes quickly changes with the transition to adequate nutrition postnatally. In the neonatal period pulsatile GH hypersecretion occurs [17] and is associated with a switch from low to elevated circulating IGF-I. This suggests that the influence of suboptimal nutritional restricting IGF-I secretion is removed before GH hypersecretion resolves [18]. It is believed that transient GH hypersecretion may initiate typical early catch-up growth.

Further into childhood, there have been contrasting findings reported with both increased and decreased GH secretory profiles [19, 20]. Lower stimulated GH levels have not been found in short SGA children and anecdotally they appear to be higher [19]. The growth response to a given dose of GH treatment appears to be less in SGA than GH deficient or even girls with Turner syndrome suggesting that short SGA children may have partial GH resistance contributing to shorter stature [21]. Consistent with this view higher GH doses are used to treat short SGA children [22].

Studies that have reported serum IGF-I, IGF-II, and IGFBP-3 in short SGA children have been conflicting. Relative adiposity is a key regulator of serum IGF-I with insulin regulating hepatic IGF-I production. Thus, when short prepubertal SGA children are compared to normal prepubertal children matched for age as well as adiposity (weight) prepubertal SGA children had higher serum IGF-I, IGF-II, and IGFBP-3 values [23]. This can be explained through fasting hyperinsulinemia (which occurs as a consequence of reduced insulin sensitivity) in SGA children which is correlated with higher fasting plasma IGF-I levels [24].

Metabolic Sequelae in SGA

A stressful environment during critical periods of fetal development could influence metabolism well into adult life. The intrauterine milieu of the baby is sensitive to

changes in the mother. Intrauterine period is the time for rapid growth including replication, differentiation and maturation of various tissues. Changes in the intrauterine environment could lead to changes and programme the tissues to help improve the survival advantage of the fetus. Changes that would be advantageous during adverse fetal conditions could adversely influence adult health [25].

The Dutch Famine Study [26] demonstrated that exposure to famine (adverse nutrition) at different periods of gestation resulted in varied effects in later life. Initial studies by Barker et al. linked low birth weight to an elevated rate of mortality from ischemic heart disease. Birth weight served as an indirect marker of poor nutrition during intrauterine life in these cohorts [27]. Among these children with low birth weight, the small for gestational age (SGA) infants are well characterized.

Later metabolic consequence of adverse intrauterine milieu is demonstrated as a temporal sequence in SGA infants by alterations in the glucose metabolism from birth through childhood, adolescence and adulthood. A temporal relationship exists between birth weight and insulin sensitivity [28, 29]. Impaired development in fetal life which is manifested as thinness at birth is associated with insulin resistance (reduction in insulin sensitivity) in adult life [29, 30]. Insulin resistance predisposes to several metabolic diseases including type 2 diabetes mellitus [29].

The evolution of insulin resistance starts with a period of hyperinsulinism and hypoglycemia. SGA children are at a risk for hypoketotic hypofattyacidemia, hyperinsulinemic neonatal hypoglycemia [31]. This evolves rapidly into reduction in insulin sensitivity along with a normal capacity to secrete insulin during childhood and progresses by adolescence to features suggestive of the metabolic syndrome and dyslipidemia.

During a Dutch national audit on prevention of neonatal hypoglycemia, SGA was noted to be the most common cause with an odds ratio of 4.9 in comparison with term appropriate-for- gestational-age infants [32]. Hypoglycemia typically occurs early and occasionally persisted for several weeks which is amenable to diazoxide [31]. There are no known mutations responsible for hyperinsulinemic hypoglycemia in these children [31].

Several studies by Barker et al. noted an association of low birth weight with alteration of glucose metabolism in adult life [29]. This led to the theory that proposed a higher risk for type 2 diabetes mellitus in later life for individuals born with a low birth weight [29]. To explore this hypothesis, several studies were undertaken to prove the association between SGA and alteration in glucose metabolism, as SGAs were neonates at the lowest end of the spectrum of children born with low birth weight. The hypothesis was proposed to evaluate the existence of changes in glucose metabolism from childhood as a link to the later risk for metabolic disorders in later life.

Studies were undertaken in young children born SGA to determine if there were any alterations in glucose metabolism to establish the above hypothesis. Infants born SGA demonstrated elevated insulin concentrations, insulin to glucose ratio, total cholesterol, LDL cholesterol and triglycerides even at 72 h of age [33]. Prepubertal term SGA children with a birth weight $< 10^{th}$ percentile had a reduction in insulin sensitivity by 60% along with compensatory hyperinsulinemia when matched to appropriate for gestational age (AGA) children [34, 35].

Among children born AGA and SGA, a progressive reduction in the weight at birth is associated with a progressive reduction in insulin sensitivity [34]. Thus, insulin resistance does not happen only in those of very low birth weight. This change in insulin sensitivity is observed with lower birth weight even within a normal range of birth weight [30]. It happens as a continuum of risk of insulin resistance as the birth weight falls from average. Others studies from various parts of the world have subsequently confirmed these early findings of reduction in insulin sensitivity among SGA children [34–37].

The "thrifty phenotype hypothesis" [38] was proposed by Hales et al. based on epidemiological studies that had linked the reduction in birth weight to later type 2 diabetes mellitus. He speculated that compromised fetal nutrition could make the growing individual nutritionally thrifty and lead to later insulin resistance and deficiency. Glucose regulation was normal, if the undernutrition continued during postnatal life. But, postnatal exposure to overnutrition, exposed defects in β-cell function and insulin sensitivity, ultimately leading to type 2 diabetes [38].

Children born SGA had a reduction in insulin sensitivity along with compensatory hyperinsulinemia to maintain normoglycemia [34]. Furthermore, Veening and colleagues demonstrated that maximal insulin secretory capacity was similar between AGA and SGA prepubertal children using the hyperglycemic clamps [39]. These findings demonstrated the presence of reduction in insulin sensitivity during childhood with normal beta-cell secretion and challenged the Hales thrifty phenotype hypothesis.

Demonstration of fasting hyperinsulinemia at 1 y of age by Soto et al. was another early evidence of altered metabolism due to developmental programming in SGA children [40]. Hofman et al. demonstrated a reduction in insulin sensitivity among prepubertal children who were born SGA compared to prepubertal children born AGA [34].

Among young adults born SGA, hyperinsulinemic euglycemic clamp demonstrated a reduction in insulin sensitivity, together with hypertriglyceridemia and increased truncal adiposity [41]. The above cross-sectional studies suggested that a reduction in insulin sensitivity was present from infancy and persisted through childhood into adulthood where early markers of syndrome X were evident among SGA children.

Some evidence suggested that the reduction in insulin sensitivity was due to reduced peripheral insulin sensitivity as found in young adult males [42]. Evaluation of skeletal muscle biopsies in low-birth-weight individuals exhibited reduced muscle expression of several proteins involved in glucose transport and insulin signaling such as protein kinase C-zeta, the insulin-sensitive glucose transporter Glut-4, and the two subunits of phosphoinositol 3-kinase [43].

The effect of accelerated weight gain among SGA children on insulin sensitivity yielded conflicting results. Most of the studies demonstrated a reduction in insulin sensitivity with accelerated weight gain after correcting for adiposity. Risk for glucose intolerance, type 2 diabetes mellitus and coronary heart disease were higher in children with low birth weight and Ponderal index, along with a childhood "catch-up" in growth [44, 45]. Risk for coronory heart disease in later life were related to the low birthweight in children, who stayed thin till 2 y of age with a rapid gain in BMI through childhood [46]. Twelve of 18 studies that included 763 children in a recent systematic review, noted that accelerated weight gain between birth and later years (7–21 y) was associated with reduced insulin sensitivity [47]. However, the systematic review had not been able to determine if weight gain during a particular period in the postnatal life had greater deleterious effect on insulin sensitivity [47]. Similarly, there were no conclusive findings between rapid postnatal weight gain and lipids in midchildhood [48, 49].

Reduced prenatal growth was linked to later high blood pressure and this effect could be due to insulin resistance [49]. A link had been proposed between low birth weight and vascular development. It had been postulated that there is a deficiency in the synthesis of elastin in the walls of aorta and large vessels of growth retarded foetuses and this could lead to change in the mechanical properties of the vessels and could result in loss of compliance. This could predispose these individuals to a higher blood pressure [50]. Children and young adults born with a low birth weight demonstrated endothelial dysfunction [51]. This could have a bearing on the development of hypertension and diabetes in later life. A study on renal development in growth retarded stillbirths revealed a reduction in the number of nephrons [52]. The levels of inactive renin were lower in those born with a lower birth weight and in the babies who had a smaller abdominal circumference at birth [53]. Lower level of inactive renin was associated with higher systolic and diastolic blood pressures at 50–53 y.

Body Composition

SGA children had lower lean mass during early childhood and increased visceral fat mass compared to AGA children. A small cohort of SGA and LGA children followed up longitudinally had similar BMI and body composition until 4 y of age. At 6 y of age, these SGA children had a higher BMI with a lower lean mass and increased abdominal fat mass principally seen as visceral fat as shown by MRI [54]. A phenotype similar to young SGA children of lower lean but increased fat mass was demonstrated at later ages too.

Mothers had been encouraged to supplement additional calories for SGA children in the past to promote quick weight gain. Evidence now reveals that this practice might be deleterious to infants born SGA. Studies by Singhal and his team had revealed accelerated gain in weight with the supply of nutrient and calorie dense formulas to SGA newborns. This was associated with an increased total body fat at 5 to 7 y of age [37].

Puberty and Gonadal Function

Although puberty onset occurs within the normal age range in SGA boys and girls [55], the cadence of puberty may be accelerated [37, 56]. Evidence suggests 4 to 6 mo earlier onset of menarche [55, 56]. This slightly earlier onset of puberty was noted in SGA females and not males [56]. The pubertal growth spurt, peak-height velocity, and duration of puberty were normal in SGA children [55]. However, the timing of the peak-height velocity occurred earlier in SGA males and females [55].

Multiple studies across the world reported an association between SGA and premature or exaggerated pubarche. These children had higher levels of androgen along with more abundant pubic and axillary hair [57]. Premature adrenarche was indicated by elevated serum levels of DHEAS and/or androstenedione in the absence of premature pubarche. These suggested that subtle alterations in adrenal function happened among SGA children more commonly than was clinically evident [58]. A subgroup of SGA girls had rapid weight gain during childhood followed by premature adrenarche and pubarche prior to the onset of early puberty and early menarche. They had a subsequent elevated risk during their postmenarcheal years for polycystic ovarian syndrome (PCOS) [58, 59]. SGA adolescent girls exhibited biochemical features of PCOS even in the absence of overt clinical features. Non-obese girls born SGA had a tenfold increased incidence of hyperandrogenism, altered LH and FSH, anovulation, and hyperinsulinemia when compared to slim AGA girls [60]. Girls with low birth weight and early 'catch-up' growth had evidence of increased adiposity by 4 y of age. These girls subsequently developed insulin resistance, increased visceral fat, dyslipidemia, increased levels of DHEAS and leptin, reduced levels of sex hormone binding globulin, and adiponectin [61].

Evidence of alterations in the hypothalamic pituitary gonadal axis exist in SGA children [61]. These structural and functional change manifest as reduction in size of testes and ovaries, reduced uterine volume, and hypersecretion of FSH in infancy (suggesting diminished production of inhibin B and oestrogen by gonads) [62, 63]. These studies revealed altered ovarian development among girls and male subfertility (assessed by semen analysis) associated with low birth weight [62, 64].

Authors' Contribution WC and AA contributed equally to the article. WC is the guarantor for this paper.

Declarations

Conflict of Interest None.

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