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SHORT REVIEW

Prematurity and insulin sensitivity

V. Mericq
Institute of Maternal and Child Research, Faculty of Medicine, University of de Chile, Santiago, Chile

ABSTRACT. Nowadays, an increased number of premature infants survive. The medical challenge is to reduce their post-natal morbidities with a special focus towards a decrease in metabolic risks. In this manuscript, we will examine available evidence of perinatal, infancy, and childhood consequences of prematurity on insulin sensitivity and glucose homeostasis. Moreover, we add some recent data on how nutritional intervention could modify these risks.
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INTRODUCTION

Advances in neonatal care have allowed an increased proportion of premature infants of low birth weight (LBW) and extremely LBW to survive. These infants represent a challenge to lower their incidence of post-natal chronic morbidities. Among these, concern has been raised with regard to the association between LBW and increased incidence of metabolic diseases in later life, including obesity, insulin resistance (IR), and others (1, 2). Initial observations were made in retrospective studies of English adults, but later these observations have been replicated in young adults and children with different ethnic backgrounds (3-6). This association has been clearly shown in individuals born at term but small for gestational age (SGA) (4-7). The current working hypothesis to explain the development of the long-term risks after being born with LBW (proxy of prenatal growth restriction) is based on an adaptive response to *in utero* malnutrition interacting with patterns of growth in infancy and childhood, where a decrease in insulin sensitivity (IS) is a hallmark (7, 8). Thus, the cost of catch-up growth (CUG), by definition, accompanied by fast growth may cause long-term consequences (7, 9). This putative association in very LBW (VLBW) premature newborns [birth weight (BW) <1500 g and or gestational age <32 weeks] regardless of gestational age has not been clearly demonstrated (10). Since the advances of neonatal care are recent (3-4 decades) it might be probably too soon to examine the long-term consequences in this regard. In this manuscript, we will examine available evidence of perinatal, infancy, and childhood consequences of prematurity in IS and glucose homeostasis.

IS AND GLUCOSE HOMEOSTASIS DURING THE PERINATAL PERIOD

During the 1st week of post-natal life, infants born prematurely are at risk of abnormalities of glucose homeostasis and glucose/insulin homeostasis has major differences compared to infants. Several ethical restrictions limit research in the perinatal period in these infants. Studies should not be invasive, blood samples should be minimized and withdrawn from peripheral vessels but should allow extrapolating the obtained data to other inaccessible tissues, and lastly the smallest sample of patients should be examined. Al these limitations have somehow been overcome by few kinetics studies using isotopic substances together with the availability of spectrometric mass quantification. In addition, premature infants of VLBW always require parenteral glucose administration.

Glucose production

All available studies have used IV glucose at different rates. In pre-term infants, glucose is continuously produced in spite of glucose IV administration, at similar rates compared to term newborns. However, complete suppression occurs only when glucose concentration reaches 250 mg/dl. This fact contrasts with the adult, in whom "glucose production" is suppressed when this substance is administrated parenterally at a rate similar to or bigger than endogenous production. Indeed, there is a negative correlation between glucose production and BW in pre-term infants. To evaluate whether this effect is related to IS, a hyperinsulinemic euglycemic clamp has been performed in newborns (11). When insulin was administered at rates 0.5 to 4 mU × kg^{-1} × min^{-1} there was a decrease of 41-58% of glucose production compared to pre-insulin administration. This concept is applicable to term and pre-term newborns and has a remarkable contrast when compared to adult response during the clamp. Probably these differences are most likely related, at least in part, to the ontogeny of glucose transporters (glut-2) in liver and pancreatic β-cell.

Hypoglycemia

Controversy exists regarding definition oh hypoglycemiaand therefore the incidence in different reports varies from 7 up to 57%. Battaglia et al. (12) reported cord glucose concentrations to be around 54-108 mg/dl and thus appears safe to target a blood glucose concentration over 60 mg/dl at this period, similar to what is consid-

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Correspondence: V. Mericq, MD, Institute of Maternal and Child Research, Faculty of Medicine, University of de Chile, Santa Rosa 1234, 2° piso, Casilla 226-3 Santiago, Chile.

E-mail: vmericq@med.uchile.cl

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ered for other periods of life. This recommendation is based on studies on pre-term infants where number, frequency or intensity of hypoglycemia was negatively correlated with neurodevelopment. Pre-term infants are at risk of hypoglycemia mainly due to decreased glycogen and fat deposits which occur during the 3rd trimester, mainly after the 34th week of gestation as shown by cord leptin (13). In addition, brain/body proportions are increased and near 90% of glucose utilization is used by this organ. Alternative substrates however are not available in pre-term newborns leaving the brain unprotected to hypoglycemia. Levitsky et al. (14) showed that ketone bodies and non-esterified fatty acids concentrations are decreased in pre-term *vs* term newborns. Glucose sensing is also immature in β cells (15) and could also contribute to the inability of decreasing insulin regulation during hypoglycemia. Hypoglycemia can also occur in pre-term infants as a consequence of transient hyperinsulinism or so-called stress-induced hyperinsulinism defined as persistent neonatal hypoglycemia due to hyperinsulinism that subsequently resolves. The molecular basis of this type of hyperinsulinism is yet unknown, but these patients respond well to diazoxide (16).

Hyperglycemia

Hyperglycemia is the other abnormality in glucose/insulin homeostasis that can be present during the perinatal period in as high as 68% of pre-term infants. This incidence contrasts with 5% encountered in term newborns. As explained above, pre-term infants are unable to suppress glucose production within a large range of glucose and insulin concentrations, insulin secretory response is inappropriate, insulin processing is immature and there is an increased proportion of Glut-1/glut-2 in fetal tissues which limits sensitivity and hepatocyte reaction to glucose/insulin increments during hyperglycemia. In addition, increased concentrations of tumor necrosis factor-α present in intrauterine growth retardation (IUGR) induce(s) IR (11). All the conditions described above induce us to be cautious when assessing IS at this early time after birth in pre-term newborns.

STUDIES OF IS IN SGA VS *APPROPRIATE FOR GESTATIONAL AGE PRE-TERM INFANTS DURING THE PERINATAL PERIOD*

Studies on glucose/insulin abnormalities within the preterm period, considering SGA or appropriate for gestational age (AGA) infants are scarce.

To study whether intrauterine growth restriction is associated with decreased sensitivity to insulin and the effect of glucocorticoid therapy, Leipala et al. (17) studied VLBW pre-term newborn infants (AGA and SGA) at a mean age of 7±3 days. IS was assessed with an abbreviated minimal model with iv glucose. Basal IS did not differ between AGA and SGA, but steroids decreased IS only in the SGA group.

A similar observation was performed in a larger group of pre-term newborn in South Africa (18). SGA infants had higher post-prandial (standardized milk feed) insulin levels at 60 min than AGA neonates despite similar glucose levels. As we have recently described for a term cohort (6), they also found that post-natal growth velocity correlated negatively with BW and IR independently of each other. In a more recent study performed in Beijing, China, Wang et al. studied 296 single newborn [177 males (M),119 females (F)], 76 of them born SGA (37 pre-term, 39 term). They obtained a pre-prandial heel blood sample on day 4 of life. Both full-term and pre-term SGA neonates had higher insulin concentrations, insulin/glucose concentrations than did their gestational age-matched AGA neonates (19).

IS IN SGA VS *AGA PRE-TERM INFANTS DURING CHILDHOOD*

It is well known that LBW newborns are also exposed to stressful conditions postnatally, which are reflected in higher neonatal morbidity and mortality. This has led to the hypothesis that post-natal morbidity may as well contribute to the metabolic modifications observed in LBW children, independently of the adequacy of their BW to gestational age. If early post-natal morbidity is relevant in conditioning long-term metabolic changes, prematurity may be an important confounding factor as well as the patterns of post-natal growth, neither factor has been assessed in historical cohorts studies. We studied 60 VLBW children aged 5.7±0.7 yr, evaluated by a short iv glucose tolerance test (IVGTT). We took advantage of a contemporary cohort of VLWB children born prematurely, who had been closely followed up from birth up to 7 yr in a clinic from a well-defined area in Santiago, Chile. As a consequence of the strong geographical stratification in this city, this was an excellent indicator of socioeconomic homogeneity in our study group. A particular strength of our study was the analysis of early post-natal growth using instant growth rates that are independent of size at birth, which is essential if a separate assessment of the effects of LBW and CUG is desired. These VLBW children had therefore no endocrine bias whatsoever. Twenty of these children were SGA and 40 were AGA. The effects of current body mass index (BMI), BW SD score (SDS), post-natal growth rates, and indicators of post-natal morbidity were evaluated. In this cohort of premature, VLBW children, IUGR rather than LBW was associated with increased fasting insulin. This link was independent of gestational age and other indicators of post-natal stress such as early requirements for ventilator and nutritional support. In addition, fasting and first-phase insulin secretion was related to instant post-natal growth velocity (which is independent of size at birth) which was in accordance with our previous observations in term newborns. Interestingly, at this age, adiposity was the main determinant of IS and insulin secretion (20). Thus, fast growth has a cost in long-term consequences (21, 22) probably at least in part through an acquisition of an altered adipose partitioning, with an increased proportion of trunk fat which can be detected early when an accelerated post-natal weight gain is present (23-26).

Recently experimental evidence for suppressed thermogenesis favoring catch-up in fat during CUG has been reported (27). This suppressed thermogenesis would lead to a redistribution of glucose from skeletal muscle to adipose tissue during catch-up linking CUG and later ap-

pearance of metabolic syndrome (26, 28). It is also noteworthy that early post-natal growth in pre-term infants has been negatively correlated with cord blood leptin (29).

Our findings are in agreement with those by Fewtrell et al. (30) whom in a prospective follow-up of 385 pre-term children at 9-12 yr, with BW<1850 g who found that post-load glucose were negatively correlated with BW independent of gestation and post-natal growth and childhood weight gain was the most important factor influencing insulin concentrations.

Recently, a somehow discordant finding was reported from Hofman et al. in New Zealand (31). They recruited 85 pre-pubertal children 4 to 10 yr of age; 50 of them had been born VLBW (38 AGA/12 SGA), 35 born at term [22 AGA (controls) and 13 SGA], from an endocrine clinic. IS was measured with the use of an IVGTT with paired insulin and glucose determinations. They found that children who had been born with VLBW, regardless of their previous growth *in utero*, had a reduction on IS compared to controls.

The authors commented very little on the interactions between size at birth and early post-natal growth on determining IS, shown to be quite relevant in several recent reports (5, 8, 9, 32). In this regard, it is noteworthy that term SGA children in this study were rather short, as they seem to have been recruited at a Pediatric Endocrinology clinic. This is in contrast with most population-based studies, showing that most (up to 90%) children born SGA, either at term or premature, experience complete CUG before 4 yr of age (33). Therefore, we suggest caution when extending these observations to other populations.

Indeed, in different epidemiological studies the most common growth pattern related to later disease risk is the combination of LBW and subsequently becoming overweight or obese during childhood (34). However, the timing of this "fast growth" is under discussion. Bhargava et al. (35) found that an early "adiposity rebound" during childhood (after 2 yr) even in the absence of overweight or obesity, was associated with a higher prevalence of impaired glucose tolerance and Type 2 diabetes in young adults. However, their data do not rule out that an inappropriately high rate of weight and/or length gain may start even earlier. In the recent study by Leunissen, the period of "detrimental " fast growth in young adults born at term were the first 3 months of life (8).

A similar study in adults subjects born pre-term is lacking. In a preliminary study of 56 children born with VLBW at a mean age of ≈ 7 yr (21 SGA) and normal BMI SDS, we found that total fat mass and trunk fat mass was higher in those born SGA. Interestingly, we also detected a positive association between 6 to 9 months of corrected age weight gain and resting energy expenditure (36).

Detailed observations in contemporary cohorts indicate that the BMI in pre-pubertal children is directly related to the rates of weight gain during early infancy. This also seems to be the case for LBW children, whose CUG seems to put them at risk of obesity and IR in spite of being thinner than normal children up to age 3 yr. In this regard, a study by Lucas et al. (37) observed a higher 32-33 split proinsulin in adolescents born pre-term aged 13-16 yr who had participated of a randomized intervention trial of neonatal nutrition with an nutrient-enriched formula compared to those receiving a low nutrient formula. Identification of those infants showing a rapid post-natal weight gain may help focalize preventive measures aimed at controlling the current epidemics of obesity and its complications.

Nutrition is a key factor in terms of early growth trajectory and could be a modifier on these risks. Trials comparing different nutritional interventions in VLBW premature infants have shown discordant effects on post-natal growth (38-40).

As currently there is no information regarding to the effect of nutrition on long-term body composition and metabolic variables in VLBW premature newborns, we designed a study with the aim of assessing body composition and fasting insulin in those premature infants (no.=560) receiving longer periods (6 months or more) of pre-term formulas [higher protein + docosahexaenoic acid (DHA)] compared to a similar cohort (no.=529) who received these formulas solely during the period admitted in the Neonatal intensive care unit (NICU). The aim of this study was to evaluate growth, body composition [dual energy X-ray absorptiometry (DEXA)] and fasting insulin and proinsulin. A subset of these subjects was included in the body composition and fasting insulin arm of the study. Bone mineral density, content and lean mass were not different at 1 and 2 yr between groups. However, total fat mass (%) was lower by the 2nd yr and trunk fat mass was already lower at 1st and at 2nd yr in the group that received longer periods of pre-term formulas. These body composition changes were accompanied by a decrease in fasting insulin by 1st and 2nd yr. Although long-term follow-up of these children is needed, these results are promising and suggest that pre-term infants fed formulas enriched with DHA may have a better subsequent metabolic profile (36, 41).

DHA, the most important omega-3 fatty acid, is an important component of neural and retinal membranes, and rapidly accumulates in the brain during gestation and the post-natal period. Positive associations have been shown between maternal intake of fish, seafood, and omega-3 fatty acids during pregnancy and/or lactation and visual and cognitive development. In addition to growth and neurodevelopmental effects, DHA has gene-inductor properties which may benefit metabolism. The long-chain n-6 [arachidonic acid (ARA)] and n-3 [DHA and eicosapentaenoic acid (EPA; 20:5n-3)] fatty acids are important biomediators that can affect growth and body composition through diverse mechanisms. In a recent study in rats, the animals were fed diets enriched in carbohydrates (control) or fish oil (rich in DHA). A protective effect of DHA was observed; after 4 weeks, the animals with diets containing fish oil ingested more food calories than with other diets. However, fish oil-fed animals weighed less and had less body fat and liver triglyceride content was lower. Fish oil feeding blunted the normal post-prandial decline in fatty acid degradation genes [peroxisome proliferator-activated receptor (PPAR)-α, mitochondrial carnitin palmitoyl transferase-1 (CPT-1), and acyl-CoA oxidase (ACO)] and blunted the normal post-prandial rise in triglyceride synthesis genes [sterol regulatory element-

binding protein (SREBP)1-c, fatty acid synthase (FAS), stearoyl-CoA desaturase (SCD) 1]. Therefore, the direct post-prandial effect of fish oil ingestion was to decrease the propensity for hepatic triglyceride, decrease total body weight, total body fat, and hepatic steatosis (42).

IS IN SGA VS AGA PRE-TERM INFANTS DURING ADULTHOOD

Two main studies in young adults have been reported. Finken et al. performed a prospective follow-up in 346 subjects from the Project on Preterm and Small-for-gestational-age infants cohort in the Netherlands, in whom fasting glucose, insulin, and C-peptide levels were measured at 19 yr. BW SDS was unrelated to the outcomes. Rapid infancy weight gain until 3 months post term was weakly associated with higher insulin level (p=0.05). Adult fatness was positively associated with insulin and C-peptide levels and homeostasis model assessment of IR (HOMA-IR) (all p<0.001). In addition, rapid infancy weight gain until 3 months predicted higher insulin levels at 19 yr, but the association was weak. Instead, adult obesity strongly predicted higher insulin and C-peptide levels as well as HOMA-IR. The effect of adult fat mass on these parameters was dependent on its interaction with BW SDS. Thus, those individuals who were lean (absolute adult fat mass ≤ median for sex) by 19 yr, independent of their BW, had a similar HOMA, however among those subjects considered obese (absolute adult fat mass > median for sex) those being born with LBW had higher HOMA compared to those born with appropriate weight. In this study, both sexes were shorter and lighter than population reference means while the means for waist circumference and waist-to-hip ratio were greater.

The other large population study was performed in Finland. The authors achieved a recruitment of ≅40% of the invited cohort. One hundred and sixty-three young adults (age range, 18 to 27 yr) with VLBW and 169 subjects who had been born at term and were not SGA were included. Subjects underwent a standard 75-g oral glucose-tolerance test, measuring insulin and glucose concentrations at baseline and at 120 min, blood pressure and serum lipid levels, and in a subset of these subjects they determined body composition by means of DEXA. The 2 groups were similar with regard to age, sex, and birth hospital. As compared with the subjects born at term, the VLBW subjects were shorter (≅5 cm) and had lower BMI (≅2-6%) due to lower lean body mass, a 6.7% increase in the 2-h glucose concentration, a 16.7% increase in the fasting insulin concentration, a 40.0% increase in the 2-h insulin concentration and a 18.9% increase in the IR index determined by HOMA. Adjustment for the lower lean body mass in the subjects did not attenuate these relationships. When separating those VLBW born SGA and AGA, those born SGA had a 7.3% increase in the 2-h glucose concentration and a 20% increase in the fasting insulin concentration. Furthermore, in those VLBW born SGA an increase in 1 SDS change of weight between BW- and corrected age 0 increased their fasting insulin further to 30%. This relationship was not observed in those VLBW born AGA (43). In this latter report VLBW young adults had similar percentage of fat mass, ratio of trunk fat/limb fat and waist-to-hip ratio compared to subjects born at term and AGA, however lean body mass adjusted to current height was 3.3% lower in F and 5.3% lower in M born with VLBW.

It is important to note that this later cohort was born between 1978 and 1985 in Finland and in the former Netherlands cohort was born in 1983; in-hospital feeding practices as well as those after discharge and survival rate have changed dramatically these last decades and their findings with regard to timing of fast post-natal growth determining IS and body composition may not be valid to newer generations.

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