Birth weight and gestational age: Early life management strategy to population health for glucose disorders

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Abstract

Non-Communicable Disease (NCD) including dysglycemia is becoming an epidemic public health issues in many countries around the world. Similarly. Low Birth Weight (LBW) is increasing world-wide as more and more babies being kept alive with advancement of health care. This issues of NCD and LBW is by far more common in developing countries and worse situations occur in certain Asians countries where LBW reaches almost 20 per 100 population live birth.

LBW is associated with a higher risk for the development of diabetes and other metabolic disorders. Those being born Small for Gestational Age (SGA) and of LBW is associated with Type 2 Diabetes Mellitus (T2DM) in a non-genetic manner, and programming of muscle insulin action and signaling represents an early mechanism responsible for this association. Also, insulin secretory abnormalities in LBW may result from appropriate fetal adaptation ("programming") to a suboptimal nutritional state during intrauterine life but ultimately are maladaptive when presented with a high-carbohydrate diet after weaning. With the superimposition of age-related or dietary insulin resistance, insulin secretory responses are inadequate, resulting in progressive glucose intolerance.

The care of maternal health and prenatal care is of paramount importance to improve the birth weight and reduce the rate of LBW and prematurity. Postnatal care is similarly of great importance to further reduce the impact of LBW on non-communicable disease with the burden of obesity and increasing the metabolic demand upon the pancreatic cells.

Introduction

Metabolic syndrome is a constellation of metabolic abnormalities including centrally distributed obesity, decreased high-density lipoprotein cholesterol, elevated triglycerides, elevated blood pressure, and hyperglycaemia. It is associated with the development of diabetes and cardiovascular disease.

Currently, more than 75% of the disease burden in Oman is attributable to non-communicable diseases, with cardiovascular disease as the leading cause of death [1]. The distribution of chronic diseases and related risk factors among the general population is like that of industrialized nations; 12% of the population has diabetes, 30% are overweight, 20% are obese, 41% has high cholesterol, and 21% has metabolic syndrome [1].

Low Birth Weight (LBW) is increasing world-wide as more and more babies being kept alive with advancement of health care. Many of these babies nowadays are born less than 1 kilogram in weight and even less than 750 gram in weight. Although in many developed countries the average birth weight is between 3.5 and 4.0 kg, most developing countries average birth weight is less than 3 kg.

LBW may be due to Intra-Uterine Growth Retardation (IUGR), prematurity, or both; epidemiological studies do not always separate the two conditions [2]. LBW is a key indicator of health status throughout the world (ref). Prematurity is defined as a gestational age of less than 37 weeks. LBW is defined as a birthweight less than 2,500 grams. Babies weighing less than 1,500 grams are categorized as very low birth weight and those less than 1,000 grams as extreme low birth weight. IUGR is defined as a birthweight below the 10th percentile for gestational age [2].

LBW is a surrogate marker of an adverse fetal environment, is associated with development of insulin resistance and Type 2 Diabetes (T2DM), insulin resistance and obesity.

Thrifty hypothesis suggests that T2DM and other various components of metabolic syndrome result from inadequate intrauterine conditions for optimal fetal growth (ref). Several studies have demonstrated a higher risk of diabetes or impaired glucose tolerance in relation to LBW [3]. Despite number of critics, thrifty phenotype has downplayed an important role for genetic factors in the aetiology of T2DM and recently concluded that "environmental, probably nutritional factors operating in early life play a major causative role in T2DM. Barker et al. concluded that T2DM and hypertension have a common origin in sub-optimal development in utero, and that syndrome X should perhaps be re-named "the small-baby" [4]. It is suggested that the association between LBW and diabetes development in adulthood reflects the long-term effects of reduced growth of the endocrine pancreas and other tissues in utero, which may be a consequence of maternal undernutrition.

Epidemiological evidence

Studies in several countries have shown that children who were small at birth have an inability to respond to an oral glucose challenge

[4-7]. Thinness at birth, as measured by a low ponderal index (birthweight/length), is associated with the occurrence of 'insulin resistance syndrome', which includes impaired glucose tolerance, raised blood pressure and disturbed lipid metabolism, in adult life [7-11]. Researchers in the mid-1980s found an inverse relationship between 'syndrome x', which includes T2DM, hypertension, hyperlipidaemia, and birthweight, and renamed it as 'small baby syndrome' [8]. A review of 32 publications revealed a strong relationship between birthweight or thinness at birth, indicated by a low ponderal index and later development of T2DM, and metabolic syndrome [10].

Muscle mass and metabolic syndrome

Skeletal muscle is the most plentiful tissue in the body and the major pool of protein in the body. It transports glucose in an insulin-dependent physiological mechanism by the Glucose-Transporter-type-4 (GLUT4) and contributes in the preservation of serum amino acids concentration. By its mass and energetic requirements, it is fundamental for the systemic metabolic balance (ref). Babies who are thin at birth lack muscle as well as fat, and muscle in adult life is the major site of insulin action [12,13]. It is thought that at some point in middle to late gestation, the thin neonate became undernourished, and in response its muscles became resistant to insulin and, hence, later development of T2DM [9,10,14-16]. Animal studies show that, in an adaptation to the poor nutrition, the expression of hormone receptors does change, where insulin and catecholamines receptors increased but expression of glucagon receptors decreased [17-19]. Skeletal muscle responsible for the most of insulin-stimulated glucose clearance, and flaws in muscle insulin action denote an initial indicator for diabetes risk [20-22]. Healthy population with LBW has reduced muscle mass and hence implying a role for skeletal muscle in the pathogenesis of insulin resistance in LBW.

Also, LBW people display a disproportionately amplified, incomplete fatty acid oxidation and a decreased glucose oxidation, compared with normal birth weight individuals, and hence have an increased risk of developing insulin resistance and T2DM [23-25]. Therefore, the higher amino acid levels in LBW individuals could be a consequence of their reduction in skeletal muscle insulin sensitivity due to overfeeding with a possible increased skeletal muscle proteolysis and/or could potentially contribute to an impaired insulin sensitivity [26-30]. It has been shown that LBW individuals have a higher fasting blood glucose level after the control diet compared with normal birth weight individuals and the increased gluconeogenesis, occurring parallel to an increased hepatic fatty acid oxidation, may contribute to this [29,31].

Pancreatic secretions

Many metabolic studies have demonstrated both glucose intolerance and hyperinsulinemia in LBW individuals [32]. While insulin sensitivity is reduced in few studies of both children and adults, additional studies have emphasized the role of β-cell dysfunction as a key contributor to LBW-associated T2DM [32-34]. Collectively, these data demonstrate the seemingly heterogeneity of LBW-associated diabetes and recommend that both insulin resistance and secretory abnormalities contribute to the final phenotype in humans. Hyperinsulinemia in population of LBW reflects insulin resistance, even with using the less precise homeostasis model assessment or intravenous glucose tolerance modelling approaches [35-38]. Potential contributors to the variability in insulin sensitivity in LBW are likely to include the population under study, methods used for metabolic assessment, the underlying cause of aberrant fetal growth, postnatal

catch-up growth, and other postnatal risk factors, including aging, obesity, and inactivity [38-41].

There are two main principal possibilities when considering the origin of hyperinsulinemia and subsequent glucose intolerance and T2DM [39, 42]. firstly, abnormal insulin clearance despite normal insulin sensitivity and develop progressive glucose intolerance [42-44]. Secondly, abnormalities in β-cell function could also contribute to the early hyperinsulinemia and glucose intolerance [16,30,32,45]. Abnormal β-cell function or mass has been linked to LBW-related metabolic disorders with possibility of either altered β-cell mass or a functional β-cell defect resulting in abnormal glucose-stimulated insulin release [16,32,33,45]. Whether β-cell mass reduction is due to lower insulin gene transcription, biosynthesis, and/or accumulation is still not yet fully understood, but differences in insulin content clearly cannot account for hyperinsulinemia. Instead it points to intrinsic dysregulation of glucose-stimulated insulin secretion [46].

Researchers found that the secretory defect in undernutrition pancreatic islets is initially characterized by inability to modulate insulin secretion relative to ambient glucose, with a secondary decline in glucose-stimulated insulin secretion with aging [32,47]. With age advancement there are more inability to increase insulin secretion to compensate for age-related insulin resistance and thus develop progressive glucose intolerance [36,40,42,48].

LBW people may have glucokinase mutations and this reduced glucokinase expression during fetal life reduces fetal insulin secretion and, therefore, reduces fetal growth [49-51]. Hence, the fetal insulin hypothesis states that, maternal undernutrition results in a low fetal glucose and nutrient milieu, which "programs" (low) fetal glucokinase activity and (high) hexokinase activity to ensure appropriate insulin secretion [32,52,53]. Of course, alterations in expression/function of other key genes that regulate insulin synthesis/secretion and the in vivo environment of undernutrition pancreatic islets may also modulate insulin secretion [32,52-55]. It is likely that the precise mechanisms that contribute to spontaneous LBW are critical in determining the final β-cell phenotype.

The inverse relationship between birthweight and glucose disorders

Al Salmi et al. found that in an affluent Western country with a good adult health profile, birth weight has an inverse relationship with indexes of glycemia, and individuals with LBW were predisposed to higher rates of glycemic dysregulation in adult life [56]. In their study, 4,502 participants with birth weights mean ± SD of 3.4 ± 0.7 kg. They found that FPG, PLG, and A1C were strongly and inversely correlated with birth weight. The odds ratios (95% CI) for high (> 90th sex-specific percentile) FPG, PLG, and A1C were 0.83 (0.71-0.96), 0.74 (0.65-0.84), and 0.81 (0.70-0.94), respectively, for a 1-kg increase in birth weight after adjustment for age and sex. In those with Low Birth Weight (LBW), the risks for having IFG, IGT, and diabetes and for all abnormalities combined were increased by 1.75, 2.22, 2.76, and 2.28, respectively, for women and by 1.40, 1.32, 1.98, and 1.49 for men compared with risks for those with normal birth weight. These trends applied across categories of age and BMI. These associations were independent of Body Mass Index (BMI) and of other factors significantly correlated with glycemic dysregulation [56].

Many researchers have reported the association between LBW and the increased risk of, and the earlier onset of type 1 diabetes during adulthood, giving rise to the "thrifty hypothesis". This hypothesis as

stated earlier proposes that inadequate nutrition programmes the foetus to develop resistance to an insulin-stimulated uptake of glucose in late life [57-62]. This inverse relationship between LBW and, impaired glucose tolerance and elevated serum insulin, occurs across a whole range of ages and in both sexes and racial backgrounds [3,10,37,61-64]. It may be determined by a genetic defect in insulin action that manifests itself in utero as reduced growth, and in later life as an impairment of an insulin-stimulated uptake of glucose. In this scenario it is proposed that the poorly nourished mother essentially gives the foetus a forecast of the nutritional environment into which it will be born. Processes are set in motion, leading to a postnatal metabolism adapted to survival under conditions of poor nutrition. The adaptations only become detrimental when the postnatal environment differs from the mother's forecast, with an overabundance of nutrients and consequent obesity [10].

A U-shaped curve relationship exists between birthweight and, glucose as seen in the Pima Indians and the Nurses' Health Study (NHS) [63,64]. As such, both LBW individuals and heavy birthweight individuals are at higher risk of developing as adult. The heavy birthweight phenomenon has been attributed to gestational diabetes, which by its self is associated with increased risk of in adult off spring [63].

Hertfordshire study

In a study of men in Hertfordshire in 1991, glucose tolerance tests were performed on 64-year-old men for whom birthweight records were available. The proportion of men with impaired glucose tolerance (2-hours (h) plasma glucose 7.8-11.0 millimoles/litre (mM/L)) or (2-hplasma glucose > 11.0 mM/L) steadily increased with decreasing birthweight. This relationship was continuous across the birthweight categories, with those men who were smallest at birth (< 2.5 kg) being nearly seven times more likely to have impaired glucose tolerance than those who were heaviest at birth (> 4.3 kg) [65].

In the same Hertfordshire cohort, researchers found an inverse relationship between birthweight and the current presence of metabolic syndrome [4]. Metabolic syndrome was defined as glucose intolerance (2-h glucose > 7.8 mM/L), systolic blood pressure > 160 mmHg, and a fasting plasma triglyceride concentration equal to or above the median concentration for that population (≥ 1.4 mM/L). Metabolic syndrome increased with decreasing birthweight, so that men with the smallest weight at birth were 18 times more likely to have the metabolic syndrome than those who were heaviest at birth. The prevalence of metabolic syndrome fell from 30% to 6% between those who were small, and those who were heavy at birth [4].

The effect of obesity during childhood

Obesity in childhood has a greater effect on the development of metabolic syndrome than does obesity in adulthood [66]. However, the Helsinki cohort, born 1924-1933, showed that the development of insulin resistance was associated with thinness at birth, and continued thinness in childhood, followed by the development of obesity in adult life [35,67]. The foetal growth restriction leads to a reduced cell number in the endocrine pancreas and subsequent accelerated growth in childhood leads to excessive metabolic demands on the limited cell mass. Men and women, in a Dutch study, exposed to a brief period of intense starvation in utero but who were well nourished as children, had higher plasma glucose concentrations, higher pro-insulin and insulin concentration, and therefore exhibited insulin resistance [41].

Conclusion

LBW is a significant risk factor for T2DM, understanding the pathophysiology of LBW-associated glucose intolerance is important for both prevention and therapy. The care of maternal health and prenatal care is of paramount importance to improve the birth weight and reduce the rate of LBW and prematurity. Postnatal care is similarly of great importance to further reduce the impact of LBW on non-communicable disease with the burden of obesity and increasing the metabolic demand upon the pancreatic cells. Early detection of various metabolic risk factors in this specific group of population is an important strategy from public health perspective to allow early intervention and management.

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