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Birth weight and gestational age: Early life management strategy to population health for cardiac diseases

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Abstract

Non-communicable diseases (NCD) is a leading cause of mortality and morbidity worldwide throughout the globe over the last few decades accounting for more than 50% of total premature mortality. Developing countries bear the worse burden of these NCD. Cardiovascular disease (CVD) is the world's leading cause of mortality, equating to 17.5 million deaths per year, which is projected to increase to 22.2 million deaths per year by 2030. Similarly, low birth weight (LBW) is increasing around the world where most of this prevalence commonly seen in the developing countries but as well as in the well-developed countries where advancement of health care managed to increase the survival of the very LBW babies.

In recent years, there has been great interest in the early development of the fetus and the impact of growth during the gestational period on the development of diseases in later life, and that termed a 'critical period'. Disproportionate growth of different organ systems in utero can occur because different tissues have different critical periods of growth at different times.

Studies have confirmed that there is a significant and specific inverse relationship between birth weight and the risk of CVD in adulthood. LBW, which reflects adverse effects on development in the uterus, contributes to this phenomenon of CVD programming in early life. It is not only the existence or absenteeism of genes that control our destiny, but the way in which gene expression may be eternally transformed by, for example, the pre-natal nutritional environment. Hence, epidemiological findings suggest that the risk of disease in adult life is programmed, and/or imprinted by the environment encountered before where reduced growth before birth is associated with impaired cardiac function.

The epidemiologic evidence clearly points to an inverse association between birth weight and many hemodynamic cardiovascular risk markers. LBW is associated with an adverse metabolic profile later in adulthood that is characterized by higher levels of insulin resistance, triglycerides (TG), and total- and LDL-cholesterol. The is a role of prenatal environmental factors in predisposing the individual to coronary heart disease later in life and, consequently, reemphasize the need for proper prenatal care. These findings emphasize the need for optimum nutrition and medical care during pregnancy. Additionally, timely and more intensive preventive programs, that specifically target various cardiovascular risk factors, are needed in persons born with LBW.

Introduction

CVD is the foremost common cause of mortality world-wide, with almost 18.0 million deaths per year, which is expected to surge to 22.2 million deaths per year by 2030 [1]. Its occurrence and risk factor forms differ broadly across different populations. In Oman, the overall cumulative incidence of CVD was 9.4% with an incidence density of 17.6 per 1000 person-years. Prevalence of poor glycaemic control, hypertension, obesity, dyslipidaemia, albuminuria, and current smoking were 40.0%, 56.3%, 39.0%, 77.3%, 18.7%, and 7.8%, respectively [2]. Barker hypothesis of early origins of adult disease, indicates that adverse prenatal environment stimulates foetal responses that permanently alter the "programming" of many of its physiologic systems, thus predisposing the individual to various diseases throughout post-natal life [3-6]. Cardiogenesis is the development in which the heart is formed from progenitor cells with looping and septation [7,8]. In early gestation, after cardiogenesis, mononucleated cardiomyocytes increase the mass of the heart by hyperplastic growth [7,8]. Then, a transition period upon which a process of a decline in the proportion of mononucleated cardiomyocytes and a corresponding increase in the proportion of cardiomyocytes that are binucleated or polyploid [7,8]. After which, binucleation occurs when mononucleated cardiomyocytes undertake deoxyribonucleic acid (DNA) synthesis and nuclear mitosis without cytokinesis [7,8]. These binucleated cardiomyocytes do not proliferate and subsequent increases in cardiac mass occur via hypertrophy of binucleated or polyploid cardiomyocytes [7,8]. Interestingly, this process begins before birth and complications during pregnancy especially in late gestation may impact on cardiomyocyte endowment [9]. Therefore, any insults to the heart during this developmental transition period can have a lifelong effect, especially as cardiomyocytes begin withdrawing from the cell cycle at around the time of birth and may proceed to pathological later in life and thus, lead to health consequences in adult life [7-9].

Epidemiological studies have proven that that LBW is associated with an increase in CVD. This association is independent of the recognized lifestyle-related CVD risk factors, such as smoking, ethnicity, body mass index (BMI) and socioeconomic grouping.

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Epidemiological evidence

The "foetal origins" hypothesis states that undernutrition in middle to late gestation, which leads to foetal growth, programmes for later coronary heart disease or, most importantly, its risk factors [6]. Many studies have shown a close relationship between geographical differences in mortality from CVD and differences in infant mortality [6,10-12]. Epidemiological data has established that LBW, or intra uterine growth retardation (IUGR), is a risk factor for CVD [5,13-25].

In a cohort of 13,249 English men from Hertfordshire and Sheffield, those who had LBW and remained small at 1 year of age had 3 times the risk of death from CVD than males who were heavier at 1 year of age [26].

Also, researchers found that there is a significant and specific inverse relationship between birth weight and the risk of CVD in adulthood [27-30]. In humans, reduced growth before birth is also associated with altered left ventricular mass [31], with IUGR foetuses having a larger heart relative to their body weight [32]. Left-ventricular-hypertrophy (LVH) in adulthood is also linked with harmful CVD outcomes [33].

A systematic review of 16 observational studies found that a 1 kg higher birth weight being associated with a 10-20% lower risk of subsequent ischemic heart disease [27]. The prevalence of coronary heart disease (CHD) is associated with low infant weight within each social class and in both smokers and non-smokers in men born during 1920-30 in Hertfordshire in England [21].

In the same study of men born in Sheffield showed that individuals who were small at birth were at an increased risk of CVD, and the trends were paralleled by similar trends in its major risk factors, namely hypertension and non-insulin-dependent diabetes [17]. Major coronary risk factors were raised blood pressure, high cholesterol and fibrinogen concentrations, and impaired glucose tolerance, were all associated with impaired early growth independent of social class, smoking, alcohol consumption, and obesity. The Bogalusa Heart Study supports a relationship between birthweight and the later development of several important cardiovascular factors, including insulin resistance, low density lipoproteins (LDL), and blood pressure, in young African-Americans and Caucasians [24]. A meta-analysis showed a significant inverse relationship between birthweight and total cholesterol level [25]. For each 1 kg (2.2 lb) lower birth weight, insulin resistance, TG, total- and LDL-cholesterol increased by 2.3 units, 8.7 mg/dL, 5.4 mg/dL and 4.6 mg/dL, respectively. Moreover, comparing the relationship of birthweight with these outcomes in individuals below and above the 50% percentile of birth weight (3.3 kg) shows that the effects of birth weight on later homeostasis model assessment of insulin resistance (HOMA-IR) and TG levels tend to be stronger in the lower birthweight group.

Birthweight and the arterial system

Intrauterine underdevelopment, as a consequence of premature birth, may be associated with decreased synthesis of elastin relative to collagen in the large arteries, leading to a stiffer arterial system and an increased risk of CVD in later life [34]. The relationship between birthweight and vascular function may result from programming of the vascular wall by foetal nutrition or environment, or it may be a marker for a genetic association between early growth and endothelial function [34,35].

Elastin begins to develop early in foetal life and rates of elastin synthesis in blood vessels increase to a maximum in the perinatal period, thereafter, falling rapidly [35]. There seems to be a critical period during development of the aorta and large arteries when elastin is laid down. Failure to synthesise an adequate amount of elastin during this period is apparently impossible to rectify later (ref). The turnover of elastin is extremely slow and there is no appreciable synthesis in the adult aorta [34]. Therefore, the synthesis of elastin in the aorta and large arteries may be reduced in foetuses with growth impairment, leading to permanent stiffness in these arteries and raised blood pressure in later life [34]. Furthermore, it was found that children with LBW exhibit haemodynamic changes associated with increased large arterial stiffness at an early age [36,37]. These haemodynamic changes may lead to the development of hypertension in later life.

Indirect evidence shows that aortic pulse wave velocity, a measure of the aorta's elasticity, was related to aortic size at birth. In a study of middle-aged men and women, aortic compliance was lower in those with LBW [38]. In addition, prematurity is associated with increased aortic pulse wave velocity and therefore a stiffer aorta, independent of blood pressure [39].

Various range of hormones and signaling pathways determine cardiomyocyte growth. Most importantly insulin-like growth factor (IGF) and renin–angiotensin system (RAS) signaling pathways that play important roles in heart growth [40-42]. In prenatal environment life, the IGF signaling pathway may play an important role in the physiological growth of the heart (both proliferation and hypertrophy) [40,41]. In the hearts of IUGR, there is an increased glucose uptake and metabolic response to insulin to maintain myocardial energy supply and subsequent myocardial function and growth [42]. In the context of LBW, if a switch to the foetal metabolic phenotype in the heart does occur after birth and is permanent, this may be one mechanism leading to increased vulnerability to developing CVD in adult life in individual born with LBW [42-44].

Conclusion

LBW is associated with an adverse metabolic profile later in adulthood that is characterized by higher levels of insulin resistance, TG, and total- and LDL-cholesterol. The is a role of prenatal environmental factors in predisposing the individual to CHD later in life and, consequently, reemphasize the need for proper prenatal care. These findings emphasize the need for optimum nutrition and medical care during pregnancy. Additionally, timely and more intensive preventive programs, that specifically target various cardiovascular risk factors, are needed in persons born with LBW.

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