Available online at ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com
Diabetes & Metabolism 36 (2010) 11–20

Review

Fetal origins of insulin resistance and the metabolic syndrome: A key role for adipose tissue?

T. Meas [a,*,b,c]

[a] *U690, Inserm, hôpital Robert-Debré, 75019 Paris, France*
[b] *AP–HP, Department of Internal Medicine B, Hospital Lariboisière, 75205 Paris cedex 13, France*
[c] *Université Paris-7-Denis-Diderot, 75205 Paris cedex 13, France*

Received 29 August 2009; received in revised form 2 September 2009; accepted 2 September 2009
Available online 7 October 2009

Abstract

For several years now, the epidemiological data have shown an inverse relationship between birth-weight and the development in later life of cardiovascular disease and metabolic disorders. The term "small for gestational age" (SGA) describes a neonate whose birth-weight is two standard deviations (SD) below the reference mean, corrected for gestational age and gender. SGA is associated with increased risks of developing hypertension, insulin resistance and type 2 diabetes. However, the association with an atherogenic lipid profile is less clear. Nevertheless, all of the components of the metabolic syndrome are present. Yet, in spite of the large body of data in the literature, the biological mechanisms underlying this association are still unclear. To explain the association, various hypotheses have been proposed, pointing to the role of a detrimental fetal environment or genetic susceptibility, or interaction between the two, and to the particular dynamic changes in adiposity that occur during catch-up growth. However, not only quantitative, but also qualitative, abnormalities of adipose tissue have been observed, suggesting a critical role of this organ in the development of metabolic complications.

Keywords: SGA; Low-birth-weight; Catch-up growth; Metabolic syndrome; Adipose tissue; Review

Résumé

Contribution de l'environnement intra-utérin au développement de l'insulinorésistance et du syndrome métabolique à l'âge adulte : rôle clé du tissu adipeux ?.

Une corrélation négative entre le poids de naissance et la mortalité cardiovasculaire a été mise en évidence pour la première fois voici bientôt 20 ans. Depuis, de nombreuses études sont venues confirmer ce résultat. Le petit poids de naissance est défini comme un poids et/ou une taille de naissance inférieur(e) à deux écart-types, rapporté pour l'âge gestationnel et selon la distribution de référence. Le petit poids de naissance pour l'âge gestationnel est aussi lié au développement d'une HTA, d'une obésité, d'une insulinorésistance, voire d'un diabète de type 2. L'effet sur le profil lipidique semble plus modeste. Ainsi, les différents composants du syndrome métabolique sont liés à l'antécédent de petit poids de naissance. Plusieurs mécanismes physiopathologiques ont été proposés pour expliquer les liens entre le petit poids de naissance et le développement, à l'âge adulte, de pathologies cardiovasculaires et métaboliques. Le rôle de l'environnement délétère intra-utérin ou celui des gênes de susceptibilité, voire l'association des deux, ont été évoqués. Le rattrapage pondéral, qui survient dans les premières années de la vie, semble largement contribuer à ces observations. Le lien avec l'index de masse corporelle (IMC) au moment de l'observation a été souligné. Le rôle de la croissance du tisse adipeux à la fois durant la période fœtale et postnatale semble déterminant pour le développement ultérieur de troubles métaboliques chez les sujets qui ont présenté un petit poids de naissance. L'adaptation de certains organes durant la vie fœtale pourraient devenir inappropriée une fois la période de restriction passée. Cependant, ces mécanismes restent pour le moment hypothétiques.

Mots clés : Petit poids de naissance pour l'âge gestationnel ; Syndrome métabolique ; Rattrapage pondéral ; Tissu adipeux et composition corporelle ; Revue générale

* Inserm U690, hôpital Robert-Debré, 48, boulevard Sérurier, 75019 Paris, France.
E-mail address: talyphilip@free.fr.

1262-3636/$ – see front matter © 2009 Published by Elsevier Masson SAS.
doi:10.1016/j.diabet.2009.09.001

1. Introduction

The idea that fetal and early life events result in permanent alterations or developmental "programming" was first proposed by Barker et al. and Barker [1,2], following a series of epidemiological observations. In humans, the link between fetal undernutrition *per se* and long-term abnormalities in glucose regulation has been clearly demonstrated in the follow-up of individuals born during the Dutch famine of World War II [3]. Young adults, exposed *in utero* to the famine, demonstrated higher 2-h plasma glucose values after oral glucose challenge than did controls born either before, or conceived after, the famine. Furthermore, exposure to famine during the late gestational period was associated with the highest 2-h plasma glucose levels. Barker et al. [1] found a relationship between the environmental influences that impair growth and development in early infancy, and the risk of ischaemic heart disease. To test this hypothesis, 5654 men born between 1911 and 1930 in six districts of Hertfordshire, England, were traced, and their weight during infancy recorded. Those with the lowest weights at birth and at age of 1 year had the highest death rates due to ischaemic heart disease. Similarly, Hales et al. [4] found a relationship between a reduction in birth-weight and either glucose intolerance or type 2 diabetes. Using a definition of the metabolic syndrome based on the occurrence of glucose intolerance, hypertension and hypertriglyceridaemia, the prevalence of the syndrome—also called "syndrome X"—was six times higher in men aged 65 years who weighed 2.5 kg or less at birth compared with those who weighed 4.5 kg or more [5]. For several years now, many studies in different populations have confirmed these initial findings. Moreover, these studies have confirmed a strong association between low-birth-weight, and insulin resistance and other metabolic disorders.

2. Definition of "small for gestational age" (SGA)

To study the relationship between birth-weight and the development of metabolic disorders later in life, published reports have either considered birth-weight as a continuum or defined SGA as the consequence of a restrictive fetal environment. Traditionally, the term has been used to describe a neonate whose weight and/or crown–heel length at birth is at least two standard deviations (SD) below the mean for gestational age, based on data derived from an appropriate reference population. Some authors also define SGA as a birth-weight or length below the third or the 10th percentiles for gestational age. The term "intrauterine growth retardation" (IUGR) is often used interchangeably with SGA. However, as IUGR implies an underlying pathological process that prevents the fetus from achieving its usual growth potential, the term should be restricted to describing infants whose small size can be attributed to a specific (pathological) cause and whose prenatal growth has been confirmed by intrauterine growth assessments. As the factors influencing intrauterine growth are numerous, only the main causes are presented in Table 1.

Table 1
Factors associated with small for gestational age (SGA) births.

Medical complications	
Preeclampsia	Antiphospholipid syndrome
Acute or chronic hypertension	Anaemia
Antepartum haemorrhage	Malignancy
Severe chronic disease	Uterine abnormalities
Severe chronic infection	Uterine fibroids
Systemic lupus erythematosus	
Maternal social conditions	
Malnutrition	Drug use
Low pregnancy body mass index	Smoker
Low maternal weight gain	Alcohol abuse
Delivery at age < 16 or > 35 years	Illicit drug use
Low socioeconomic status	
Fetal conditions	
Multiple birth	
Malformation	
Chromosomal abnormality	
Inborn errors of metabolism	
Intrauterine infection	
Environmental factors	
High altitude	
Toxic substance use (such as tobacco)	
Placental abnormalities	
Reduced blood flow	Haematoma
Reduced area of exchange	Partial abruption
Infarction	

3. Birth-weight and cardiovascular mortality

The suggestion that coronary heart disease might have its origins during fetal development arose from the similarity of the geographical pattern of death rates among babies in Britain during the early 1900s [6] and the pattern of today's death rates from coronary heart disease. The usual certified cause of death in newborn babies at that time was low-birth-weight. Early epidemiological studies pointed to the possible importance of "programming" for coronary heart disease based on the examination of men and women in middle and later life whose body measurements had been recorded at birth. Altogether, 16,000 men and women born in Hertfordshire between 1911 and 1930 were traced from birth to the present day. Death rates from coronary heart disease were threefold higher in those at the lower end of both the weight range at 1 year of age and the birth-weight distribution (< 8.1 kg) compared with those at the upper end of the weight range at age 1 year (> 12.7 kg) [1].

The association between low-birth-weight and coronary heart disease has also been confirmed by studies carried out in Wales [7] and among women in the United States. Of 80,000 women followed in the US Nurses' Health Study, there was a fall in the relative risk of non-fatal coronary heart disease across the range of birth-weights [8]. An association between low-birth-weight and the prevalence of coronary heart disease was also found in a study carried out in South India [9]. Among Indian men and women aged 45 years or older, the prevalence of heart disease fell from 18% in those who weighed 2.5 kg at birth to 4% in those