Adipose Tissue: A Metabolic Regulator. Potential Implications for the Metabolic Outcome of Subjects Born Small for Gestational Age (SGA)

Arianna Maiorana, Chiara Del Bianco and Stefano Cianfarani

Rina Balducci Center of Pediatric Endocrinology, Department of Public Health and Cell Biology, Tor Vergata University, 00133-Rome, Italy. Address correspondence to: Stefano Cianfarani, e-mail: stefano.cianfarani@uniroma2.it

■ Abstract

Adipose tissue is involved in the regulation of glucose and lipid metabolism, energy balance, inflammation and immune response. Abdominal obesity plays a key role in the development of insulin resistance because of the high lipolytic rate of visceral adipose tissue and its secretion of adipocytokines. Low birth weight subjects are prone to central redistribution of adipose tissue and are at high risk of developing metabolic syndrome, type 2 diabetes and cardiovascular disease. Intrauterine adipogenesis may play a key role in the

fetal origin of the pathogenesis of metabolic syndrome, type 2 diabetes and cardiovascular disease. Therefore, knowledge of the behavior of visceral adipose tissue-derived stem cells could provide a greater understanding of the metabolic risk related to intrauterine growth retardation, with potential clinical implications for the prevention of long-term metabolic alterations.

Keywords: diabetes • SGA • adipose tissue • glucose metabolism • lipids • insulin resistance • low birth weight

Adipose tissue and insulin resistance

Pathophysiology of visceral adipose tissue: the role of free fatty acids

dipocytes are highly specialized cells that maintain whole body energy homeostasis by regulating glucose and lipid metabolism. For a long time, adipocytes have been considered to be an energy depot that stores and mobilizes triglycerides [1]. Recently, adipocytes have also been recognized as an endocrine tissue because of the discovery of several adipocyte-derived molecules, including lipid metabolites and adipocytokines [2].

Adipose tissue contains functionally distinct cellular subtypes, the white adipocyte, devoted to energy stor-

age, and the brown adipocyte, which dissipates energy through thermogenesis. In the rat, brown adipose tissue is the major site of heat production. Brown fat also plays a major role in heat production in the neonates of many mammalian species. Its quantitative contribution to energy metabolism at maturity in large mammals, including humans, is uncertain. The storage of triglycerides and fatty acids in white adipose tissue occurs through the ability of insulin to stimulate significantly both glucose uptake and lipogenesis. Defects in fuel partitioning into adipocytes either because of increased adipose mass or increased circulating free fatty acids, results in dyslipidemia, obesity, insulin resistance and type 2 diabetes [3].

The association between type 2 diabetes and obesity is well established. Several studies have docu-

Figure 1. Action of adipocyte-derived free fatty acids (FFA) on glucose homeostasis. FFAs induce muscle insulin resistance by inhibiting insulin-mediated glucose uptake, and hepatic insulin resistance by affecting insulin-mediated suppression of hepatic glucose output. Chronic exposure to FFAs impairs insulin secretion from β -cells and, in the adipose tissue, reduces insulin-mediated glucose uptake and increases lipolysis. Modified from [44].

mented that the incidence of diabetes rises steeply with increasing body weight [4-6]. The parallel rapid growth of overweight in obese individuals and type 2 diabetes is striking, and has led to the coining of the term 'diabesity' to emphasize the link between these two conditions [7]. Obesity is an insulin resistance state, and both obesity and insulin resistance are risk factors for the development of type 2 diabetes [8, 9]. In addition, the pattern of fat distribution is also an important predictor of insulin sensitivity. Individuals with preferential upper body fat accumulation (android) are more insulin resistant, hyperinsulinemic and dyslipidemic than people with a preponderance of lower body fat (gynecoid) [10, 11].

Increased visceral fat has been shown to be specifically related to insulin resistance. This association has been attributed to the enhanced lipolytic activity of visceral fat cells, with increased delivery of free fatty acids (FFA) into the portal (causing hepatic insulin resistance) and systemic (causing muscle insulin resistance) circulation [12, 13]. Patients with type 2 diabetes are characterized by day-long elevation in plasma FFA concentration, which is not suppressed after meals [14] or in response to insulin [15]. Chronically elevated plasma FFA concentrations cause insulin resistance in muscle and liver [15-17] and impair insulin secretion [18, 19] (Figure 1). Furthermore, depots of fatty acids stored in the form of triglycerides have been found in the muscle [20, 21] and liver [22, 23] of type 2 diabetic patients. The adipocytes of subjects with type 2 diabetes are enlarged cells with diminished capacity to store fat. When adipocyte storage capacity is exceeded, lipids 'overflow' into muscle and liver and possibly into the

β -cells of the pancreas [8]. This ectopic fat deposition in muscle and liver has been referred to as one element of lipotoxicity [18, 24-26].

Muscle insulin resistance results in decreased glucose uptake [27] and consequently in impaired glucose oxidation and glycogen synthesis [8, 28]. In the liver, insulin resistance results in the impaired ability of insulin to suppress hepatic glucose production (HGP) [27-29] (Figure 2).

Increased intramyocellular triglyceride content is associated with impaired glucose tolerance and type 2 diabetes and is a better predictor of impaired insulin

action than visceral adiposity [30]. Ectopic fat deposition leads to insulin resistance, as the intracellular metabolites of triglyceride metabolism interfere with insulin signaling, glucose transport and glycogen synthesis in muscle, and augment hepatic gluconeogenesis. In cases of dysfunctional adipose tissue, which is insulin resistant with a limited ability to store the energy excess, the triglyceride surplus is deposited in liver, skeletal muscle, heart and visceral adipose tissue [7].

Subjects born small for gestational age (SGA) are prone to central redistribution of adipose tissue and are at high risk of developing insulin resistance, type 2 diabetes, metabolic syndrome and cardiovascular disease [31].

The role of adipocytokines

Adipose tissue produces a wide variety of signaling molecules involved in inflammation, food intake and insulin sensitivity, which are known as adipocytokines. In type 2 diabetes, this adipocyte function is defective: fat cells, particularly from visceral adipose tissue, produce excessive amounts of proinflammatory, insulin resistance-provoking molecules and undersecrete insulin-sensitizing cytokines [30, 32, 33].

There is increasing evidence to suggest that chronic inflammation, insulin resistance, type 2 diabetes and atherosclerosis represent different stages of the same process. Release of $\text{TNF-}\alpha$, IL-8 and IL-10 by adipose tissue from individuals with a BMI of 45 kg/m^2 is greater than in subjects with a BMI of 32 kg/m^2 [34]. The discovery of high circulating levels of several acute-phase proteins and inflammatory cytokines has led to the view that obese individuals are characterized

Figure 2. FFA action on liver (A), muscle (B) and β -cells (C). **A:** In the liver, FFAs increase lipid oxidation and accumulation of acetyl CoA. Acetyl CoA stimulates the rate-limiting enzymes for gluconeogenesis eventually leading to increased glucose output. Finally, elevated plasma FFAs inhibit the insulin signal transduction system [24, 113, 114]. **B:** In muscle, FFAs reduce glucose oxidation by affecting the redox potential of myocytes and inhibiting key glycolytic enzymes. Furthermore, FFAs increase IRS-1 serine phosphorylation, through activation of protein kinase C, thus inhibiting insulin signaling. Finally, ceramide accumulation interferes with glucose transport and inhibits glycogen synthesis via inhibition of protein kinase B [24, 115-117]. **C:** In the pancreas, lipotoxicity is an important cause of β -cell dysfunction [18, 24, 118]. If short-term elevation (e.g. after a meal) of plasma FFAs enhances insulin secretion [119], long term exposure to FFAs (>48 hours) impairs insulin secretion and eventually leads to β -cells apoptosis [120, 121]. Increased formation of ceramides from accumulated acetyl CoA augments the nitric oxide formation that causes apoptosis of β -cells [118]. This has been demonstrated *in vitro* in human β -cells incubated with FFAs [122], and *in vivo* in rodents [123]. FFA: free fatty acids. IR: insulin receptor. PEPCK: phosphoenolpyruvate carboxyl kinase. G6PD: glucose-6-phosphatase. NO: nitric oxide. Acetyl CoA: acetyl coenzyme A. PKB/Akt: protein kinase B. IRS-1: insulin receptor substrate-1. MMP: mitochondrial membrane potential.

by a state of low-grade inflammation which links obesity to insulin resistance and the metabolic syndrome [3].

Twenty different adipocytokines have been identified so far and are classified into three groups: 1) cytokines produced mainly in white adipose tissue (e.g. leptin, resistin); 2) cytokines produced exclusively by adipocytes of white adipose tissue (e.g. adiponectin) and 3) cytokines produced primarily in other tissues or

organs with simultaneous adipose tissue production (e.g. TNF- α) [35]. Adipocytokines may be even classified according to their putative physiological role into two groups: 'insulin resistance-inducing factors' such as resistin, TNF- α , IL-6, PAI-1, angiotensinogen, adipsin, acylation-stimulating protein (ASP) and retinol binding protein-4 (RBP-4) and 'insulin-sensitizing factors' such as adiponectin, leptin [35], visfatin [36] and omentin [37] (Table 1).

The metabolic effects of the adipocytokines are probably mediated by a common pathway involving the activation of 5'AMP-activated protein kinase (AMPK) that represents a sensing mechanism of the energy status of the cells. The activation of AMPK increases β -oxidation and decreases fatty acids esterification to triglycerides reducing accumulation of lipids in skeletal muscle, liver and other tissues [3].

Adipocytokines in children born small for gestational age

Low birth weight has been associated with increased risk of developing insulin resistance, type 2 diabetes and cardiovascular diseases in adulthood. The thrifty phenotype hypothesis [38] suggests that the fetus adapts to an adverse intrauterine environment by diverting limited nutrients to favor the survival and development of vital organs, such as the brain, at the expense of growth. Important metabolic pathways would be permanently programmed during fetal life, leading to metabolic disturbances in adulthood [31, 39]. There is evidence suggesting that the degree of weight gain

and catch-up growth in BMI in postnatal life correlate with insulin resistance [40-43].

Leptin

Leptin, the *ob* gene product, is primarily produced and secreted by mature adipocytes and binds to its receptors in the hypothalamus. Leptin serves as a major 'adipostat' by repressing food intake and promoting

energy expenditure. Leptin secretion correlates with adipose tissue mass and nutritional status, and is greater from subcutaneous than visceral adipose tissue [3]. High leptin levels in obese individuals are thought to be a consequence of leptin resistance. Leptin effects, particularly on energy intake and expenditure, are mediated via hypothalamic pathways, but leptin also exerts a direct action on peripheral tissues including muscle and endocrine pancreas [3] (Figure 3).

The existence of an 'adipo-insular axis', describing the insulin promotion of leptin secretion through activation of *ob* gene transcription has recently been proposed. Leptin, in turn, is able to inhibit insulin release (Figure 4) through central and direct action on β -cell insulin synthesis [44, 45] (Figure 3). Consistent with this model, ablation of leptin receptor from β -cells results in enhanced basal insulin secretion and fasting hypoglycemia [46].

In SGA children, increased leptin levels have been reported in cord blood [47] and in the first year of life, independently of BMI [48]. High serum leptin values with a loss of the regulatory effect of BMI and gender, suggest that SGA children develop an adaptive leptin resistance beneficial for their catch-up growth [48]. Nonetheless, Martinez-Cordero *et al.* found lower cord blood leptin levels in SGA than adequate for gestational age (AGA) infants [49]. Furthermore, in the Hague-nau study, leptin levels were found to be decreased in young adults

Table 1. Adipocytokines and their effects on metabolism

Adipocytokine	Production site	Effect on glucose metabolism	Other effects
Leptin	Adipose tissue, placenta	Insulin sensitivity	↓ Food intake. ↑ Energy expenditure. ↑ Immunocompetence, phagocytic activity, proinflammatory cytokine production by phagocytes. ↑ Platelet aggregation, arterial thrombosis, angiogenesis. ↑ Proliferation and migration of vascular smooth muscle cells, role in reproductive function.
Adiponectin	Adipose tissue	Insulin sensitivity	Antiatherogenic properties, inhibition of adhesion of monocytes to endothelial cells, inhibition of macrophage transformation into foam cells. ↓ Triglycerides and LDL. ↑ HDL.
Visfatin	Visceral adipose tissue, bone marrow, liver, muscle	Insulin sensitivity	↓ Glycemic levels. Induction of adipocytic differentiation and accumulation of triglycerides in pre-adipocytes. Potentiation of pre-B colony formation.
Omentin	Visceral adipose tissue, stromal vascular fraction*	Insulin sensitivity	↑ Insulin-stimulated glucose uptake.
TNF- α and IL-6	Adipose tissue, stromal vascular fraction*, macrophages	Insulin resistance	↑ Inflammation and atherogenesis (TNF- α). ↑ Inflammation, ↓ food intake, ↑ hypertriglyceridemia (IL-6).
Resistin	Immune cells, adipose tissue, pre-adipocytes	Hepatic insulin resistance	↑ Inflammation
ASP and adipsin	Adipose tissue	Insulin resistance	↑ Deposition of lipids and triglycerides in adipocytes.
PAI-1	Visceral adipose tissue, stromal vascular fraction*	Insulin resistance	↑ Microthrombification and atherosclerosis.
RBP-4	Adipose tissue	Insulin resistance	

Legend: * Stromal vascular fraction: pre-adipocytes, fibroblasts, endothelial cells, smooth muscle cells, pericytes, monocytes and macrophages.

Figure 3. Central and peripheral actions of leptin. In the hypothalamus, leptin activates neurons located in the arcuate nucleus which express the neuropeptide precursor proopiomelanocortin (POMC) leading to a reduction in food intake and increased energy expenditure [124]. The inhibition of food intake is due to the repression of orexigenic pathways such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the activation of anorexigenic pathways such as proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART). The food intake-suppressing effects of leptin could be exerted through melanocortin MC4 receptor signaling, by oxytocin neurons which project from the paraventricular nucleus of the hypothalamus into the nucleus of the solitary tract [44, 125]. In muscle, leptin activates 5'AMP-activated protein kinase (AMPK) both directly and indirectly through the activation of hypothalamic-sympathetic axis [126]. AMPK inhibits acetyl CoA carboxylase-1 (ACC1), a key enzyme of the *de novo* fatty acids synthesis. The inhibition of ACC1 leads to reduced intracellular levels of malonyl CoA [3], the major substrate for long chain fatty acid synthesis that also suppresses fatty acid oxidation by inhibiting carnitine palmitoyltransferase (CPT-1) and acts as a signal molecule in appetite regulation [127-129]. Thereafter, fatty acids are allowed to enter the mitochondria where they undergo β oxidation [3]. Ultimately, leptin promotes fatty acid oxidation and reduces ectopic fat accumulation in non-fat tissues, increasing insulin sensitivity [3, 130]. Finally, the suppressive effect of leptin on insulin production is mediated by both the autonomic nervous system and direct actions via leptin receptor on β -cells [44].

born SGA, even after correction for gender, BMI and hyperinsulinemia [31]. This could be due to a greater adiposity in adults born SGA.

Adiponectin

Unlike the other adipocytokines, adiponectin levels correlate inversely with body mass [50, 51]. Recent studies have shown that insulin reduces levels of adiponectin mRNA in a dose- and time-dependent way [52]. Also β -adrenergic agonists [53] and glucocorticoids inhibit adiponectin gene expression and secre-

tion, suggesting that decreased adiponectin production could play a role in catecholamine- and glucocorticoid-induced insulin resistance. In contrast to most adipocytokines, adiponectin expression and serum concentrations are not increased but reduced in a variety of obese and insulin resistant states. In obese rats, a reduction of adiponectin mRNA is present only in the visceral tissue [54]. A reduction in body weight achieved by food restriction is capable of increasing adiponectin mRNA levels in visceral adipose tissue [54]. Human adiponectin gene expression is lower in

the visceral than in the subcutaneous adipose tissue of lean subjects [55]. Even in adipocytes differentiated *in vitro* from precursor mesenchymal cells, adiponectin expression is lower in visceral adipocytes than subcutaneous adipocytes [56].

Figure 4. The adipo-insular axis. The effect of leptin on insulin levels is due to the inhibition of proinsulin synthesis by both central actions and direct actions on β -cells [45]. In turn, insulin plays a crucial role in the regulation of leptin gene expression in white adipose tissue. A candidate transcription factor, adipocyte determination- and differentiation-dependent factor 1/sterol regulatory element binding protein 1 (ADD1/SREBP1), links changes in insulin levels to *ob* gene expression in mice [131]. ADD1/SREBP1 expression increases after treatment with insulin and transactivates the leptin gene. Conversely, as fat stores increase, rising plasma leptin concentrations would reduce insulin levels, diminishing the formation of adipose tissue.

Several studies have examined human adiponectin gene expression in the adipose tissue of obese subjects, but the results have been inconsistent. Some reports found a reduction in mRNA adiponectin in subcutaneous adipose tissue [57, 58], or in both subcutaneous and visceral adipose tissue depots [55]. Nonetheless, there is an inverse correlation between serum adiponectin and BMI, and individuals with high adiponectin concentrations are at lower risk of developing type 2 diabetes [59].

The adiponectin gene is located on chromosome 3, very close to the diabetes susceptibility locus, and plays a role in the development of type 2 diabetes [60]. Adiponectin levels inversely correlate with a risk of type 2 diabetes. Administration of adiponectin causes glucose-lowering effects and ameliorates insulin resistance in mice [61, 62]. In addition, adiponectin has anti-atherogenic properties, inhibiting monocyte adhesion to endothelial cells and macrophage transformation into foam cells *in vitro* [63].

We previously reported significantly reduced adiponectin levels in SGA children [60]. Adiponectin was inversely related to height, corrected stature, weight and BMI and directly related to birth weight [60]. In subsequent studies, adiponectin has been reported to be reduced [31, 64, 65], unchanged [49, 66, 67] or increased [67, 68] in SGA subjects.

Resistin

Resistin is a protein expressed in preadipocytes undergoing differentiation [69]. In patients with type 2 diabetes or obesity, both resistin levels and resistin expression in fat cells are increased [66, 70], correlating with hepatic, but not muscle, insulin resistance [71]. In humans, the major source of resistin is the immune cells rather than the adipocytes [68, 72], resistin being a potent inflammatory agent [73]. Insulin inhibits resistin expression in adipocytes [74, 75]. Therefore, the elevated basal plasma resistin levels found in patients with type 2 diabetes [76, 77], despite increased insulin concentrations, may be the result of adipocyte insulin resistance. Resistin inhibits the phosphorylation of hepatic AMPK, decreasing β oxidation and increasing fatty acid esterification in triglycerides, and eventually leading to lipid accumulation [78]. Resistin levels have been reported to be reduced in short SGA children [79].

Tumor necrosis factor- α

TNF- α is implicated in insulin resistance as follows. TNF- α is overexpressed in adipose tissue in obesity and affects insulin signaling by modulating insulin receptor substrate-1 (IRS-1) function via serine phosphorylation [80]. It also affects GLUT4 expression [81], and reduces adiponectin expression in adipose tissue [82]. Finally, it stimulates lipolysis and activates the inflammatory pathways [83]. TNF- α knockout mice do not undergo the development of insulin resistance induced by a high-fat diet, suggesting a role for

this cytokine in mediating FFA-induced insulin resistance [84].

In SGA subjects, Jaquet *et al.* demonstrated an association between higher fasting insulin-to-glucose ratios and polymorphism in TNF- α /-308A [85]. Results for fasting insulin concentration and insulin excursion under OGTT were comparable [85]. These results were subsequently confirmed [86], suggesting that adipose tissue plays a key role in the interaction between intrauterine environment and genetic predisposition in the development of insulin resistance.

In conclusion, data on the adipocytokines in SGA subjects are still contradictory and inconclusive (Table 2).

Fat partitioning and lipolysis

Obese patients with an excess of visceral adipose tissue have elevated plasma C-reactive protein concentrations associated with elevated IL-6 and TNF- α lev-

els and reduced adiponectin concentrations [7]. Expanded visceral adipose depot not only leads to altered NEFA metabolism but also to a proinflammatory profile that might contribute to the insulin resistance and altered glucose homeostasis in visceraally obese patients.

In addition, the excess of intra-abdominal fat may represent a marker of the relative inability of subcutaneous adipose tissue to act as an 'energy sink' in a calorie surplus state because of excess energy intake and/or reduced energy expenditure. This would result in ectopic fat deposition in liver, skeletal muscle, heart, β -cells and even visceral adipose tissue [7].

Transgenic fatless mice show liver and muscle insulin resistance and eventually develop diabetes [87]. Surgical implantation of adipose tissue in these mice improves liver and muscle insulin sensitivity [88]. Mice with implantation of subcutaneous adipose tissue in the intra-abdominal cavity show reduced weight, improved insulin sensitivity, reduced body fat percentage,

reduced fat mass, reduced adiponectin and leptin [89]. In humans, the severe insulin resistance found in patients with lipodystrophic conditions [90] is also consistent with the role of subcutaneous adipose tissue as a depot buffering the energy excess [91]. Therefore, visceral obesity may also be a marker of defective fat partitioning between adipose tissue, skeletal muscle, liver and heart. There are some differences in the mechanism of accumulation and/or metabolism between visceral and subcutaneous adipose tissue [92].

In db/db mice, four weeks of beta 3-adrenoceptor agonist administration decreased body weight gain and reduced white fat [93]. The Iwao study, using the microdialysis technique in Wistar rats, showed that the lipolysis induced by isoproterenol (a β -adrenergic agonist) is higher in mesenteric than in abdominal subcutaneous adipose tissue at all

Table 2. Adipocytokines in SGA subjects

Adipocytokine	Occurrence	Study
Leptin	↑ in cord blood	Shekhawat <i>et al.</i> [47]
	↑ 1 st year of life	Jaquet <i>et al.</i> [48]
Adiponectin	↓ in cord blood	Martinez-Cordero <i>et al.</i> [49]
	↓ in young adults	Levy-Marchal <i>et al.</i> [31]
	↓ in pre-pubertal children	Cianfarani <i>et al.</i> [60]
	↓ in young adults	Levy-Marchal <i>et al.</i> [31]
	↓ in first two years of life	Iniguez <i>et al.</i> [64]
	↓ in dried blood spots of newborns	Klamer <i>et al.</i> [65]
Resistin	Normal in adolescents	Ibanez <i>et al.</i> [66]
	Normal in cord blood	Martinez-Cordero <i>et al.</i> [49]
	Normal in pre-pubertal children	Evangelidou <i>et al.</i> [67]
	↑ in pre-pubertal children	Evangelidou <i>et al.</i> [67]
TNF- α /-308A polymorphism	↑ in pre-pubertal children	Lopez-Bermejo <i>et al.</i> [68]
	↓ in pre-pubertal short, SGA children	Willemsen <i>et al.</i> [79]
IL-6, PAI-1, angiotensinogen, adipsin, ASP, RBP-4, visfatin, omentin	Association with higher fasting insulin-to-glucose ratio in young adults	Jaquet <i>et al.</i> [85]
	Association with prenatal growth and postnatal insulin resistance	Casano-Sancho <i>et al.</i> [86]
IL-6, PAI-1, angiotensinogen, adipsin, ASP, RBP-4, visfatin, omentin	No data on SGA subjects	

isoproterenol concentrations, while basal lipolysis was identical in the two depots [94].

Omental fat has been reported to be relatively resistant to insulin suppression of lipolysis *in vitro* and sensitive to β 3-adrenergic stimulation of lipolysis [95]. *In vivo* studies confirmed that omental adipose tissue is insulin-resistant, even if it extracts one fourth of the insulin passing through. The non-suppressible omental lipolysis in the postprandial state could explain why abdominal obesity is strongly associated with hepatic insulin resistance, since elevated plasma FFA are able to reach the liver [96].

SGA and visceral adiposity

Reduced fetal growth is associated with increased risk of developing insulin resistance, metabolic syndrome or one of its components (hypertension, dyslipidemia, impaired glucose tolerance and type 2 diabetes) and cardiovascular disease in adulthood [97-100].

Insulin resistance has also been detected in young adults and children born SGA [101-105], even in early life [106]. Metabolic syndrome has been found in young adults born SGA: in the Haguenau cohort, at 22 years of age 2.3% of individuals born SGA were affected by the metabolic syndrome compared with only 0.3% in the AGA group [31].

Recent observations emphasize that not only fetal growth but also early postnatal life is critical for the development of insulin resistance and metabolic syndrome. SGA children who experience catch-up growth in childhood are at risk of metabolic consequences. A longitudinal study of a Finnish cohort reported that the highest death rate from coronary heart disease occurred in boys who were thin at birth but whose weight caught up so that they had an average or above average body mass from the age of 7 years [107].

The Hertfordshire study group has recently demonstrated in a case-control study of 32 men of 64-72 years old with a low or high birth weight using dual-energy X-ray absorptiometry (DXA) that, after adjustment for weight and height, the low birth weight group had a higher percentage body fat and fat mass, but lower fat-free soft tissue, muscle mass and muscle-to-fat ratio. Lifelong differences in body composition and fat distribution between the low and high birth weight groups are consistent with programming in early life [40].

Other surveys have shown that catch-up growth in BMI is associated with higher fasting plasma insulin concentration, insulin resistance, and increased total and LDL cholesterol in childhood [41], and correlates with adiposity [43]. SGA children who experienced

catch-up growth have a redistribution of fat tissue. Ong and colleagues found that SGA children who showed catch-up growth between zero and two years were fatter and had more central fat distribution at five years than SGA children without catch-up growth [108].

By using DXA, Ibanez *et al.* showed that SGA children exhibit greater accumulation of total body and abdominal fat than AGA children between the ages of 2 and 4 years, despite having already completed their catch-up growth between birth and 2 years of age [109].

In the Haguenau cohort [31], BMI catch-up growth

Figure 5. Adipocytic differentiation of adipose-derived stem cells. Cells grown in adipogenic medium after two weeks assume a rounded shape and lipidic droplets in the cytosol that stained positively with Oil-Red-O, lipid dye.

was significantly related to insulin resistance and metabolic syndrome. However, individuals who experienced greater catch-up were not as obese as young adults, suggesting that fat distribution is more crucial than weight [31]. It has been shown that, after weight loss (chronic diseases, famine, voluntary slimming, fetal or neonatal growth retardation), the subsequent catch-up growth induces excessive fat deposition during nutritional rehabilitation with a disproportionate rate of fat deposition relative to lean tissue recovery. There is an exacerbated suppression of energy expenditure and increased body fat gain during refeeding on a high-fat diet [110-112]. Body fat has a greater energy density and lower energy cost in terms of synthesis/maintenance than proteins. It would provide the organism with a greater capacity to rebuild rapidly an

efficient energy reserve, and hence to optimize its survival capacity in the face of recurrent shortage of food [110].

Intrauterine regulation of adipogenesis may be an important mechanism involved in the fetal origins of diabetes and cardiovascular diseases. Studying the differentiation of visceral adipose tissue in SGA children would help to unravel whether a fetal programming of adipogenesis is responsible for the high risk of developing metabolic syndrome in adulthood. Adipocytic mesenchymal stem cells retain the capacity to differen-

tiate into fat cells that maintain human-specific adipocyte characteristics (Figure 5).

Adipose-derived stem cells (ADSC) could be more prone in SGA subjects to differentiate into a functionally different visceral adipose tissue after birth. The study of the differentiation capacity of visceral fat could help to understand the mechanisms involved in the pathogenesis of metabolic syndrome. Interventions aimed at normalizing fat partitioning in childhood could prevent insulin resistance and metabolic syndrome in subjects born small for gestational age.

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