Adipose Tissue Plasticity in Catch-Up–Growth Trajectories to Metabolic Syndrome

Hyperplastic Versus Hypertrophic Catch-Up Fat

Abdul G. Dulloo

In the mid-1980s, at a time when the concept of syndrome X was being introduced by Reaven (1) to draw attention to the cardiovascular risks associated with insulin resistance and compensatory hyperinsulinemia, Tanner (2) was emphasizing a fundamental property of human growth as a target-seeking function:

> Children, no less than rockets, have their trajectories, governed by control systems of their genetic constitution and powered by the energy absorbed from the environment. Deflect the child from its natural growth trajectory (by acute malnutrition or a sudden lack of a hormone), and a restoring force develops, so that as soon as the missing food or the absent hormone is supplied again, the child hastens to catch-up toward its original growth curve. When it gets there, the child slows again, to adjust its path onto the old trajectory once more. How the child does this we do not know.

What was also unknown (and unforeseen) then was that the "restoring force" that drives catch-up growth—long viewed as an essential feature of recovery from the deleterious effects of poor growth on development and health—could emerge as a major risk factor for disease entities of syndrome X, now more commonly known as the insulin resistance syndrome or metabolic syndrome.

There is now compelling evidence, from both epidemiological and clinical studies, that suggests that people who had low birth weight (often a marker for fetal growth constraints) or who showed reduced growth rate during infancy and childhood, but who subsequently showed catch-up growth, have higher susceptibility to abdominal obesity, glucose intolerance, type 2 diabetes, or cardiovascular diseases later in life (3–7). The risks for later obesity and type 2 diabetes seem particularly high when catch-up growth occurs early in postnatal life (4,6,7)—a pattern of accelerated growth that is common in individuals born small for gestational age. Independently of the timing of catch-up growth, however, the dynamic process of catch-up growth is characterized by a disproportionately faster rate of fat deposition relative to that of lean tissue, with this phenomenon of preferential catch-up fat intimately associated with hyperinsulinemia (8,9). The development of insulin resistance interlinked with catch-up fat could thus be an early feature of the mechanisms by which catch-up growth confers increased risk for metabolic syndrome later in life. Of central importance to our understanding of the pathophysiology of catch-up growth, therefore, is the issue of whether (and how) processes that regulate fat storage during catch-up fat may lead to a state of insulin resistance and impaired glucose tolerance.

From a standpoint of systems physiology, three fundamental autoregulatory control systems could be implicated in preferential catch-up fat: compensatory hyperphagia, an increase in fat mass at the expense of lean body mass, and an increase in metabolic efficiency, i.e., energy conservation mechanisms operating through suppressed thermogenesis and embodied in the concept of a thrifty energy metabolism. The fact that the phenomenon of preferential catch-up fat persists in the absence of hyperphagia or altered lean body mass (9,10) underscores a central role for suppressed thermogenesis as a fundamental physiological reaction to growth retardation and consequential body fat depletion or delayed adipose tissue development. It has been proposed (8,9) that because skeletal muscle is a major site for both thermogenesis and insulin-mediated glucose disposal, a reduction in muscle metabolic rate will result in diminished glucose utilization and glucose sparing, thereby leading to compensatory hyperinsulinemia. As depicted schematically in Fig. 1, this in turn would serve to redirect the spared glucose toward de novo lipogenesis and fat storage in adipose tissue. Various features of this muscle-adipose glucose redistribution hypothesis are supported by studies conducted in a rat model of postweaning semistarvation and refeeding in which an enhanced metabolic efficiency for catch-up fat during catch-up growth was exhibited (10–13). Whether such a thrifty catch-up–fat phenotype can be programmed or imprinted in response to catch-up growth, and, hence, long lasting so as to continue operating beyond the phase of catch-up growth, is not known. However, studies in men born small for gestational age are consistent with key components of the model presented in Fig. 1, namely, the existence of a state of suppressed thermogenesis as judged from their lower preprandial and postprandial resting energy expenditure, even after adjustments for weight, height, lean tissue mass, or organ size (14), and diminished muscle PI 3-kinase signaling (15)—a pathway that cross-links insulin signaling and thermogenesis in skeletal muscle (16).

In this issue of *Diabetes*, Isganaitis et al. (17) point to additional mechanisms, centered on perturbations in white adipose tissue plasticity, that could modulate the impact of a programmed thrifty catch-up–fat phenotype on glucose homeostasis. The studies were conducted in mice

From the Institute of Physiology, University of Fribourg, Fribourg, Switzerland.
Corresponding author: Abdul G. Dulloo, abdul.dulloo@unifr.ch.
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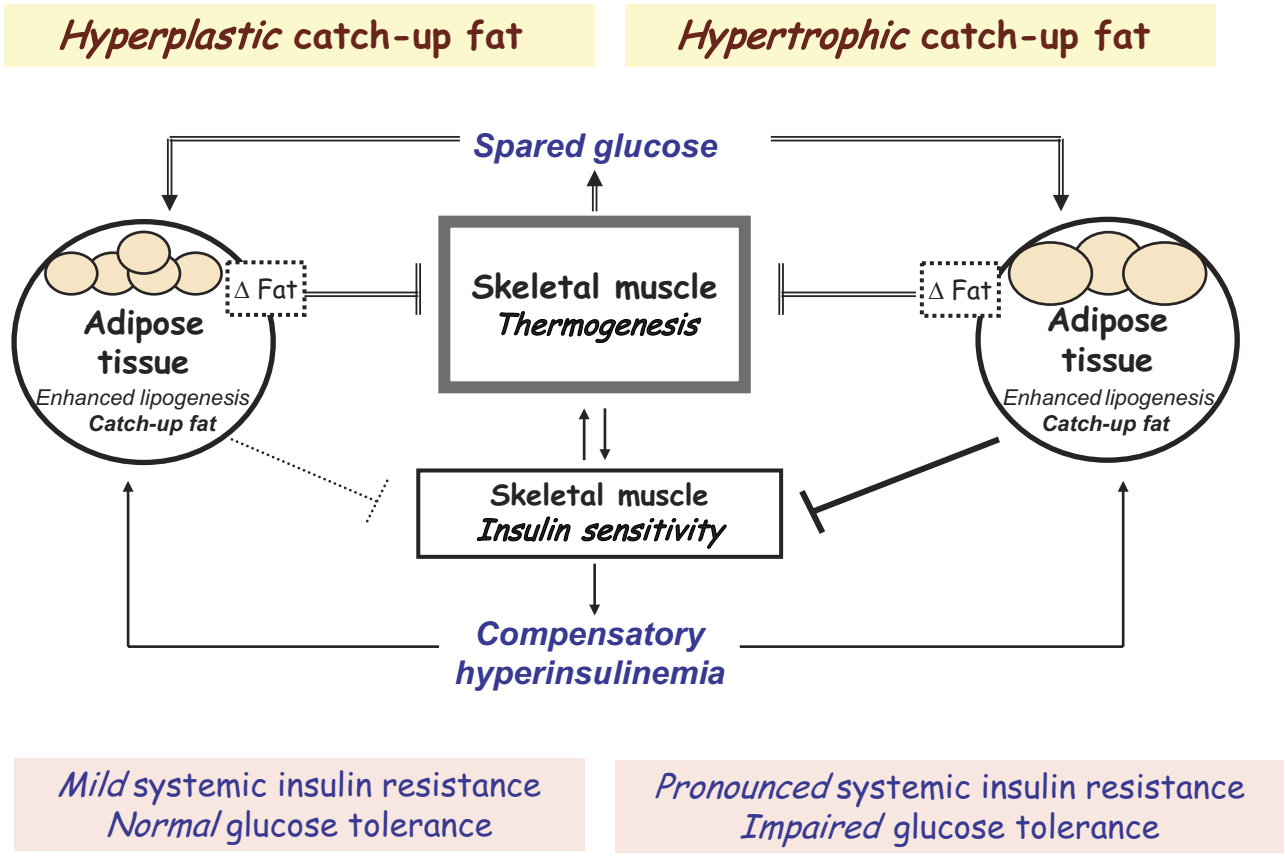

FIG. 1. Conceptual model depicting mechanisms by which the thrifty catch-up–fat phenotype, driven by suppressed thermogenesis, may cross-link with the development of insulin resistance and glucose intolerance. The depletion (or delayed growth/development) of the adipose tissue fat stores suppresses skeletal muscle thermogenesis, which during refeeding leads to concomitant glucose sparing and muscle insulin resistance. The resulting compensatory hyperinsulinemia serves to redirect the glucose spared from oxidation in skeletal muscle toward de novo lipogenesis and fat storage in white adipose tissue. In hyperplastic catch-up fat, a greater number of smaller adipocytes, coupled with lipogenesis, provide an efficient buffering capacity against the spared glucose and, hence, help to achieve normal glucose tolerance. By contrast, in hypertrophic catch-up fat, the low capacity for adipogenesis, coupled with lipogenesis, generates enlarged adipocytes, which are more prone to release proinflammatory cytokines and/or to spillover of lipids to nonadipocytes (with consequential ectopic lipotoxicity). This further exacerbates insulin resistance in skeletal muscle and other insulin-sensitive tissues, thereby resulting in more pronounced systemic insulin resistance and impaired glucose tolerance. The outcome of catch-up growth toward a hyperplastic or a hypertrophic catch-up–fat phenotype is determined by interactions among genetics, epigenetics, and environment.

that, as they previously showed, exhibit rapid postnatal catch-up growth (after malnutrition-induced low birth weight) and that subsequently develop progressive glucose intolerance and obesity in the absence of hyperphagia and impaired lean tissue growth (18) (i.e., a murine model of postnatal catch-up growth whose obesity later in life seems to reside in a "programmed" suppression of thermogenesis). By applying state-of-the-art techniques of gene profiling and histology to white adipose tissue harvested during postnatal catch-up–fat deposition, Isganaitis et al. (17) found that key genes controlling the flux of glucose toward lipogenesis were upregulated, whereas the expression of genes implicated in adipocyte differentiation/proliferation was unaltered; these data are consistent with unaltered adipocyte number and marked adipocyte hypertrophy at the end of catch-up growth. These findings, together with their other observations that adipocyte number still failed to increase several weeks after the completion of catch-up growth, support the argument for the programming of a thrifty hypertrophic catch-up–fat phenotype that incorporates defective adipogenic mechanisms. However, in light of apparently contradictory results indicating that postnatal catch-up growth after fetal malnutrition programs proliferation of preadipocytes in rats (19), it remains to be demonstrated whether the defect in enhancing adipogenesis observed during catch-up–fat deposition and beyond in the mice studied by Isganaitis et al. (17) is specifically a programmed response to early postnatal catch-up growth or the consequence of an inherent, genetically determined low capacity of this mouse strain to mount an enhanced adipogenic response to excess fat accumulation. In other words, genetic-epigenetic interactions could be critical in defining hyperplastic catch-up fat versus hypertrophic catch-up fat. As depicted in Fig. 1, a hypertrophic catch-up–fat phenotype is more likely to predispose to diminished adipose tissue insulin sensitivity, enhanced secretion of proinflammatory adipokines that induce insulin resistance in all insulin-sensitive tissues, and spilling over of lipids to nonadipose tissues with consequential risks for ectopic lipotoxicity (20)—all of which would confer enhanced susceptibility for later development of various components of the metabolic syndrome.

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