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Is there a human model for the 'metabolic syndrome' with a defined aetiology?

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To the Editor

The term the 'metabolic syndrome' has its origins in the seminal studies of Reaven [1], who identified a cluster of conditions that commonly occur together in an individual patient. This cluster has since been confirmed in epidemiological studies worldwide and a large database of metabolic variables has been created. Various committees, either sponsored by the National Institutes of Health (NIH), or by other associations, have taken this database and established criteria for the term the 'metabolic syndrome' to be applied to individual patients. At least five different committees have defined similar phenotypic features to describe the 'metabolic syndrome', including insulin resistance, glucose intolerance or diabetes, low HDL-cholesterol, high triacylglycerol, obesity and hypertension [2–6].

Various committees have provided a valuable service in transforming large databases into quantitative risk criteria. Examples are desirable levels of blood pressure, serum lipid levels, body weight and glucose concentration. When a committee structure, however, attempts to define a 'syndrome', it is not surprising that the result provokes considerable controversy. The essence of the controversy seems to arise from the lack of clarity of the aetiological basis for the 'metabolic cluster' [7].

Is there a human model for the metabolic syndrome?

At the NIH, we have studied 50 patients with various forms of lipodystrophy and we found that 80% of them have the 'metabolic syndrome' by the National Cholesterol Education Program criteria [2], with similar results using criteria from three out of four of the other committees (the World Health Organization, the European Group for the Study of Insulin Resistance and the American Association of Clinical Endocrinologists) [2, 4–6]. The only exception is the International Diabetes Federation criteria, which require obesity. The age of our patients ranges from 8 to 68 years (median age 23 years). The majority of our patients have severe insulin resistance and diabetes, high triacylglycerol and LDL levels, and low HDL. Some of our lipodystrophy patients have elevated blood pressure; however, the

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majority of them are normotensive. They lack subcutaneous fat tissue with different degrees of severity and they have ectopic accumulation of adipose tissue in the liver and muscles. While superficially these patients may appear to be the opposite of the most prevalent component of the metabolic syndrome, i.e. obese or with increased abdominal girth, they actually have the even more fundamental feature of insulin resistance. In fact, patients with lipodystrophy have features shared by the obese patients, but these features are quantitatively more severe (Table 1).

Thus, the morbidity of obesity is not a function of expanded adipocyte mass, but is much more related to the ectopic fat accumulation and other factors that lead to insulin resistance. Using these criteria, it may be reasonably stated that lipodystrophy represents an example of a human model of the ‘metabolic syndrome’.

Can lipodystrophy be used to establish a model for an aetiological basis for the metabolic syndrome?

First, it must be acknowledged that lipodystrophy is not a single condition. There are many different forms of lipodystrophy that have genetic or acquired aetiologies. However, all these forms of lipodystrophy share common metabolic features: insulin resistance, excessive ectopic lipid deposition, severe hypertriacylglycerolaemia, low HDL and high LDL. All these features are shared by the ‘metabolic syndrome’, as it has been previously suggested by Savage et al. in one particular form of lipodystrophy caused by a dominant-negative peroxisome proliferator-activated receptor γ (PPARγ) mutation [8]. At first blush, it may be presumed that these abnormalities result from the loss of the lipid storage compartments. However, it is now clear that the fat cell is an endocrine organ that produces many adipokines, cytokines and hormones. This realisation has evolved from the seminal discovery of leptin [9].

While there are many adipokines that have been described, the only one to be given to humans is leptin. Thus, it is now possible to ask what effect leptin administration has in patients with a ‘metabolic syndrome’ who are leptin-deficient and who will respond to the hormone. Leptin administration in hypoleptinaemic patients with lipodystrophy improves insulin resistance, reduces ectopic fat and corrects triacylglycerol and LDL levels in the blood, without having any effect on the lipid storage compartment [10]. Thus, lipodystrophy represents a hypoleptinaemic state in which one can demonstrate that leptin replacement corrects the ‘metabolic syndrome’. In this sense, this leptin-deficient state represents a human model for the ‘metabolic syndrome’. Further, it shows that a single therapy aimed at a defined target can be effective when the aetiological basis of the process is known. This finding is characteristic of hormone replacement in a hormone-deficient state.

Target of leptin therapy

The major phenotypic features of lipodystrophy that are affected by leptin include excess energy intake, insulin resistance, hyperinsulinaemia, hyperglycaemia, ectopic fat accumulation and dyslipidaemia. Our knowledge of the mechanisms by which leptin corrects these abnormalities depends on studies conducted in rodents. Thus, leptin may have a number of downstream effects that act in concert to correct the metabolic dysfunctions (Table 2). In humans, leptin has only been administered by peripheral injection and it cannot be determined whether the effects are mediated by receptors in the central nervous system, on multiple peripheral tissues or both.

Non-alcoholic fatty liver disease is strongly associated with the ‘metabolic syndrome’ and a significant number of these patients progress to non-alcoholic steatohepatitis (NASH). In

lipodystrophy, ectopic fat accumulates in the liver, resulting in hepatic steatosis that can eventually progress to NASH and cirrhosis. Treatment with leptin is associated with a reduction in hepatic triacylglycerol content, liver volume, serum transaminases and pathological features of NASH.

Further, polycystic ovarian syndrome (PCOS) is frequently seen in association with the 'metabolic syndrome'. Studies have shown that more than 40% of the women with PCOS have the metabolic syndrome, which is much higher than in age-matched women in the general population. Many pre-menopausal women with lipodystrophy have amenorrhoea, enlarged ovaries and signs of hyperandrogenism consistent with PCOS. In lipodystrophic women, leptin increases serum oestradiol, decreases testosterone levels, improves luteinising hormone responses to luteinising hormone-releasing hormone stimulation and normalises menses.

Possible deficiencies of the model

Correction of the leptin deficiency state improves most but not all the features that relate to the 'metabolic syndrome'. The major exception is HDL-cholesterol. While there is a dramatic reduction in triacylglycerol, LDL and total cholesterol levels, there is no significant change in HDL. The reasons for this are not clear. Further, as previously stated, hypertension is not a common feature of the various forms of lipodystrophy.

In addition, it is possible that the leptin effect is purely pharmacological rather than a physiological correction of a deficient state. In this regard, it appears that leptin administration has its major efficacy in leptin-deficient states and is relatively ineffective in hyperleptinaemic states [11]. This situation is similar to insulin replacement in type 1 diabetes mellitus, which is clearly a hormone-deficient state.

We do not feel, however, that these arguments negate our suggestion that lipodystrophy provides an example of a human model of the 'metabolic syndrome' with a defined aetiology.

Conclusion

We describe an example of a human model of the 'metabolic syndrome' that has a defined aetiological basis. The desirable aspect of this model is that it has a specific therapeutic target with regards to the metabolic derangement. Although lipodystrophy has many aetiologies and leptin affects different central nervous system and peripheral functions, leptin administration corrects most of the metabolic defects.

The major quest in the common 'metabolic syndrome' is to find a common aetiology or a therapeutic target that corrects all of its heterogeneous features. This may or may not be found, but if it is, we have provided a human model for the form that this may take.

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Abbreviations

NASH	Non-alcoholic steatohepatitis
NIH	National Institutes of Health

PCOS	Polycystic ovarian syndrome
PPARγ	Peroxisome proliferator-activated receptor γ

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Table 1

Comparison between the phenotypic characteristics of obesity and lipodystrophy

Phenotypic characteristics	Obesity	Lipodystrophy
Total fat mass	High	Low
Leptin level	High	Low
Energy intake	High	High
Ectopic fat	Moderate	High
Insulin resistance	Moderate	Extreme

Table 2

Mechanism of leptin action in rodents

Action	Mechanism
Satiety: CNS action	Arcuate nucleus and other hypothalamic nuclei
Insulin resistance and glucose metabolism: CNS and/or peripheral action	Decrease in ectopic fat
	Phosphorylation of insulin receptor substrates
	Activation of phosphoinositide-3-kinases
	Recruitment of GLUT4 transporters to the cell surface
Dyslipidaemia: CNS and/or peripheral action	Decrease in ectopic fat
	Increases in fatty acid oxidation • Activation of AMP-activated protein kinase • Increase in production of PPARγ • Increase in production of PPARgamma; coactivator-1α
	Decrease in lipogenesis • Repression of stearoyl-CoA desaturase-1 • Reduction in sterol regulatory element binding protein-1c gene expression • Inhibition of carbohydrate-regulatory element binding protein

CNS, Central nervous system