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Genetic Forms of the Cardiometabolic Syndrome: What Can They Tell the Clinician?

A well-worn medical aphorism states that "when you hear hoof beats, think of a horse and not a zebra." When applying this principle to the cardiometabolic syndrome (CMS), the horse would be represented by the prevalent CMS phenotype that affects approximately 30% of individuals in Westernized societies, while the zebra is represented by very rare conditions—such as lipodystrophy syndromes—that share some features with the more prevalent CMS. For instance, familial partial lipodystrophy types 2 and 3 result from heterozygous mutations in LMNA, *encoding nuclear lamin A/C, and in* PPARG, *encoding peroxisome proliferator-activated receptor (PPAR)-γ, respectively. Patients with either subtype of partial lipodystrophy exhibit an increased ratio of central to peripheral fat stores, dysglycemia, dyslipidemia, and hypertension, with predisposition for developing insulin-resistant diabetes and atherosclerosis end points. Sometimes, however, the zebra serves as a model that can help us understand the horse, so that the rare partial lipodystrophies might offer some insight into pathogenesis and treatment of the more prevalent CMS. (JCMS. 2007;2:45–48) ©2007 Le Jacq*

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Over the past 5 years, the cardiometabolic syndrome (CMS), defined as the clustering of multiple metabolic abnormalities that together increase cardiovascular disease (CVD) risk, has attracted considerable interest and debate. Researchers and clinicians have gauged its validity and potential to identify individuals at risk for diabetes and/or CVD.[1,2] Whatever definition or phenotype is used, the etiology of the CMS is complex and is determined by the interplay between genetic and environmental factors that affect the development of obesity, insulin resistance, and inflammation. The CMS appears to have a component of genetic susceptibility, as evidenced by clustering of the syndrome in families, although typically without the presence of a defined genetic mutation or polymorphism.

A strategy that has earlier been successfully applied to understand a complex risk phenotype was to thoroughly study individuals with a defined molecular lesion (often a rare single-gene disorder) who displayed elements of a common phenotype. For instance, study of patients with the rare genetic dyslipoproteinemia familial hypercholesterolemia yielded new understanding of the pathogenesis of elevated plasma low-density lipoprotein cholesterol (LDL-C). This knowledge was rapidly translated toward the development of statin drugs to lower LDL cholesterol and to prevent future atherosclerosis—not just in patients with familial hypercholesterolemia, but in all individuals at risk for CVD with elevated LDL cholesterol. Following this example, many investigators have begun to actively search for other rare monogenic disorders that might lead to new understandings of more prevalent phenotypes, including the CMS.

Does the Cardiometabolic Syndrome Exist as a Distinct Entity?

A primary concern when searching for genetic subtypes of any so-called syndrome is whether or not the syndrome actually exists. A recent provocative article argued that the CMS, or its doppelganger *metabolic syndrome* (MetS) was not a true medical syndrome, because it: (1) had no unifying pathology; (2) did not confer a CVD risk that was greater than the sum of its parts; (3) lacked an unambiguous definition; and (4) was not proven to alter intervention and treatment decisions.[2]

Nonetheless, the word *syndrome* is derived from the Greek roots *syn* and *dromos* that jointly mean "running together."[3] Following the literal definition, the CMS/MetS can rightfully be designated a syndrome because its constituent elements, such as hypertriglyceridemia, depressed high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, elevated plasma glucose, and abdominal obesity "run together" more often than predicted by chance alone.[1] Whether the defining elements constitute an actual disease state is a different issue, but strictly speaking these elements define both a syndrome and a clinical phenotype. Many phenotypes studied by human geneticists are defined by cut points imposed on continuous quantitative traits; the CMS/MetS merely incorporates several quantitative traits simultaneously. Furthermore, the CMS/MetS has a unifying or cornerstone anthropometric pathology, namely increased visceral or central obesity.[1] The CMS/MetS concept is at minimum a convenient way for clinicians to research and follow the complex metabolic disturbances

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associated with visceral obesity and insulin resistance. Also, rare genetic forms of the CMS/MetS—specifically, lipodystrophy syndromes—might help to clarify the pathogenic sequence of events progressing from fat redistribution to insulin resistance to the biochemical components of the CMS/MetS definition, and finally to the development of diabetes and CVD. These are shared features of both lipodystrophies and the CMS/MetS.

Genetic Mechanisms Underlying the Prevalent CMS/MetS Phenotype

Genes could potentially influence the development of the CMS/MetS in at least 2 ways.[4] First, each component of the CMS/MetS—obesity, dyslipidemia, dysglycemia, and high blood pressure—itself has a genetic basis with numerous identified and proposed candidate genes and polymorphisms.[4] Thus, variants associated with individual components of the CMS/MetS phenotype could underlie association with the entire syndrome. Second, some candidate gene products might act within a common pathway that affects more than 1 CMS/MetS component; replicated single-gene associations of this type include the association of the gene encoding the adipocytokine adiponectin with diabetes, hypertension, and dyslipidemia, and of the gene encoding the G-protein β-3 subunit with both hypertension and obesity.[4] Such genes might also be candidates for association studies with the complete CMS/MetS phenotype.

Familial Partial Lipodystrophy: A Possible Monogenic Model of CMS/MetS

Study of monogenic forms of the CMS/MetS might help us better understand the more prevalent syndrome. Inherited lipodystrophies are a group of disorders characterized by loss of fat in specific anatomic sites.[5] In many types of lipodystrophy, fat accumulates in nondystrophic adipose tissue and in ectopic sites,[5] resulting in an extreme form of the repartitioning of fat between peripheral subcutaneous and visceral stores that is seen with simple caloric excess. Because lipodystrophic patients have insulin resistance that progresses to type 2 diabetes, inherited lipodystrophies have been proposed as monogenic model systems for the CMS/MetS.[6] For instance, Dunnigan-type familial partial lipodystrophy (FPLD) subtypes 2 and 3 (FPLD2; Mendelian Inheritance in Man [MIM] #151660 and FPLD3; MIM #604367, respectively) result from heterozygosity for mutations either in *LMNA* (MIM 150330; National Center for Biotechnology Information [NCBI] NM_170707) encoding nuclear lamin A/C, or in *PPARG* (MIM 601487; NCBI NM_015869) encoding peroxisome proliferator-activated receptor (PPAR)-γ, respectively.[6] Mutations in *LMNA* are thought to cause mechanical abnormalities of the nucleus and to perturb interactions with transcription factors, while mutations in *PPARG* are thought to affect the differentiation of adipose tissue.[6] While FPLD2 and FPLD3 largely resemble each other, FLPD3 appears to be associated with: (1) less extensive adipose tissue loss,[7] (2) more severe signs of insulin resistance, (3) more severe hypertension, and (4) earlier onset of type 2 diabetes.[6] Individuals with both forms of FLPD, but especially women with FLPD2, have markedly increased CVD risk.[8]

Stages of Lipodystrophy

Close phenotypic evaluation of FPLD2 and FPLD3 patients has revealed distinct stages of disease evolution.[6] For instance, the initial metabolic disturbance is insulin resistance, followed by development of dyslipidemia, with hypertension and diabetes occurring later in disease evolution, and CVD occurring later still.[6] The clarified progression of abnormal phenotypes in FPLD points toward a rational staged treatment regimen to delay the development of the CVD end points. Understanding these stages of progression might have value not only for FPLD patients, but perhaps also for patients with the common CMS/MetS phenotype.

While the causative mutation in FPLD is present at birth, the first notable clinical manifestation is redistribution of fat beginning in the early second decade of life, around adolescence. Subcutaneous fat loss affects the extremities and gluteal region and is considered both irreversible and also the trigger for development of the subsequent metabolic abnormalities.[5] In animal models, stressed *LMNA*-deficient cells first develop chromatin and nuclear envelope damage, followed by alterations in transcriptional activation of protective genes.[9] In contrast, *PPARG* mutations in FPLD3 may affect differentiation or endurance of adipocytes, or they might have completely independent metabolic effects.[6] By either mechanism, fat loss affects triglyceride storage and increases free fatty acid (FFA) flux. It remains unclear, however, whether certain biochemical changes such as hyperinsulinemia or disordered adipocytokines might actually precede the clinically apparent fat loss. Evaluation of asymptomatic molecularly diagnosed pediatric subjects will help to clarify this issue.

Mid-stage FPLD generally spans the third and fourth decades of life and features unique biochemistry on the background of anthropometric changes.[10,11] Most mid-stage nondiabetic FPLD individuals would meet the National Cholesterol Education Program (NCEP) criteria for MetS.[12] Patients live with abnormal serum biochemistry for years before the loss of glycemic control and onset of diabetes.[10,11] The core metabolic defect is insulin resistance, with elevated plasma insulin, C-peptide, plasma FFAs, triglycerides, and C-reactive protein, and depressed plasma HDL-C, leptin, and adiponectin.[11] Insufficient storage capacity in peripheral subcutaneous adipose tissue could redirect triglycerides into nondystrophic adipose tissue and ectopic sites, such as liver and skeletal muscle. Circulating FFAs may antagonize insulin's peripheral activity and are also lipotoxic to pancreatic β cells, resulting in impaired insulin secretion and ultimately in the loss of glycemic control.

Late-stage FPLD2 and FPLD3 are marked by diabetes onset by the fourth decade of life for the former and somewhat earlier for the latter. Also, despite less extensive adipose loss in FPLD3

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compared with FPLD2, the metabolic disturbances are more pronounced, suggesting that PPAR-γ deficiency affects metabolism through more than just adipose tissue loss.[6] The final stages of FPLD are characterized by the development of diabetic complications—both macrovascular, such as CVD, and microvascular, such as retinopathy, nephropathy, and/or neuropathy.

Treatment of the Stages of FPLD

There is no accepted treatment for patients with FPLD at the earliest stage of disease, when the first clinical manifestation is redistribution of fat. Future treatments in at-risk carriers might be directed toward preservation of subcutaneous fat depots before irreversible loss occurs. Administration of thiazolidinedione (TZD) drugs and/or leptin showed very modest beneficial effects on fat-mass repletion in later stages of disease,[13–15] suggesting that these treatments might be useful at earlier stages. Based on animal studies, fat transplantation is another theoretic approach to improve the overall metabolic state,[16] but in humans, technical issues would complicate fat autotransplantation, and the need for long-term immunosuppression would additionally complicate fat xenotransplantation.

In patients with mid-stage FPLD, troglitazone improved multiple metabolic variables, and modestly increased subcutaneous fat depots.[13] But troglitazone also conferred a high risk of hepatotoxicity.[13] Treatment of mid-stage FPLD also includes CVD prevention, with control of incipient hypertension and dyslipidemia, following guideline recommendations for primary CVD prevention.[17] Pharmacologic options for dyslipidemia include fibric acid derivatives, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and sterol absorption inhibitors, such as ezetimibe. Options for blood pressure management include metabolically neutral agents, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers. The C-reactive protein elevation is consistent with the proinflammatory nature of insulin resistance, possibly warranting aspirin administration. Also, type 2 diabetes onset might be delayed by treatment with TZDs, statins, and/or ACEIs, which could also delay progression to late-stage FPLD. Future treatments may include preemptive use of insulin sensitizers and/or leptin with or without adiponectin.

Late-stage FPLD is characterized by diabetes onset, which in turn causes profound changes in the metabolic traits. At this stage subjects are, by definition, at high risk for CVD because of diabetes[12] and treatment is directed to control of glycemia, dyslipidemia, and hypertension to prevent complications. CVD prevention includes control of elevated blood pressure and dyslipidemia and administration of aspirin. Some agents, in particular ACEIs and angiotensin receptor blockers, might further delay the onset of microvascular complications, particularly nephropathy. Future treatments may also include leptin with or without adiponectin.

Final-stage FPLD is characterized by onset of diabetic macrovascular and microvascular complications. Therapeutic goals now include stabilization of metabolic variables, palliation, and secondary CVD prevention. Treatment of final-stage FPLD is defined both by secondary prevention of macrovascular complications and by continued optimization of metabolic control to prevent deterioration of microvascular complications. It also might become necessary to mobilize the established chronic care and rehabilitation paradigms for dealing with irreversible tissue and organ damage causing permanent neurologic deficits, heart failure, amputation, blindness, and kidney failure.

Central Obesity in FPLD and the CMS/MetS

In FPLD, the genetically programmed deficiency of peripheral adipose stores results in early redirection of FFAs into visceral fat stores and a disturbed balance between visceral and peripheral fat. In contrast, in the more prevalent CMS/MetS, the redirection of FFAs into visceral fat probably occurs more as the result of saturation of peripheral subcutaneous fat stores. Any intervention that can prevent, delay, or reverse the excess central fat will be predicted to have a beneficial effect on the downstream metabolic consequences for both FPLD and the CMS/MetS. Thus, diet, weight loss, and exercise are obvious first-line interventions for the prevention and treatment of the CMS/MetS.[18] Lifestyle modifications are indicated for CVD prevention in general, and the presence of the CMS/MetS highlights an increased urgency because multiple risk factors can be simultaneously reduced.

Other treatments for common obesity, such as pharmacologic suppression of appetite, pancreatic lipase inhibition, and surgical approaches, may not be optimal in FPLD unless they can substantially reduce central adipose tissue mass. For instance, sibutramine blocks the uptake of noradrenaline and serotonin in the hypothalamus and produces a 5% to 10% weight loss, but at the expense of increased blood pressure. Rimonabant is a cannabinoid-1 receptor antagonist that decreases hunger, thus reducing food intake and ultimately central obesity, with improved metabolic parameters observed in a wide range of patients, although not yet specifically in FPLD patients.[18–22] Finally, while cure rates for the CMS/MetS exceeding 95% have been reported following bariatric surgery,[23] the utility of such dramatic measures in FPLD patients is uncertain.

Other Potential Treatments for FPLD

Future treatments for maintaining balanced distribution of adipose stores; improving insulin sensitivity, glycemic control, and metabolic control; and reducing microvascular and macrovascular complications in FPLD may also be applied in management of the CMS/MetS, type 2 diabetes, and/or acquired lipodystrophy syndromes. The central role of stearyl coenzyme A desaturase-1, an enzyme whose regulation has significant effects on metabolic rate, obesity, and hepatosteatosis implicates this enzyme as a potential drug target.[24] Treatments might also come from among new agents under development,

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including new selective agonists for PPAR-α, γ, and δ; dual ligands for PPAR-α and γ; and target gene-selective PPAR receptor modulators that might selectively affect adipose differentiation.[25] Also, some of the new classes of drugs for management of dyslipidemia might be appropriate for management of hypertriglyceridemia, prophylaxis of pancreatitis, and secondary prevention of CVD in FPLD.[26] Finally, medications once thought to be specific for 1 enzyme or 1 target pathway, such as TZDs, statins, or ACEIs, could exert as beneficial effects by targeting multiple metabolic risk factors, and these treatments could benefit several CMS/MetS components simultaneously.

Implications of FPLD for the CMS/MetS

FPLD2 and FPLD3 resulting from mutations in *LMNA* or *PPARG*, respectively, among all lipodystrophies, are an appropriate model of the more prevalent CMS/MetS, because these genetic syndromes: (1) are characterized by relatively gradual fat redistribution to central depots rather than outright global fat loss from birth; (2) are progressive, evolving relatively slowly by defined stages over years; and (3) recapitulate most of the clinical and biochemical attributes of the more prevalent CMS/MetS, including increased visceral fat stores, dysglycemia, dyslipidemia, hypertension, and predisposition to diabetes and CVD. Treatments that prove to be successful in modulating the natural metabolic history of FPLD might also prove to be useful in the treatment of thxe CMS/MetS. We also note that in patients who receive highly active antiretroviral therapy in acquired immune deficiency syndrome, the CMS/MetS is steadily growing in clinical importance,[27] and insights regarding pathogenesis and treatment from FPLD patients might also prove to be relevant for this condition.

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