Gut Hormones, Obesity, Polycystic Ovarian Syndrome, Malignancy, and Lipodystrophy Syndromes

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This is the third in a series of four articles on presentations at the World Congress on the insulin resistance syndrome (IRS), reviewing relationships between insulin resistance and gut hormones, obesity, polycystic ovarian syndrome, malignancy, and lipodystrophy syndromes.

Gut hormones

Steve Bloom (London, U.K.) discussed satiety signals, noting that obesity is "key to the [insulin resistance] syndrome" and that it ultimately is caused by overeating. Childhood obesity is on the rise, with 40% of children expected to be overweight by 2010. He asked, what explains the reduction in hunger after a meal? Bulk in the stomach and nutrients in the circulation appear not to be the cause. There must be specific signals from the gut to the brain, neural and/or hormonal. It appears that, when stimulated, a small area in the proximal gastric fundus, near the esophagus, sends vagal signals mediating satiety. Studies have attempted to replicate gut hormonal signals by infusion, with cholecystokinin (CCK) decreasing food intake but causing pancreatitis and acting as a growth factor for pancreatic acinar cells, which could cause increased pancreatic cancer risk. Ghrelin decreases after meals and may be a negative satiety signal, as its direct effect is to stimulate food intake. Pancreatic polypeptide may be a factor, and the distal small bowel and colon produce glucagon-like peptide (GLP)-1, oxyntomodulin, and peptide YY (PYY), additional candidate satiety signals.

Gut hormones may cause satiety in three forms: *1*) acute toxicity, causing nausea and vomiting, a physiologic effect in that it is seen with gastroenteritis; *2*) subacute postprandial elevations decreasing food intake for ~6 h; and *3*) chronic elevation seen in gut disease with anorexia. $PYY_{1–36}$ is produced by L-cells in the small and large intestine, with highest concentration in the rectum (1). It is released into circulation and metabolized by dipeptidyl deptidase (DPP)4 to $PYY_{3–36}$ (2), acting to delay gastric emptying at physiologic concentrations (3–5). PYY levels are elevated after partial ileal resection (6), in malabsorption, in acute gut infection, and, interestingly, after jejeunoileal bypass bariatric surgery (7), in association with elevation in oxyntomodulin, suggesting a dual hormonal mechanism of the reduction in appetite following this procedure.

$PYY_{3–36}$ is a selective neuropeptide-Y (NPY)-2 receptor agonist, "switching off the NPY circuit in the brain." PYY infusion leads to long (>24 h) decreased food intake, showing the need for a correct experimental model. In study of 12 obese versus 12 lean individuals given a 90-min $PYY_{3–36}$ infusion followed 120 min later by a meal, food intake decreased in both groups (8), in association with a reduction in ghrelin, perhaps in part mediating the reduction in food intake. During a saline control infusion the obese group had lower PYY levels, suggesting obesity to be "a PYY deficiency condition," an observation that has been confirmed in multiple studies. The effect of PYY is dose dependent up to a certain level, leading Bloom to suggest that PYY may be a therapeutic target.

Oxyntomodulin (OXM), which decreases acid production by the oxynto cells of the stomach, is a preproglucagon-derived 37–amino acid peptide mainly produced by the intestinal L-cells, containing the glucagon amino acid sequence but without glucagon-like effects. Released in proportion to meal size, higher levels are associated with lower body weight. Chronic oxyntomodulin administration leads to weight loss, even with pair feeding, suggesting effects both on food intake and energy expenditure. In a human clinical trial of 26 individuals self-administering saline versus OXM three times daily for 4 weeks, there was 2 kg greater weight loss with the active agent, with reduced calorie intake throughout the period of study and reduction in leptin levels. One treated person developed nausea and was found to be a slow metabolizer with very high levels. OXM has some GLP-1–like effect, but there was no evidence of increased insulin levels and no evidence of the hypothalamic arcuate nucleus activation occurring with GLP-1. Analogs have been developed for prolonged (1 week) duration of action, with evidence of greater weight loss, less insulin release, and less nausea than with GLP-1, with evidence of additive effect with other agents, including rimonabant. Bloom concluded that this agent may be "nature's own way of switching off appetite . . . it mimics the JI [jejeunoileal] bypass without the risks of surgery."

Judith Korner (New York, NY) discussed the effects of gut surgery on hormones and incretins. The minority of obese individuals are successful in maintaining weight loss following a diet (9). In

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Abbreviations: CVD, cardiovascular disease; FFA, free fatty acid; GLP, glucagon-like peptide; GnRH, gonadotropin releasing hormone; IGF, insulin-like growth factor; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; NPY, neuropeptide-Y; OXM, oxyntomodulin; PCOS, polycystic ovary syndrome; PPAR, peroxisome proliferator–activator receptor; PYY, peptide YY; RGZ, rosiglitazone; SSPG, steady-state plasma glucose.

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contrast, bariatric surgery is highly effective (10). Gastric banding involves placement of an inflatable ring around the proximal stomach leaving a small gastric pouch, while roux-en-y gastric bypass involves both gastric size restriction and anastamosis of the small pouch of stomach directly into the mid-intestine. In a study comparing banding with bypass, there was a 48 vs. 62% loss of excess weight, with 49 vs. 84% resolution of diabetes (11). Korner has found differential gut hormonal responses to the two procedures, with greater postprandial suppression of ghrelin and stimulation of PYY after bypass (12). After gastric bypass, glycemic improvement is seen within 2 weeks, leading to the questions of what are the mechanisms of weight loss and maintenance after bariatric surgery, of why hunger does not increase after surgery, and of why there is greater weight loss and diabetes improvement with bypass. Although the development of "dumping syndrome" after high carbohydrate loads may condition patients to reduce sugar ingestion, this is at most a partial explanation. Many investigators have therefore sought neurohormonal mechanisms to explain the effects of bariatric surgery. Bypass is associated with early postprandial hypoglycemia, and some investigators have observed nesidioblastosis in cases of severe hypoglycemia (13), although other investigators have found the development of hypoglycemia following bypass surgery in association with postprandial hyperinsulinemia but without evidence of islet cell hyperplasia (14). Korner's group has observed an exaggerated postprandial GLP-1 response but a significant decrease in glucose-dependent insulinotropic peptide after bypass. She suggested that expedited delivery of nutrients to the hindgut may stimulate release of PYY and GLP-1, which may accentuate the "ileal brake," increasing satiety, suggesting an endocrine explanation for the effect of the procedure.

David Cummings (Seattle, WA) discussed ghrelin and the regulation of appetite and body weight, noting that there are two groups of appetite/weight control molecules: those related to acute food ingestion, signaling from the hindbrain via the vagus nerve, and those long-term regulators related to body fat stores. Ghrelin is a 28–amino acid acylated peptide, highly conserved across species, which has a separate action (for which it was named) in stimulating growth hormone. Ghrelin may have a short-term effect in stimulating appetite but also appears to have a long-term role in modeling body fat stores. Physiological doses rapidly stimulate appetite and food intake, suggesting that it may participate in meal initiation and premeal hunger, transiently increasing food intake, decreasing meal latency, increasing meal initiation, and having related behavioral effects in animal models on foraging and hoarding. Ghrelin also increases gastric motility, emptying, and acid secretion. Ghrelin rises before and falls shortly after every meal (15), with ghrelin surges predicting voluntary meal initiation (16), suggesting that ghrelin is the source of mealtime hunger. Grazing animals that are fed continuously have stable levels throughout the day with small increases before each food ingestion episode. In animals and humans exhibiting intermittent food ingestion, the number of habitual meals per day predicts the number of ghrelin peaks, which appear to be controlled by sympathetic nervous system activity. Nutrients, particularly carbohydrate and protein, rather than fat, suppress ghrelin in a dose-dependent fashion. Interestingly, after carbohydrate ingestion, there is a rebound exceeding baseline levels, potentially explaining a decreased duration of satiety after high carbohydrate meals. The reduction in ghrelin levels requires nutrient in the distal small intestine and appears to be mediated by the enteric nervous system, involving serotonin and insulin secretion.

The long-term effects of ghrelin suggest an important signaling role as well. Ghrelin levels rise with weight loss, whether due to cancer, calorie restriction, cachexia, Huntington's disease, anorexia/bulimia nervosa, or chronic exercise (the latter without decrease in nutrient intake) and decreases with weight gain from overfeeding, high fat or sugar, glucocorticoids, antipsychotics, valproic acid, or treatment of celiac disease or of anorexia nervosa (17). Interestingly, low-fat dietary weight loss is not associated with change in ghrelin levels (18), perhaps because the reduction in fat leads to increase in carbohydrate and protein ingestion, more effectively suppressing ghrelin. Ghrelin receptors are present in the arcuate nucleus, on the vagus nerve along the pathway to the nucleus and tractus solitarius, a brain stem group receiving viscerosensory information, and then relaying to NPY/Agouti-related peptide neurons via catecholaminergic signals. There are also ghrelin receptors in the hindbrain and in midbrain/mesolimbic reward centers, with the ghrelin receptor expressed on dopamine receptors in the ventral tegmental area, presumably integrating dopaminergic and proopiomelanocortin pathways.

Chronic ghrelin administration increases body weight, with effect even in individuals with underlying illnesses, suggesting a potential therapeutic role. Ghrelin also increases the preference for fat and decreases energy expenditure by reducing sympathetic nervous system output. An important question is whether excessive ghrelin plays a role in human weight gain. Obesity is usually associated with low ghrelin levels, but Prader Willi syndrome is associated with high ghrelin levels (19), presumably related to the extreme weight gain in this condition, and, interestingly, relatively higher ghrelin levels are predictive of future weight gain. In animal studies, a variety of approaches have been taken to reduce ghrelin activity. These include antibodies to ghrelin, receptor antagonists, one being developed by Abbott, and an anti-ghrelin spiegelmer. The latter term denotes a DNA-binding molecule similar to an antamer but composed of L-oligonucleotides to prevent nuclease degradation. One such molecule, NOX-B11, being developed by Merck, also appears promising. All these approaches appear to lead to body weight reduction, with particular interest in their potential role in maintenance of weight loss following diet or another pharmacologic manipulation.

Obesity

Tracy McLaughlin (Stanford, CA) discussed aspects of obesity related to insulin resistance, noting that 58% of individuals she studied with BMI 30–34.9 kg/m^2 were in the most insulin-resistant tertile of the population but that 13% were insulin sensitive. Of those with BMI 25–29 kg/m^2, 25% were insulin sensitive and 44% insulin resistant; of those with BMI $<$25 kg/m^2, 60% were insulin sensitive but 15% insulin resistant. She reviewed several studies addressing the question of whether insulin resistance and hyperinsulinemia can cause weight gain. In a 14-year follow-up of 647 healthy nonobese Italians, subjects in the lowest insulin quartile gained 1.8 kg, while those in the highest quartile gained 2.3 kg, a non–significant difference (20). Another study comparing individuals gaining versus losing weight showed that both groups had

similar fasting insulin and that in the most obese tertile the highest fasting insulin predicted less rather than more weight gain. In a 3-year study of 192 nondiabetic Pima Indians, those who were more insulin sensitive gained 7.6 kg, while the more insulin-resistant group gained 3.1 kg (21). In her study of 20 obese healthy women with baseline BMI 31.9 kg/m^2 following a hypocaloric liquid diet for 2 months, half were insulin sensitive with steady-state plasma glucose (SSPG) 91 mg/dl, and half were insulin resistant with SSPG 225 mg/dl. There was no correlation of either the fasting insulin level or the SSPG with weight loss (22). Thus, she concluded that endogenous hyperinsulinemia is not associated with weight gain and does not impede weight loss.

McLauglin then reviewed a study suggesting that weight loss does improve insulin sensitivity for individuals who are obese and insulin resistant. Of 25 obese insulin-resistant individuals at 3 years' follow-up after weight loss, insulin sensitivity had improved both in those maintaining weight loss and, to a lesser extent, those who regained part of the weight. Although insulin-resistant individuals show greater insulin sensitivity with weight loss, those already insulin sensitive (to a greater extent than the resistant individuals after weight loss) did not have further increase in insulin sensitivity with weight loss. Insulin-resistant obese individuals constitute a particularly high-risk group for elevated blood pressure, dyslipidemia, and associated abnormalities (23). Among obese individuals studied by her group, those in the most insulin-resistant SSPG tertile were 4, 6.5, 3, and 4 times more likely to have hypertension, hypertriglyceridemia, low HDL, and impaired fasting glucose than those in the most insulin-sensitive tertile.

McLaughlin also commented on the concept that measures of visceral fat would be more likely to be related to insulin resistance than would measures of overall obesity. There is some evidence that visceral adipocytes may be particularly able to deliver free fatty acid (FFA) via the portal system, as catecholamine-stimulated lipolysis is greater and as insulin has a lesser effect in suppressing lipolysis in omental adipocytes. McLaughlin pointed out, however, that the concept that upper versus lower body or visceral versus subcutaneous fat distribution determines insulin resistance is not in keeping with all available evidence, as subcutaneous fat contributes 70% of circulating FFA to systemic concentrations, and as basal lipolysis, which is proportional to fat cell size, is greater in subcutaneous than in visceral adipocytes of equal size.

Samuel Cushman (Bethesda, MD) discussed adipocyte size characteristics, reflecting on the "double-edged sword" of insulin resistance occurring in association both with excess and with insufficient numbers of adipocytes. Furthermore, an animal model not expressing GLUT4 in adipocytes develops skeletal muscle insulin resistance, giving further evidence of the complex relationship between adipocytes and systemic insulin response. In vivo, there are larger and smaller adipocytes. Hyperplastic obesity (increased adipocyte number) has been thought to be associated with normal insulin sensitivity, while hypertrophic obesity (increased adipocyte size) has been thought to lead to insulin resistance. Rosiglitazone (RGZ) treatment of Zucker rats improves glucose tolerance after 6 days. Insulin levels decrease after 2 days, with progressively further benefit at 10 and 14 days. Using a cell size sorter to analyze cell size distribution, there is a peak of small cells initially, with larger sizes over time, confirmed by a subsequent study with repeated biopsy of single animals to reduce variability, perhaps explaining the change in insulin sensitivity. No evidence of proliferation of stem cells could be demonstrated. Apoptosis rates were low and appeared to increase somewhat with RGZ. He interpreted these studies to show that stem cells differentiate to preadipocytes, with further differentiation to mature adipocytes modulated by peroxisome proliferator–activator receptor (PPAR)γ, with RGZ treatment appearing to affect the preadipocyte to mature adipocyte progression. Similarly, analysis of adipose tissue biopsies performed on obese insulin-sensitive versus insulin-resistant individuals found that the insulin-sensitive individuals had more large and fewer small cells. This is, Cushman pointed out, the opposite of the prevailing view based on earlier research. The insulin-sensitive individuals ' adipocytes had higher sterol regulatory element-binding protein, PPARγ1 and -γ2, and adiponectin, suggesting that although larger the cells were more highly differentiated.

The polycystic ovary syndrome

Andrea Dunaif (Chicago, IL) discussed hyperandrogenemia and risk factors for the metabolic syndrome in obese girls, stressing the importance of the developmental origin of the polycystic ovary syndrome (PCOS). PCOS may be a good model for metabolic syndrome in adolescents, and there may be important influences of androgens on metabolic risk. In PCOS, there is increased gonadotropin releasing hormone (GnRH), selectively increasing Luteinizing hormone, and suppressing follicle stimulating hormone, preventing follicle production and increasing ovarian androgen production. Testosterone decreases the sensitivity of the hypothalamus to the normal feedback effects of estradiol, decreasing GnRH pulse frequency, establishing a vicious cycle of progressive increase in androgen levels.

Seven percent of adult women have PCOS, with the prevalence twice as high in Hispanics. Diagnostic criteria established in 1990 are the presence of hyperandrogenism and chronic anovulation, after excluding other disorders. A subsequent modification was the addition of abnormal ovarian morphology on ultrasound, with any two of the three criteria considered sufficient for the diagnosis, allowing women with regular ovulatory cycles but high androgens and polycystic ovaries to be studied to allow fuller understanding of the syndrome. The cause of 80–90% of cases of oligomenorrhea is PCOS, and many girls with irregular cycles after menarche will be found to have PCOS.

There is a high prevalence of type 2 diabetes (24) and IRS (25) among adolescent girls and young women with PCOS, particularly with increasing degrees of obesity. In Dunaif's series of ~400 women, 70% of those with PCOS and BMI >30 kg/m^2 had IRS, while the syndrome was seen in ~45% of a control group of obese women. Among obese adolescent girls, 63 vs. 32% of those with vs. without PCOS had IRS, respectively (26). In women with PCOS, both thiazolidinediones and metformin decrease insulin and androgen levels (27) and increase ovulation (28) in a dose-responsive fashion. Given the evidence of increased GnRH as a mediator of PCOS, Dunaif speculated that these agents may act in part by improving hypothalamic insulin sensitivity.

A study of obese girls showed a linear relationship between BMI and circulating levels of both free and total serum testosterone (29). Testosterone levels are increased in women with IRS: the higher the testosterone, the greater the IRS prevalence (30). Women with IRS have higher androgen levels, with evidence of modest

improvement in insulin sensitivity with agents to block androgen action in PCOS (31). Both metformin and the antiandrogen flutamide are associated with weight loss, reducing both visceral and subcutaneous adipose tissue, with additive effect of the two agents in combination (32). Family studies show that ~40% of sisters of women with PCOS have elevated androgen levels, perhaps half of these also having PCOS, the remainder having high androgen levels but normal menstrual cycles, with the potential explanation that women with hyperandrogenemia but greater degrees of insulin sensitivity are more likely to have normal cycles. Overall, however, hyperandrogenism tracks with hyperinsulinemia (33). Brothers of women with PCOS have increased levels of the adrenal androgen dehydroepiandrosterone sulfate but normal levels of testes-derived testosterone, suggesting a hereditable adrenal abnormality. Interestingly, the brothers have lower disposition index on minimal model analysis of glucose tolerance, suggesting a β-cell defect (34). Genetic studies show separate heritable components for insulin resistance and for androgen excess, with transmission disequilibrium analysis showing linkage to chromosome 19 13.2 with a marker separate from the insulin receptor (35), which maps to an intron of the fibrillin 3 gene (related to Marfans syndrome and modulating transforming growth factor-β signaling). Thus, Dunaif suggested that genetic variants may lead to high androgen levels, in some individuals in utero, while in others during childhood or during puberty, then causing the cycle of abnormal gonadotropin secretion and potentially also increasing visceral fat with consequent metabolic abnormality, although it is clear that androgen excess alone, as seen in adrenal enzyme defects, does not itself cause insulin resistance, so that other genes must be required.

John Nestler (Richmond, VA) reviewed a number of aspects of PCOS related to insulin resistance. Obese women with PCOS have the same degree of insulin resistance as do individuals with type 2 diabetes (36). In a study of 254 women with PCOS, 7.5% had type 2 diabetes (37), and in the Nurses' Health Study, the rate of conversion to type 2 diabetes doubled in oligomenorrheic women, independent of weight (38). Nestler cited further studies suggesting that 30–50% of obese women with PCOS develop either impaired glucose tolerance (IGT) or frank type 2 diabetes. An important question, then, is how to prevent diabetes in women with PCOS. In his clinical practice, >95% of women with PCOS receive metformin. Nestler described a study of 43 women with PCOS, 32 with normal glucose tolerance and 11 with IGT at baseline. After >2 years, none developed diabetes, with 2 of 32 deteriorating from normal to IGT, an annual conversion rate from normal to IGT of 1.8%, approximately one-eighth of that usually reported. Nestler observed that a prospective study of metformin treatment of individuals with PCOS might show greater benefit than the 31% decrease reported with this agent among individuals with IGT in the Diabetes Prevention Program (39).

Nestler suggested that one should consider not using oral contraceptive treatment in women with PCOS. He reviewed a study of 106 women with PCOS, having 21, 45, and 50% prevalence of IRS at ages <20, 20–29, and >29 years, respectively, with 90% having at least one cardiovascular disease (CVD) risk factor, 68% having low HDL cholesterol, and 67% having elevated BMI (40). In the Nurses' Health Study, 82,439 women followed for 14 years had a 1.5- to 2-fold increased risk of CVD with irregular menses. Both second and third generation oral contraceptives are associated with doubling of CVD risk (41). For normal women, the absolute risk is extremely low, but women with PCOS may be at increased CVD risk and may take oral contraceptives for a longer period of time than women in the general population.

There are, Nestler noted, women with PCOS, perhaps <10% of those with the syndrome, who are lean and do not appear to have insulin resistance. These women still respond to administration of insulin-sensitizing agents. He suggested that women with PCOS may have any combination of three abnormalities: insulin resistance intrinsic to PCOS, insulin resistance from obesity, and an additional factor, increased ovarian sensitivity to insulin. Finally, he noted that insulin resistance appears to be related to the three- to fivefold increase in early pregnancy loss among women with PCOS. In a randomized controlled trial of 120 women with PCOS randomized to laparoscopic ovarian diathermy plus placebo versus mock surgery plus metformin, ovulation rates were similar, but metformin was associated with a higher pregnancy rate and a lower rate of fetal loss (42).

Insulin resistance and malignancy

George Fantus (Toronto, Ontario, Canada) discussed aspects of the relationship between insulin resistance and breast cancer, reviewing the clinical evidence for a role of insulin in risk and in prognosis, potential molecular mechanisms, and benefits of sensitizer treatment. Obesity is associated with increased mortality rates from cancers, including those of the pancreas, liver, and breast (43). Diabetes appears to convey up to a 50% increase in the risk of breast cancer. Conversely, among women with newly diagnosed diabetes, there is a 10–20% increased likelihood of having had breast cancer. Furthermore, the prognosis for total and cancer-related mortality and for recurrence is worse for obese individuals with breast cancer. Weight gain of at least 5 kg is also associated with poor prognosis. In a study looking specifically at metabolic syndrome, there was similar evidence of adverse prognosis, appearing to be related to increased estrogen levels. These observations appear to be explained by circulating insulin levels, which are associated with mortality and with distant recurrence rates. Conversely, in animal studies, streptozocin-induced diabetes slows tumor growth. The AspB-10 insulin analog, which exhibited increased insulin receptor binding, was found to increase mammary tumors in animal models. Insulin augments the growth response to other growth factors, such as estrogen, and breast tumors express insulin receptors A and B and hybrid insulin plus insulin-like growth factor (IGF)-1 receptors, as well as the IGF-1 and -2 receptors, although Fantus stated that the insulin effect on growth of breast tumors is not mediated via the IGF receptors.

Exercise appears to have benefit in decreasing the likelihood of breast cancer, both in women with breast cancer (BRCA) mutations (44) and in those without this risk factor (45). Metformin activates AMPK, which in turn inhibits mTOR, which is activated by the insulin/IGF pathway. The mTOR-raptor complex may play a role in tumor growth, and in an animal model of breast cancer metformin-treated mice have later breast cancer development and longer survival. Recent evidence suggests that women with diabetes treated with metformin have lower tumor development rates than do women receiving insulin or sulfonylureas (46).

Lipodystrophy syndromes

Robert Hegele (London, Ontario, Canada) suggested that the lipodystrophy syndromes may be regarded as experiments of nature, potentially explaining aspects of the overall genesis of insulin resistance. He presented a patient with familial partial lipodystrophy, showing absence of subcutaneous fat on the extremities, prominent muscles, preserved central fat, marked insulin resistance, and dyslipidemia and premature coronary disease. The condition is associated with all the components of IRS, including hypertension, central adiposity, dyslipidemia, early atherosclerosis, PCOS, acanthosis, and diabetes. There are at least three genetic subtypes: one is an autosomal recessive localized to chromosome 1, which becomes manifest in puberty, associated with abnormality genes of one of the lamins, nuclear matrix proteins that are structural components of the nuclear lamina, present in most multicellular organisms. Defects in this gene also have been associated with loss of muscle of the extremities and with cardiomyopathy. Nuclear lamins A, B, and C play roles in regulating nuclear membrane pore size, regulating trafficking of substances across the nuclear membrane. One-half of individuals with partial lipodystrophy have no abnormality of lamin A. Additional abnormalities that have been found include defects of PPARγ, lamin B, the lamin B receptor emerin (a serine-rich protein responsible for a form of muscular dystrophy), and sterol regulatory element-binding protein-1c. Acquired partial lipodystrophy may occur as a manifestation of autoimmune disease, with dermatomyositis, hyperandrogenemia, hirsutism, hepatosplenomegaly, and loss of subcutaneous fat from the face, arms, and abdomen with increased visceral fat; some individuals with this presentation have lamin B mutations. Hegele showed that lipodystrophy is caused by loss of the capacity of subcutaneous fat to store triglyceride and speculated that individuals with the more common forms of insulin resistance may overload their capacity for subcutaneous fat storage, with spillover to visceral fat depots and to liver and muscle fat contributing to the syndrome. In lipodystrophy, fat loss begins in adolescence, suggesting the potential that treatment with leptin or thiazolidinediones may be started prior to that time. After the development of fat loss, but well before onset of diabetes, dyslipidemia, high FFA, and C-reactive protein and low leptin levels are seen, with hypertension, then hyperglycemia, and then atherosclerosis and subsequent complications occurring clinically. Hegele suggested that the development of treatment approaches for lipodystrophy syndromes may allow insight into appropriate treatment of individuals with IRS.

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