EDITORIAL

DANIEL J. BROTMAN, MD
Department of General Internal Medicine,
The Cleveland Clinic

JOHN P. GIROD, DO
Department of General Internal Medicine,
The Cleveland Clinic

The metabolic syndrome: A tug-of-war with no winner

ABSTRACT

The metabolic syndrome may be viewed as a state of insulin-counterregulatory overdrive: counterregulatory hormones and fatty acids chronically duel with insulin, causing a cascade of biochemical interactions resulting in insulin resistance, hypertension, and dyslipidemia. Even before beta cells fail and type 2 diabetes ensues, the deadly quartet is quietly rehearsing.

Even before beta cells fail, the deadly quartet is quietly rehearsing

AS DISCUSSED by Nambi and colleagues in this issue of the *Journal*,[1] we now recognize that insulin resistance, obesity, hypertriglyceridemia, and increased cardiovascular tone (hypertension, in particular) cluster in certain individuals, leading to markedly elevated risk of cardiovascular disease and type 2 diabetes. This clustering has been called the *deadly quartet*, *syndrome X*, and now, the *metabolic syndrome*.

See related article, page 985

While the mechanisms behind this clustering are incompletely understood and multifactorial, we present some of the current concepts and hypotheses that address how these four seemingly distinct conditions may arise from a common pathophysiologic process.

THE ONGOING DUEL BETWEEN INSULIN AND COUNTERREGULATION

In general, we believe the metabolic syndrome can be thought of as a state of insulin-counterregulatory overdrive (FIGURE 1), in which insulin chronically duels with counterregulatory hormones, such as glucocorticoids, glucagon, and catecholamines, along with free fatty acids. These two physiologic processes become "revved up" while working against each other. In a biochemical tug-of-war, insulin is trying to store fuel, while counterregulatory hormones and fatty acids are trying to prevent fuel storage. We believe this ongoing battle causes the complex abnormalities of the metabolic syndrome.

Activation of counterregulatory hormones leads to glucose release (gluconeogenesis and glycogenolysis) and impaired cellular glucose uptake. The pancreas responds to increased glucose levels with compensatory hyperinsulinemia to turn off hepatic glucose production and push glucose into cells.

Despite increased counterregulatory activity, hyperinsulinemia accelerates fat deposition, especially in the setting of a high-calorie diet, sedentary lifestyle, or high glucocorticoid activity.

Then, when obesity develops, there is increased free fatty acid release, which further exacerbates insulin resistance.

This cycle of ongoing counterregulatory activity and hyperinsulinemia increases carbohydrate and lipid flux through the bloodstream, which damages the vascular endothelium. The battle between anabolism (insulin) and catabolism (counterregulatory hormones) also taxes the pancreatic beta cells, eventually leading to overt type 2 diabetes.

The precipitating event in a given person may be increased counterregulatory hormones, increased insulin, or both. For example, high insulin levels can precipitate a counterregulatory hormone surge, as might be seen after consumption of a high-glucose-

Insulin-counterregulatory overdrive in the metabolic syndrome: A vicious cycle

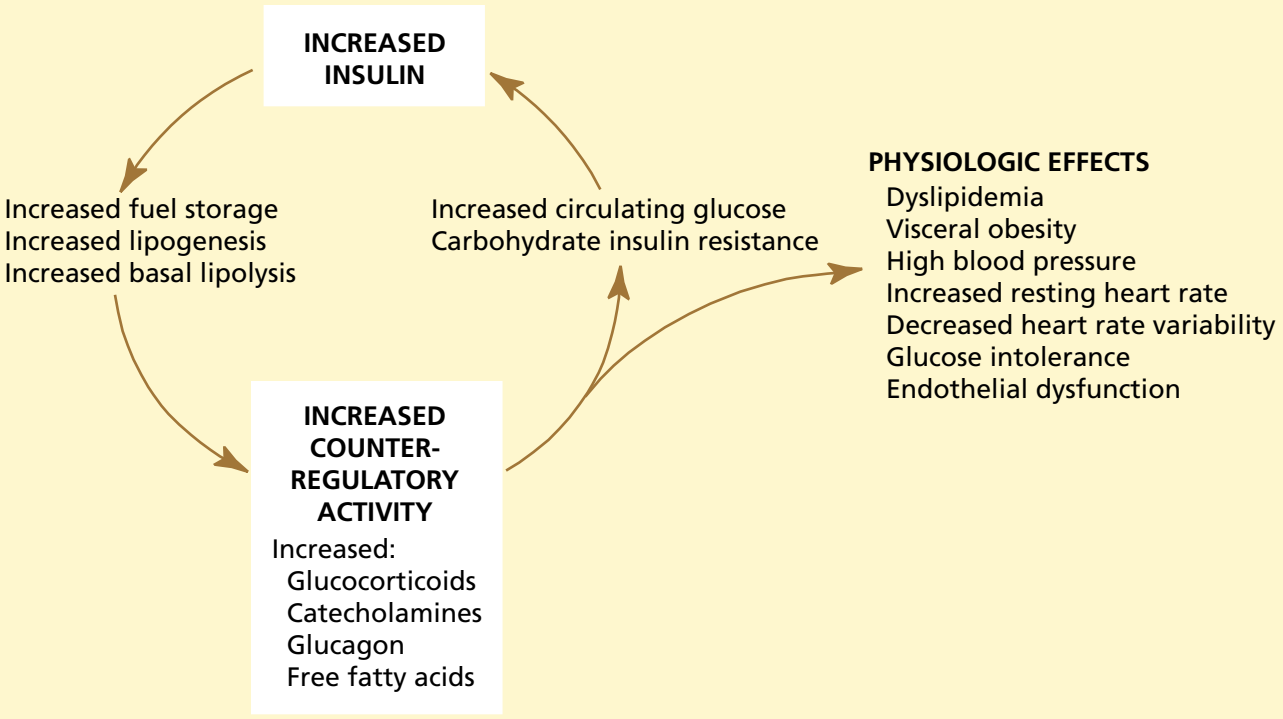

FIGURE 1. Schematic representation of insulin-counterregulatory overdrive in the metabolic syndrome.

containing meal,[2] and precipitate insulin resistance.

However, it does not really matter which is the precipitating event. Increased insulin leads to increased counterregulatory activity, while increased counterregulatory activity leads to hyperinsulinemia. The body is attempting to maintain balance between these two competing processes, and when one is increased, the other has to increase to compensate (ie, counterregulation). When counterregulatory activity begins competing with insulin, the metabolic syndrome has begun.

THE ROLE OF INSULIN RESISTANCE

As the primary anabolic hormone, insulin has two main functions:

- It facilitates cellular uptake of nutrients (carbohydrate, protein, and lipids) from the bloodstream while inhibiting nutrient release; and
- It suppresses the liver's catabolic functions—those vital functions that the liver performs during fasting or famine, such as gluconeogenesis, glycogenolysis, and ketone production.

"Insulin resistance" generally refers to *carbohydrate insulin resistance:* impaired cellular glucose uptake and accelerated hepatic glucose release.

Carbohydrate insulin resistance can result from different mechanisms, including counterregulatory hormones, high levels of certain metabolic substrates (particularly free fatty acids), environmental factors (diet and lifestyle), and abnormal insulin signal-

ing. It is unlikely that any one of these mechanisms of insulin resistance is solely responsible for the metabolic syndrome. More likely, various combinations of these factors precipitate and exacerbate insulin resistance in different individuals. Our discussion will focus on counterregulatory hormones and fatty acids.

Growth hormone and glucocorticoids: Effects on fat and protein metabolism

Two counterregulatory hormones, growth hormone and glucocorticoids, have different effects on lipid and protein metabolism that may be important in the development and maintenance of the metabolic syndrome.

Growth hormone levels are often low in the metabolic syndrome,[3] and this counterregulatory hormone may actually protect against obesity. Growth hormone facilitates lipolysis, promoting a net flux of nutrients out of adipose tissue.[4] At the same time, it leads to carbohydrate insulin resistance and compensatory hyperinsulinemia, facilitating protein uptake by myocytes and increasing metabolically active lean body mass.

High insulin competes with counter-regulatory hormones

But despite growth hormone's acute adverse effects on insulin sensitivity, chronic replacement of growth hormone in the metabolic syndrome may actually improve insulin sensitivity, dyslipidemia, and hypertension, presumably by decreasing fat mass.[5]

Glucocorticoids. The converse of growth hormone-induced insulin resistance is glucocorticoid-induced insulin resistance. Glucocorticoids block insulin's anabolic effects on carbohydrate and protein metabolism while promoting insulin-mediated lipogenesis.[6] This is why patients with Cushing syndrome develop central obesity, glucose intolerance, and muscle wasting. The phenotypic similarities between Cushing syndrome and the metabolic syndrome (truncal obesity, hypertension, and insulin resistance) suggest that endogenous glucocorticoids may play a role in the metabolic syndrome.

Some research supports this hypothesis. Patients with the metabolic syndrome do not generally have high mean cortisol levels, but glucocorticoid activity may be elevated in other respects. For example, enzymes that regenerate cortisol (from inactivated cortisone) are particularly active in visceral (intra-abdominal) fat,[7] and may augment cortisol production and lipogenesis in these fat depots. Increased endogenous glucocorticoid activity may also manifest as a blunted circadian amplitude of cortisol levels, lower morning peaks of cortisol, and elevated evening troughs.[8]

In rodent models, experimental interventions that blunt circadian glucocorticoid patterns result in the accumulation of visceral fat, even in the absence of elevated mean glucocorticoid levels.[9]

Aging's effect on growth hormone and glucocorticoid activity. Blunting of the circadian cortisol pattern is also a feature of normal aging in humans,[10] and this might predispose the elderly to visceral obesity and the metabolic syndrome.

Aging is also associated with a reduction in growth hormone and sex steroids, potentiating abdominal fat accumulation in the setting of unopposed cortisol.[11]

ROLE OF OVEREATING AND UNDEREXERCISING

Sedentary lifestyle and excess food can exacerbate insulin resistance, even in the absence of obesity.[12,13]

The body has limited carbohydrate storage capacity (less than 24 hours' worth of energy can be stored in hepatic and muscle glycogen) but virtually unlimited fat storage capacity.

If nutrients are ingested when glycogen stores are abundant and energy demands are modest, then glucose is not readily taken up by the liver or muscle, exacerbating hepatic and muscle insulin resistance. Then, excess carbohydrate is converted to fat,[14] some of which is exported from the liver as triglycerides.

When glycogen stores are depleted by physical exercise, the liver and muscles have more room for glycogen storage, resulting in improved glucose uptake and insulin sensitivity.[13,14] Exercise and diet can also improve insulin sensitivity by more complicated biochemical mechanisms.[13]

ROLE OF OBESITY

Insulin resistance is correlated with obesity and can be reversed with weight loss, suggesting that obesity is central to the pathogenesis and maintenance of the metabolic syndrome. This can be explained by two observations:

- The breakdown of fat (lipolysis) leads to insulin resistance; and
- Obesity leads to a higher rate of basal lipolysis.

Lipolysis leads to insulin resistance: The role of free fatty acids

Nonesterified (free) fatty acids are the primary breakdown product of fat cell nutrient stores. During times of catabolism (such as starvation), free fatty acids are released into the bloodstream in large quantities for other tissues to use as fuel.

High free fatty acid levels competitively inhibit insulin-stimulated glucose oxidation and uptake by the liver and muscle.[15] This is adaptive in starvation: decreased glucose utilization by the liver and muscles spares glucose for the brain and preserves cellular protein that would otherwise be consumed by gluconeogenesis.

But even in a well-fed state, adipocytes release some free fatty acids constitutively (basal lipolysis). Basal lipolysis is under hormonal control: it is upregulated by counterregulatory hormones and the renin-angiotensin-aldosterone system,[16] and inhibited by insulin. (Stimulation of lipolysis is one important mechanism by which the counterregulatory hormones exacerbate carbohydrate insulin resistance.)

Obesity leads to a higher rate of basal lipolysis

Independent of hormonal control, the overall release of free fatty acids into the bloodstream is also a function of fat mass. An obese person will have higher total free fatty acid release than a thin person, even if each fat cell is releasing the same quantity of free fatty acids.

This may contribute to higher circulating free fatty acid levels and insulin resistance in obesity.[17]

Other effects of free fatty acids

The adverse effects of high free fatty acid flux extend beyond the exacerbation of insulin resistance.

Circulating free fatty acids have two fates: they can be used as fuel (oxidized) or they can be re-esterified into triglycerides. Free fatty acids processed by the liver can be exported to the systemic circulation as very-low-density lipoprotein cholesterol and may contribute to hypertriglyceridemia.[15]

Moreover, elevated free fatty acid levels may inhibit growth hormone in the metabolic syndrome: since growth hormone promotes lipolysis, it is not surprising that free fatty acids suppress growth hormone as a feedback control.[18]

Other products of adipocytes, such as resistin, angiotensinogen, leptin, and cytokines, may also play a role in the insulin resistance of obesity.[19] But it remains uncertain whether these factors are important in the pathogenesis of the metabolic syndrome.

INCREASED CARDIOVASCULAR TONE: HYPERTENSION

The observation that hypertension is common in type 1 diabetes and may be reversible with pancreas transplantation[20] highlights the importance of insulin and counterregulatory hormones in the maintenance of normal cardiovascular tone. Patients with the metabolic syndrome tend to have hypertension, impaired endothelium-mediated vasodilatation (endothelial dysfunction), elevated resting heart rates, and decreased heart-rate variability.[8,21]

The cardiovascular effects of counterregulatory hormones trump those of insulin

Since insulin is vasodilatory at the peripheral level, while all of the counterregulatory hormones increase cardiovascular tone, it appears that the cardiovascular effects of counterregulatory hormones trump those of insulin in the metabolic syndrome. They do so by targeting the heart and the vascular smooth muscle and by impairing endothelium-mediated vasodilatation.

Catecholamines are potent counterregulatory hormones, opposing the actions of insulin on carbohydrate and lipid metabolism. (This is why patients with pheochromocy-

toma develop hyperglycemia.)

In the metabolic syndrome, norepinephrine, the primary catecholamine released from sympathetic nerve terminals, is elevated in the urine, likely reflecting increased sympathetic nervous system activity.[22]

Free fatty acids. The recent observation that free fatty acid infusion increases blood pressure, norepinephrine levels, and heart rate while decreasing heart rate variability[23] suggests that increased free fatty acids contribute to increased sympathetic activity in the metabolic syndrome. Free fatty acids may also impair endothelial function[24]

Glucagon is another counterregulatory hormone that is sometimes elevated in diabetes,[25] antagonizing insulin's anabolic effects throughout the body, but particularly in the liver. Glucagon increases cardiac chronotropy and inotropy and is an antidote for beta-blocker overdose.

Cortisol and **growth hormone** may increase cardiovascular tone through potentiation of catecholamine effects[26] and perhaps by stimulating lipolysis. Hypertension is a well-known complication of both Cushing disease (in which cortisol levels are high) and acromegaly (in which growth hormone levels are high), while Addison disease, in which cortisol levels are low, predisposes to hypotension.

It appears, then, that all counterregulatory hormones (and free fatty acids) not only antagonize the effects of insulin on carbohydrate metabolism, but also increase cardiovascular tone. It follows that any type of hormone-induced carbohydrate insulin resistance has the potential to be associated with increased cardiovascular tone (and to stress the cardiovascular system), especially when insulin production is compromised.[27]

Acknowledgments: We thank Nkem Chukwumerjie, David Gugliotti, Shaun Frost, and Adi Mehta for their helpful suggestions.

REFERENCES

1. **Nambi V, Hoogwerf BJ, Sprecher DL.** A truly deadly quartet: obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia. Cleve Clin J Med 2002; 69:985–989.
2. **Ludwig DS.** The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002; 287:2414–2423.
3. **Johannsson G, Marin P, Lonn L, et al.** Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. J Clin Endocrinol Metab 1997; 82:727–734.
4. **Ho KK, O'Sullivan AJ, Hoffman DM.** Metabolic actions of growth hormone in man. Endo J 1996; 43(suppl):S57–S63.
5. **Johannsson G, Bengtsson BA.** Growth hormone and the metabolic syndrome. J Endocrinol Invest 1999; 22(suppl 5):41–46.
6. **Fried SK, Russell CD, Grauso NL, Brolin RE.** Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. J Clin Invest 1993; 92:2191–2198.
7. **Bujalska IJ, Kumar S, Stewart PM.** Does central obesity reflect "Cushing's disease of the omentum"? Lancet 1997; 349:1210–1213.
8. **Bjorntorp P, Holm G, Rosmond R.** Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. Diabet Med 1999; 16:373–383.
9. **Dallman MF, Akana SF, Bhatnagar S, Bell ME, Strack AM.** Bottomed out: metabolic significance of the circadian trough in glucocorticoid concentrations. Int J Obes Relat Metab Disord 2000; 24(suppl 2):S40–S46.
10. **Deuschle M, Gotthardt U, Schweiger U, et al.** With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. Life Sci 1997; 61:2239–2246.
11. **Bjorntorp P.** The regulation of adipose tissue distribution in humans. Int J Obes Relat Metab Disord 1996; 20:291–302.
12. **Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H.** Effect of training on the dose-response relationship for insulin action in men. J Appl Physiol 1989; 66:695–703.
13. **Borghouts LB, Keizer HA.** Exercise and insulin sensitivity: a review. Int J Sports Med 2000; 21:1–12.
14. **Felber JP, Golay A.** Regulation of nutrient metabolism and energy expenditure. Metabolism 1995; 44:(suppl 2):4–9.
15. **Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA.** Effect of fatty acids on glucose production and utilization in man. J Clin Invest 1983; 72:1737–1747.
16. **Hennes MM, O'Shaughnessy IM, Kelly TM, LaBelle P, Egan BM, Kissebah AH.** Insulin-resistant lipolysis in abdominally obese hypertensive individuals. Role of the renin-angiotensin system. Hypertension 1996; 28:120–126.
17. **Groop LC, Bonadonna RC, Simonson DC, Petrides AS, Shank M, DeFronzo RA.** Effect of insulin on oxidative and nonoxidative pathways of free fatty acid metabolism in human obesity. Am J Physiol 1992; 263:E79–E84.
18. **Lanzi R, Losa M, Mignogna G, Caumo A, Pontiroli AE.** The control on growth hormone release by free fatty acids is maintained in acromegaly. J Clin Endocrinol Metab 1999; 84:1234–1238.
19. **Trayhurn P, Beattie JH.** Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 2001; 60:329–339.
20. **Elliott MD, Kapoor A, Parker MA, Kaufman DB, Bonow RO, Gheorghiade M.** Improvement in hypertension in patients with diabetes mellitus after kidney/pancreas transplantation. Circulation 2001; 104:563–569.
21. **Liao D, Sloan RP, Cascio WE, et al.** Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study. Diabetes Care 1998; 21:2116–2122.
22. **Reaven GM, Lithell H, Landsberg L.** Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996; 334:374–381.
23. **Manzella D, Barbieri M, Rizzo MR, et al.** Role of free fatty acids on cardiac autonomic nervous system in noninsulin-dependent diabetic patients: effects of metabolic control. J Clin Endocrinol Metab 2001; 86:2769–2774.
24. **Egan BM, Greene EL, Goodfriend TL.** Nonesterified fatty acids in blood pressure control and cardiovascular complications. Curr Hypertens Rep 2001; 3:107–116.
25. **Gastaldelli A, Baldi S, Pettiti M, et al.** Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans: a quantitative study. Diabetes 2000; 49:1367–1373.
26. **Maison P, Demolis P, Young J, Schaison G, Giudicelli JF, Chanson P.** Vascular reactivity in acromegalic patients: preliminary evidence for regional endothelial dysfunction and increased sympathetic vasoconstriction. Clin Endocrinol (Oxf) 2000; 53:445–451.
27. **Brotman DJ.** Effects of counterregulatory hormones in a high-glycemic index diet. JAMA 2002; 288:695.

ADDRESS: *Daniel J. Brotman, MD, Department of General Internal Medicine, E13, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: brotmad@ccf.org.*