Insulin Resistance and Hypertension in the Absence of Subcutaneous Fat

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When a patient presents with insulin resistance, a red flag for cardiovascular risk appears. What is the contribution of visceral fat to this syndrome? What are the risks and benefits of the treatment options for the coexistent cardiovascular risk factors?
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A 38-year-old white woman with a complex past medical history of dermatomyositis and lipodystrophy was referred for management of hypertension and hyperlipidemia.

History

Dermatomyositis was diagnosed in this patient at age 6. She was treated initially with prednisone, and the condition was considered inactive after she reached age 14. At age 21, the patient first experienced mild hypertension (blood pressure [BP], 156-166/100 mm Hg), but the workup for secondary causes was negative. BP was initially controlled with a diuretic and later with the combination of lisinopril and hydrochlorothiazide. At age 25, she underwent a total abdominal hysterectomy for high-grade cervical atypia. She described herself as being "very skinny" for as long as she could remember, and the diagnosis of generalized lipodystrophy was established when she was 28. Shortly thereafter, the discovery of hepatomegaly by CT scan prompted a liver biopsy, which revealed significant fatty infiltration.

Hyperlipidemia was first established in this patient at age 32 (total cholesterol, 302 mg/dL; low-density lipoprotein [LDL], 210 mg/dL; high-density lipoprotein [HDL], 37 mg/dL; and triglycerides, 236 mg/dL). Therapy with atorvastatin calcium, 10 mg daily, had been started 2 years earlier but was discontinued because of liver enzyme increases. Fasting glucose level was 121 mg/dL, and an oral glucose tolerance test revealed a 2-hour glucose level of 263 mg/dL.

The patient said that her liver size had begun to decrease within the last few months. A recent CT scan of the abdomen revealed a decrease in liver size and a marked reduction in the degree of fatty infiltration, compared with a CT scan performed 6 months previously. During this 6-month period, BP had decreased about

20 mm Hg to the lowest levels she had seen in years. Medications included bisoprolol/hydrochlorothiazide, 10/6.25 mg; quinapril, 40 mg; sustained-release verapamil, 240 mg; and conjugated estrogens, 0.625 mg.

The patient felt reasonably healthy and was employed as a graphic artist. She was physically active and admitted to drinking "1 to 2 beers occasionally" on weekends. She had a 20-pack-year smoking history but had quit smoking 6 years ago and denied any illicit drug use. Her family history was positive for rheumatoid arthritis and hypothyroidism in her mother, gout in her father, and hypertension in her maternal grandmother.

Physical examination

She presented as an extremely asthenic woman with no subcutaneous fat present on her face, thorax, or extremities. She weighed 53.6 kg (118 lb), and her height was 164 cm (5 ft 4 in). BP was 130/80 mm Hg in the right arm and 122/78 mm Hg in the left arm, sitting, with a heart rate of 56 beats per minute. Cardiovascular examination was entirely unremarkable, and peripheral pulses were strong and intact. Her abdomen was slightly distended, and the liver span was 14 cm, with the liver edge smooth and nontender. There was no shifting dullness on percussion or bruits on auscultation. Neurologic examination results were normal.

Laboratory data

A complete blood count revealed only mild anemia, with a hematocrit of 39%. Electrolytes were normal, and blood urea nitrogen and creatinine levels were 12 and 0.7 mg/dL, respectively. Liver function test results were mixed: albumin was 4.2 g/dL; bilirubin, 0.6 mg/dL; asparate aminotransferase, borderline at 36 U/L; and γ-glutamyltransferase, elevated at 119 U/L. Total cholesterol was 198 mg/dL; HDL, 39 mg/dL; LDL, 86 mg/dL; triglycerides, 364 mg/dL. Creatine kinase level was elevated at 509 U/L, but the erythrocyte sedimentation rate and coagulation indices were normal. Urinalysis results were normal, but creatinine clearance was elevated at 122 mL/min. Fasting glucose level was 91 mg/dL, but C-peptide was 1.7 ng/mL (normal, 0.5 to 2 ng/mL), and insulin was 36 μU/mL (normal, less than 20 μU/mL).

Main Points

- The insulin resistance syndrome depends largely on intra-abdominal, rather than subcutaneous, fat.
- Defects in the insulin signaling pathway may be caused by the effects of tumor necrosis factor-alpha (released by adipose tissue) or by activation of protein kinase C (by fatty acid moieties).
- Reduced glucose uptake in skeletal muscle may play a prominent role in insulin resistance.
- The insulin resistance syndrome includes central obesity, hypertension, dyslipidemia, elevated prothrombotic and antifibrinolytic factors, and increased risk of coronary artery disease—in the absence of diabetes.
- For controling blood pressure in patients with insulin resistance, options include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Discussion

Insulin resistance, lipodystrophy, and central obesity. Insulin resistance, in a physiologic sense, can be defined simply as an impaired response to exogenous or endogenous insulin.[1] The pattern of obesity in the insulin resistance syndrome has been characterized as "central obesity," with increased waist-hip ratio and increased visceral fat demonstrable on abdominal CT or magnetic resonance studies. Insulin resistance in this "very skinny" woman with lipodystrophy and essentially no subcutaneous or peripheral adipose tissue demonstrates that the insulin resistance syndrome is largely dependent on the presence of intra-abdominal, rather than subcutaneous, fat. In this case, the fatty infiltration of the liver could be related to the insulin resistance or be a manifestation of visceral fat deposition.[2] The relationship between the degree of fatty infiltration and the systemic BP strongly suggests a common etiology of the 2 conditions, and the reversal of fatty infiltration could be related to an improvement in insulin resistance. The terms lipodystrophy and lipoatrophy are generally synonymous and refer to conditions in which subcutaneous fat is absent. Lipoatrophic diabetes is a recognized syndrome of unknown etiology that represents a subtype of the broader condition of diabetes mellitus.[3]

Numerous mechanisms for insulin resistance in visceral adiposity have been suggested, one of which is increased fatty acid liberation into the portal vein, resulting in a greater supply of fatty acids to the muscle; the fatty acids then decrease glucose oxida-

tion.[4] It has also been shown that visceral adipocytes are larger than peripheral adipocytes and, therefore, are more prone to liberate fatty acids.[5] Defects in the insulin signaling pathway may be due to activation of protein kinase C by fatty acid moieties or to the effects of tumor necrosis factor-alpha released by adipose tissue (Figure).[4,6] Resistance is generally said to be present if the fasting insulin concentration in normoglycemic individuals is above 15 μU/mL.[7,8]

Insulin resistance and skeletal muscle. Another interesting aspect in this case is the history of dermatomyositis and the potential role of skeletal muscle glucose metabolism in the genesis of insulin resistance. In healthy persons, more than two thirds of insulin-induced glucose uptake occurs in muscle, while about 10% occurs in adipose tissue.[9] Therefore, reduced glucose uptake in skeletal muscle can have a prominent role in insulin resistance. The type of muscle fibers present may also affect glucose uptake; type 1 fibers of muscle are insulin-sensitive, while type 2b fibers tend to be insulin-resistant.[10] Decreased insulin sensitivity has been reported in muscular disorders in which fiber composition is altered[11] but not specifically in dermatomyositis.

Antibodies and insulin resistance. Antibodies to insulin or insulin receptors have been reported in association with autoimmune illnesses. Such patients usually demonstrate severe insulin resistance, elevated fasting glucose levels, and acanthosis nigricans,[3] none of which occurred in the present case.

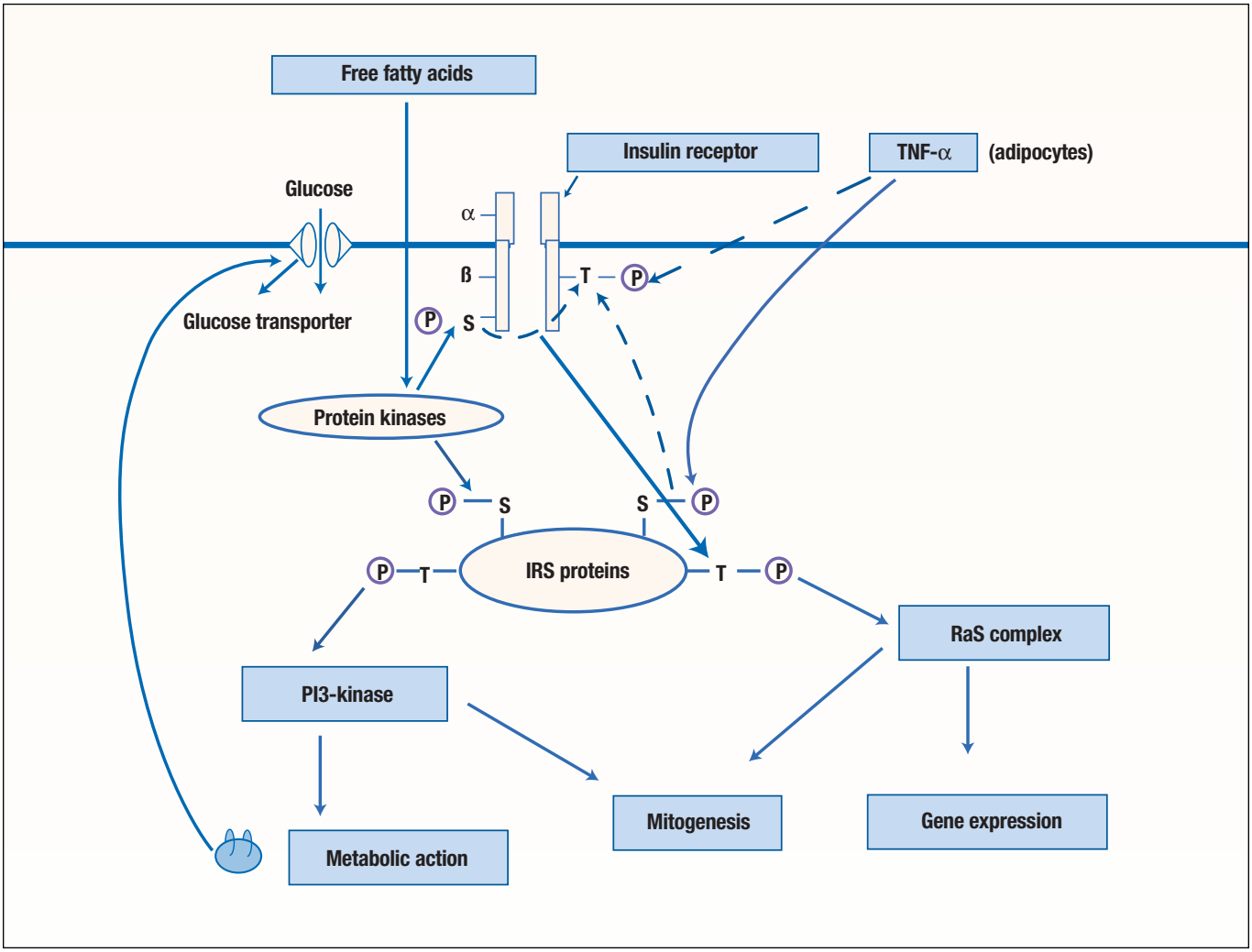

Figure. Insulin signaling pathway defects. α, α subunit; β, β subunit; TNF-α, tumor necrosis factor-alpha; T, tyrosine; S, serine; P, phosphorylation; PI3-kinase, phosphoritidyl inositol-3 kinase; RaS, rat sarcoma protein; solid arrow, stimulation; broken arrow, inhibition.[22]

The insulin resistance syndrome and associated disorders. The recognition of the clustering of several other cardiovascular risk factors with insulin resistance has expanded the meaning of the original physiologic term to include a complex syndrome of central obesity, hypertension, dyslipidemia (high triglycerides, low HDL, increased small-dense LDL), elevated prothrombotic and antifibrinolytic factors, and increased risk of coronary artery disease.[12] This constellation of risk factors in the absence of diabetes is now known by various names, including the insulin resistance syndrome, the metabolic syndrome X, and the cardiovascular dysmetabolic syndrome. Insulin resistance should be suspected if any of the conditions associated with it (see Table) are present.

Table
Causes of Insulin Resistance

Common	Uncommon
Type 2 diabetes mellitus	Type A syndrome (insulin receptor defects)
Obesity associated with central adiposity	Type B syndrome (antibody-related)
Gestational diabetes mellitus	Lipoatrophy (congenital/acquired)
Impaired fasting glucose (> 110 mg/dL)	Leprechaunism
Strong family history of type 2 diabetes mellitus	Cushing syndrome
Hypertension	Acromegaly
Polycystic ovarian syndrome	Pheochromocytoma
AIDS-related lipodystrophy	Rabson-Mendenhall syndrome
Pregnancy	Rare genetic syndromes
Hyperthyroidism	Renal failure
Cirrhosis	
Acute illness and surgery	

More recently, it has been appreciated that other conditions are associated with insulin resistance. HIV is also associated with generalized lipodystrophy.[13] Homology between the genetic sequence of 2 proteins responsible for peripheral adipocyte differentiation and cleavage of triglycerides and the HIV protease has been suggested as a possible mechanism.[13]

Hypertension and insulin resistance. The precise relationship between insulin resistance and hypertension remains unclear. The insulin resistance syndrome is associated with increased sympathetic activity and increased renal salt retention.[14] There is some evidence that a primary increase in sympathetic activity can cause parallel increases in forearm insulin resistance and BP. Catecholamines cause insulin resistance directly, as is observed in patients with pheochromocytoma.[15] On the other hand, there is also evidence that insulin can stimulate the sympathetic nervous system.[16] Whatever the pathogenesis of the syndrome, chronic hypertension is not caused by insulin alone, at least in humans. Insulin is a powerful vasodilator that acts through endothelial mechanisms to stimulate the synthesis of nitric oxide (NO) and cyclic guanosine monophosphate (GMP).[17,18] A deficiency in the NO-cyclic GMP axis, however, could diminish the vasodilating effects of insulin and contribute to increased vascular resistance.

Treatment of insulin resistance. Treatment options in insulin resistance begin with exercise and diet. Pharmacotherapy with insulin sensitizers may help reduce central adiposity and hyperinsulinemia. In the present case, metformin therapy could be considered, although it has not been shown to reduce BP consistently.

Thiazolidinediones, which are attractive therapeutic possibilities for most insulin-resistant people, would probably not be appropriate in this patient because of the presence of liver function abnormalities and the potential for liver toxicity.

For BP control in diabetes or insulin resistance, angiotensin-converting enzyme (ACE) inhibitors are clearly preferred[19] and should be continued as the cornerstone of hypertension management in this case. Angiotensin receptor blockers appear to be favorable alternatives for those intolerant of ACE inhibitors. Thiazides and β-blockers have also demonstrated long-term benefit in cardiovascular mortality and morbidity and are also useful for treating patients with diabetes.[20] Calcium antagonists do not appear to confer the same degree of cardioprotection as ACE inhibitors in patients with diabetes.[21]

Concomitant management of dyslipidemia in patients with insulin resistance is often overlooked and may be equally important as effective hypertension management. In such patients, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in-

hibitors are useful to decrease LDL levels, and fibric acid derivatives are sometimes used for management of hypertriglyceridemia. Niacin should be avoided generally, because it can worsen glucose tolerance in patients with insulin resistance.

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