Insulin resistance refers to the reduction in insulin-mediated glucose uptake in insulin-sensitive tissues, specifically in skeletal muscle. As a compensatory response, hyperinsulinemia ensues to maintain normal blood glucose levels. In epidemiological studies, fasting insulin level is commonly used as a surrogate marker of insulin resistance. In normoglycemic subjects, fasting insulin correlated well with whole-body glucose uptake \( r = -0.68 \) as measured by the “gold standard” euglycemic hyperinsulinemic clamp method, although the correlation was lower in individuals with impaired glucose tolerance or type 2 diabetes mellitus.1 Although fasting insulin is a reasonable measure of insulin resistance, it is potentially confounded by variability in insulin secretion. Thus, the indexes derived from fasting insulin and glucose, such as the Homeostasis Model Assessment (HOMA),2 the Quantitative Insulin Sensitivity Check Index (QUICKI),3 and the insulin sensitivity index (ISI) developed by Gutt and coworkers,4 have been more widely used to assess insulin resistance in clinical and population-based studies.

Although the relationship between insulin resistance and blood pressure remains controversial. Nearly 40 years ago, Welborn and colleagues6 observed that nondiabetic patients with essential hypertension had significantly higher plasma insulin concentrations than did normotensive individuals. This positive relationship has been confirmed in several longitudinal studies, but the results are not entirely consistent. In some studies, the association between hyperinsulinemia and incident hypertension disappeared after adjustment for body mass index (BMI), suggesting that the association is confounded or mediated through obesity. Therefore, the causal role of insulin resistance/compensatory hyperinsulinemia in the development of hypertension continues to be debated.

As reported in this issue of Circulation, Årnlöv and colleagues6 investigated the relationship between insulin sensitivity, using ISI, and the 4-year incidence of hypertension and blood pressure (BP) progression in 1933 nonhypertensive participants in the Framingham Offspring Study. In the overall analyses, increasing quintiles of insulin sensitivity were significantly associated with a progressively lower incidence of hypertension after adjustment for age and sex. The association was somewhat attenuated but remained statistically significant after additional adjustment for BMI. The association became nonsignificant, however, after additional adjustment for baseline systolic and diastolic BP. Stratified analyses by age, baseline BMI, and BP category revealed that in the final multivariate model, ISI was significantly associated with a lower incidence of hypertension or BP progression among younger (<51 years old) participants with a normal BMI (<25) and a baseline BP <130/85 mm Hg. Insulin sensitivity was not significantly related to hypertension in older or overweight participants or in participants with baseline BP ≥130/85 mm Hg.

This study has several strengths when compared with previous studies, including the large well-characterized community-based sample of normotensive participants, standardized and repeated measurements of BP, and the use of a validated ISI instead of fasting plasma insulin level. This study does not clearly resolve the controversy about the causal relationship between insulin resistance and hypertension, however. One major issue is how to interpret the subgroup findings. Although the authors suggested that the study had sufficient power to detect a statistically significant effect in the strictly defined subgroup (participants <51 years old with normal BMI and BP <130/85 mm Hg at baseline, n=388), the analyses implied a 3-way statistical interaction (age×BMI×BP), and it is not clear whether the 3-way interaction was statistically significant (data were not presented). Even if it were, it does not necessarily mean a biological interaction. Although a significant association in younger participants of normal weight suggests that the results are less likely to be confounded by age and BMI, the lack of a dose-response relationship between ISI and hypertension incidence and BP progression in the subgroup actually argues against a causal interpretation. It also makes it difficult to replicate the findings because of the possible differences in the distributions and cutoff points for insulin sensitivity in different populations and of the subjectivity involved in defining the subgroups by multiple variables.

Where shall we go from here? This controversy is unlikely to be completely resolved by clinical trials because of the complex and potentially reciprocal relationships between insulin resistance and hypertension. Additional large longitudinal studies with repeated measures of insulin sensitivity, BP, and other components of the metabolic syndrome are needed.
desirable but also unlikely to be conclusive because both insulin sensitivity and BP are continuous traits and there are no standard definitions or cutoff points for insulin resistance. Although most studies have attempted to address the question of whether insulin resistance predicts subsequent development of hypertension, one also may ask whether higher BP at baseline predicts hyperinsulinemia or increased insulin resistance during follow-up. In a longitudinal analysis of 9020 nondiabetic participants from the Atherosclerosis Risk in Communities Study, Carnethon and coworkers7 identified several predictors of the development of hyperinsulinemia (defined as fasting serum insulin ≥90th percentile) during 11 years of follow-up, including baseline waist/hip ratio and uric acid and HDL levels, as well as starting to smoke and becoming obese during the study. Incident hypertension was also a significant predictor of hyperinsulinemia, although the association was mediated mainly through the development of obesity during the follow-up. These analyses suggest that the relationship between hypertension and hyperinsulinemia is probably not unidirectional, and thus it might not be possible to completely address the chicken-egg question, even with carefully designed prospective studies.

Although there are several biological reasons why insulin resistance and compensatory hyperinsulinaemia precede the development of hypertension, they are not sufficiently compelling and can be argued both ways. First, several studies in humans have shown that insulin infusion led to elevated levels of norepinephrine and increased systolic BP and pulse pressure independent of blood glucose levels.8 Other studies, however, found that acute insulin infusion within the physiological range actually produced forearm vasodilation and did not elevate arterial pressure.9 Second, insulin may enhance sodium retention by directly increasing sodium reabsorption in renal tubules and indirectly through the activation of the sympathetic nervous system and renin-angiotension system. Because sodium clearly plays a role in essential hypertension, it has been suspected that insulin resistance may cause hypertension in salt-sensitive individuals. Higher sodium intake can, however, lead to insulin resistance and increase risk of type 2 diabetes mellitus,10 suggesting that hypertension and insulin resistance may not cause one another but share common causes. In particular, obesity, weight gain, unhealthy diet, and physical inactivity are major determinants of both hypertension and insulin resistance. C-reactive protein, a powerful predictor of insulin resistance and type 2 diabetes mellitus, has also been associated with increased risk of hypertension,11 suggesting that systematic inflammation may be the underlying mechanism for both insulin resistance and hypertension.

The close relationship between insulin resistance and hypertension may be better understood in the context of the metabolic syndrome. Reaven12 first described the clustering of insulin resistance with hyperinsulinemia, dyslipidemia, essential hypertension, obesity, and glucose intolerance or type 2 diabetes mellitus as “syndrome X.” In 1998, the World Health Organization provided a working definition for this syndrome and named it “metabolic syndrome.”13 In 2001, the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III)14 defined the metabolic syndrome if ≥3 of the following 5 criteria are met: central obesity, elevated triglycerides, decreased HDL, hypertension, and impaired fasting glucose or diagnosed diabetes. Conceptually, insulin resistance is considered the central feature or the root cause of the metabolic syndrome because it is strongly related to all other components of the metabolic syndrome as well as to elevated proinflammatory markers, thrombogenic factors, and endothelial dysfunction. All of these factors are thought to underlie increased risk of cardiovascular disease. In several epidemiological studies, the metabolic syndrome defined by either the World Health Organization or ATP III criterion is strongly predictive of incident cardiovascular morbidity and mortality. In comparison, the association between hyperinsulinemia and risk of coronary heart disease is less consistent and robust. Clinically, assessment of the metabolic syndrome should be more useful and practical than the measurement of fasting insulin levels.

Because insulin resistance and hypertension share common dietary and lifestyle risk factors as well as similar pathophysiological pathways, including chronic inflammation and endothelial dysfunction, the key question is whether lifestyle and pharmacological interventions that improve insulin sensitivity also reduce risk of hypertension and cardiovascular disease. Recently, Esposito and coworkers15 conducted a randomized clinical trial of the effect of a Mediterranean-style diet on the metabolic syndrome and cardiovascular risk factors. The intervention group was instructed to increase consumption of whole grains, fruits and vegetables, nuts, and olive oil and to reduce the consumption of refined carbohydrates and animal fats. During 2 years of follow-up, body weight decreased more in patients in the intervention group than in those in the control group (P<0.001). Compared with patients consuming the control diet, patients consuming the Mediterranean-style diet had significantly reduced serum concentrations of high-sensitivity C-reactive protein and blood pressure and improved insulin sensitivity and endothelial function. The prevalence of the metabolic syndrome was significantly reduced even after adjustment for differences in weight loss between the 2 groups. In the US Diabetes Prevention Program (DPP), intensive lifestyle intervention was highly effective in prevention of type 2 diabetes mellitus among participants with impaired glucose tolerance. Also, the lifestyle intervention significantly decreased blood pressure and the development of the metabolic syndrome as well as the concentrations of C-reactive protein.16 These results suggest that changes in diet and lifestyle can address the fundamental causes of the metabolic syndrome, which leads to benefits in improving insulin sensitivity and reducing multiple cardiovascular risk factors.

Several pharmacological approaches also hold promises in improving insulin sensitivity and reducing cardiovascular risk. A class of antidiabetic drugs called thiazolidinediones with insulin-sensitizing properties can also lower blood pressure, decrease triglyceride levels, increase HDL levels, and reduce proinflammatory markers.17 The metabolic effects of peroxisome proliferator-activated receptor-γ agonists are complementary to the beneficial lipid effects of statins in
treatment of patients with type 2 diabetes mellitus and the metabolic syndrome. Antihypertensive drugs such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have been shown to improve insulin sensitivity and prevent or delay the onset of type 2 diabetes mellitus. It is speculated that the effects of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers on insulin sensitivity and diabetes are partly mediated through blocking the renin-angiotensin-aldosterone system and improved vascular endothelial function in peripheral tissues such as skeletal muscles.

Abundant clinical and epidemiologic evidence demonstrates a close linkage between insulin resistance and hypertension. The study by Ärnlöv et al. reminds us of the difficulty in teasing out causes and consequences among highly correlated biological variables even through careful statistical analyses. We may never be able to fully resolve the chicken-egg question with regard to insulin resistance and hypertension, but this should not prevent us from implementing effective lifestyle and pharmacological interventions to prevent and treat insulin resistance, hypertension, and the metabolic syndrome.

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References


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