Insulin Resistance, Hypertension, and Coronary Heart Disease

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The goals of this review are two-fold: to examine the evidence in support of a role for insulin resistance and compensatory hyperinsulinemia in the pathogenesis of essential hypertension, and to evaluate the hypothesis that insulin resistance and its manifestations play major roles in the development of coronary heart disease in patients with essential hypertension. In both instances, only experimental results in human beings will be considered. Although it remains a scientific issue of great importance, the scope of this review precludes a discussion of the mechanistic link between insulin resistance/hyperinsulinemia and essential hypertension. (J Clin Hypertens. 2003;5:269–274) ©2003 Le Jacq Communications, Inc.

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INSULIN RESISTANCE, COMPENSATORY HYPERINSULINEMIA, AND HYPERTENSION

Does Insulin Resistance Exist in Patients With Essential Hypertension?

In 1966, Welborn et al.[1] studied 19 individuals diagnosed as having essential hypertension and demonstrated that patients with high blood pressure had significantly higher plasma insulin concentrations than a control population. However, it was not until about 20 years later that several research groups[2–6] confirmed the original observation of Welborn et al.[1] There is also evidence that hypertension is associated with glucose intolerance.[5–7] The combination of glucose intolerance and hyperinsulinemia strongly suggested that a defect in insulin-stimulated glucose uptake was likely to exist in some patients with hypertension, and there is now considerable evidence indicating that this is the case.[4–6,8]

These earlier observations stimulated a great deal of research activity focusing on the relationship between insulin resistance and/or compensatory hyperinsulinemia and hypertension, and there now appears to be general agreement that insulin resistance and compensatory hyperinsulinemia are commonly seen in patients with essential hypertension. However, not all patients with essential hypertension are insulin resistant and hyperinsulinemic. Since resistance to insulin-mediated glucose uptake and compensatory hyperinsulinemia are continuous variables, not dichotomous ones, obtaining a precise estimate of the frequency of abnormalities of insulin metabolism in patients with essential hypertension is not as simple as it may seem. The results of the study illustrated in Figure 1 represent an effort to address this issue by comparing the distribution of plasma insulin concentrations 2 hours after the ingestion of 75 g of glucose in 41 patients with hypertension and 41 normotensive subjects.[9] These hypertensive patients were identified

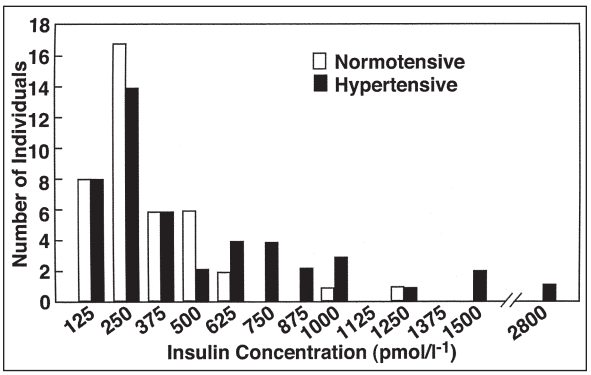

Figure 1. Frequency distribution of the plasma insulin response 2 hours after a 75 g oral glucose challenge in normotensive (clear bar) and hypertensive (filled bar) volunteers. Reprinted with permission from J Intern Med. *1992;231:235–240.*[9]

as part of a routine health survey, and the normotensive subjects were participants in the same survey, selected to match the patients with respect to variables such as sex, degree of obesity, ethnic background, type of employment, and level of physical activity. Only 10% of the normotensive subjects had 2-hour plasma insulin concentrations greater than 80 μU/mL, compared with 45% of the patients with hypertension. In light of these and other findings,[8] approximately 50% of patients with hypertension can be considered to be insulin resistant and hyperinsulinemic.

Based on the above considerations, it seems reasonable to conclude that a substantial proportion of patients with essential hypertension are resistant to insulin-mediated glucose disposal and are hyperinsulinemic. In addition, they will tend to be somewhat glucose intolerant, with elevated plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentrations as discussed subsequently. In other words, hypertension in these patients exists as one of the manifestations of the insulin resistance syndrome.

Does Insulin Resistance/Compensatory Hyperinsulinemia Play a Role in Regulation of Blood Pressure?

Insulin resistance and compensatory hyperinsulinemia appear to be neither necessary nor sufficient for essential hypertension to develop. The results noted in Figure 1 demonstrated that a significant proportion of patients with essential hypertension were insulin sensitive. Furthermore, blood pressure does not increase in all subjects who are insulin resistant and hyperinsulinemic, and for any number of reasons, hyperinsulinemia in these individuals does not lead to an increase in blood pressure. On the other hand, insulin-resistant subjects are more likely to develop hypertension than are insulin-sensitive individuals, and this situation resembles the pathophysiologic role of insulin resistance in the development of type 2 diabetes.[10] Hyperglycemia develops in insulin-resistant individuals when they no longer are able to secrete the large amount of insulin necessary to overcome insulin resistance. Similarly, it seems likely that hypertension only develops when some unknown compensatory response (or responses) is no longer able to overcome the metabolic changes associated with insulin resistance and compensatory hyperinsulinemia that favor an increase in blood pressure.

What Is Primary: Hypertension or Insulin Resistance?

There are three lines of evidence providing substantial support of the view that insulin resistance/hyperinsulinemia antedates hypertension.

1. Neither insulin resistance nor hyperinsulinemia are increased in prevalence in patients with secondary forms of hypertension.[11,12]
2. Normotensive, first-degree relatives of patients with high blood pressure who are at increased risk to develop hypertension are relatively insulin resistant and hyperinsulinemic when compared with normotensive individuals without a family history of hypertension.[13–15] Furthermore, these observations are independent of differences in overall or regional adiposity.
3. Several prospective studies have shown that baseline hyperinsulinemia, as a surrogate measure of insulin resistance, predicts the development of essential hypertension.[16–20] Perhaps the publication that is the most relevant to the focus of this review is the results observed in 1865 children and adolescents followed over a 6-year period.[19] In addition to showing that the higher the fasting insulin concentration at baseline, the greater the increase in blood pressure over the 6-year period of observation, evidence was presented that "high insulin levels seem to precede the development of a potentially atherogenic risk factor profile including low HDL-C, high triglyceride, and elevated systolic blood pressure."

The evidence summarized to this point suggests that insulin resistance and compensatory hyperinsulinemia are increased in prevalence in approximately 50% of individuals with hypertension, and the presence of these abnormalities in normotensive individuals predicts the eventual development of essential hypertension. Furthermore, there is no evidence that the decrease in insulin-mediated glucose disposal and increase in plasma insulin concentration described in patients with essential hypertension is secondary to high blood pressure, per se.

INSULIN RESISTANCE, ESSENTIAL HYPERTENSION, AND CORONARY HEART DISEASE

Although coronary heart disease (CHD) is the major cause of morbidity and mortality in patients with essential hypertension, not all hypertensive individuals are at equal risk. The following section presents evidence in support of the view that the subset of patients with hypertension at greatest CHD risk is those individuals who are also insulin resistant/hyperinsulinemic.

CHD Risk Factors in Insulin Resistant/Hyperinsulinemic Patients With Essential Hypertension

As discussed earlier, not all patients with essential hypertension are insulin resistant. As a consequence, the CHD risk factors associated with insulin resistance will vary significantly in patients with equal degrees of blood pressure elevation. The results in Figure 2 demonstrate how different two groups of patients with essential hypertension can be when the subjects with hypertension seen in Figure 1 were subdivided into hyperinsulinemic (insulin resistant) and normoinsulinemic (insulin sensitive) subgroups.[9] As shown in Figure 2, the plasma insulin concentrations in response to an oral glucose challenge are much higher in the insulin-resistant group. This is not surprising, since the two groups were stratified based on this criterion. However, it is also clear from Figure 2 that plasma glucose concentrations in response to the oral glucose challenge were also significantly higher in the insulin-resistant patients with hypertension. Since insulin resistance, hyperinsulinemia, and glucose intolerance have all been predictive of increased CHD risk,[20–23] their existence in a subset of patients with hypertension supports the view that not all patients with high blood pressure are at equal risk to develop CHD.

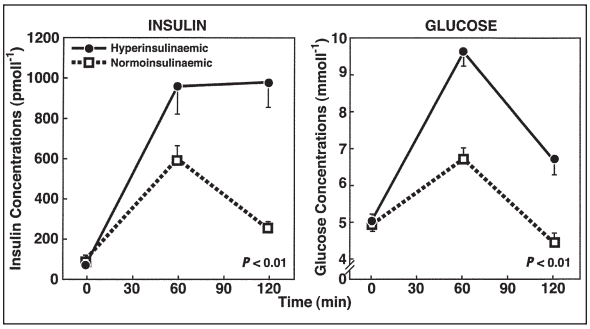

Figure 2. Plasma insulin (left panel) and glucose (right panel) concentrations in response to a 75 g oral glucose challenge in hyperinsulinemic (insulin resistant ●) and normoinsulinemic (insulin sensitive □) patients with hypertension. Reprinted with permission from J Intern Med. *1992;231:235–240.*[9]

Insulin resistance and compensatory hyperinsulinemia are associated with a dyslipidemia characterized by a high plasma TG and low HDL-C concentration.[10,24] The prevalence of both of these changes is increased in patients with essential hypertension,[25,26] and the data in Table I illustrate that an atherogenic lipoprotein profile can be seen in normotensive first-degree relatives of

Table I. Mean (±SE) Plasma Lipid and Lipoprotein Concentrations in Normotensive Individuals as a Function of Family History of Hypertension

Variable (mmol/L)	Positive Family History	Negative Family History	*P* Value
Cholesterol (C)	4.80±0.15	4.44±0.12	<0.07
VLDL-C	0.50±0.06	0.23±0.03	<0.001
IDL-C	0.34±0.07	0.21±0.02	<0.08
LDL-C	2.65±0.12	2.54±0.10	NS
HDL-C	1.34±0.06	1.47±0.05	<0.10
VLDL+IDL+LDL-C	3.47±0.14	3.00±0.11	<0.003
Ratio of C/HDL-C	3.84±0.18	3.09±0.11	<0.001
Triglyceride (TG)	1.15±0.07	0.76±0.05	<0.001
VLDL-TG	0.71±0.07	0.40±0.04	<0.001
IDL-TG	0.14±0.02	0.10±0.01	NS
LDL-TG	0.19±0.01	0.16±0.01	<0.05
HDL-TG	0.11±0.01	0.09±0.01	<0.06

VLDL=very-low-density lipoprotein; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; HDL=high-density lipoprotein

patients with high blood pressure.[14] In addition to being highly correlated with insulin resistance/hyperinsulinemia, a high plasma TG and a low HDL-C concentration are also well recognized CHD risk factors.[27–30] Of more direct relevance are the data in Table II indicating that asymptomatic patients with high blood pressure identified as demonstrating cardiac ischemia by Minnesota Code Criteria were insulin resistant, hyperinsulinemic, and dyslipidemic, with higher TG and lower HDL-C concentrations than well matched hypertensive patients whose electrocardiograms were considered normal.[31] Finally, the relationship between the dyslipidemia characteristic of insulin resistance and CHD in patients with essential hypertension has been emphasized by recent reports from the Copenhagen Male Study[32,33] demonstrating the power of a high TG and low HDL-C concentration in predicting myocardial infarction in this patient population. In the absence of measures of either insulin resistance or plasma insulin levels, these authors used the changes in lipid metabolism as markers of the insulin resistance syndrome. The results of their analysis revealed that CHD events in patients with essential hypertension varied dramatically as a function of their plasma concentration ratio of TG/HDL-C, being markedly accentuated in those whose concentration ratio was in the highest tertile (insulin resistance syndrome) and essentially unchanged in the insulin-sensitive patients in the lowest tertile of TG/HDL-C concentrations.[33]

Link Between Insulin Resistance and Endothelial Dysfunction in Patents With Essential Hypertension

The first step in the process of atherogenesis is the binding of circulating mononuclear cells (MNCs) to the endothelium.[34] The effect of hypertension on this process was evaluated by isolating MNCs from patients with hypertension and quantifying their binding to cultured endothelial cells. Using this approach we were able to demonstrate that MNCs isolated from patients with essential hypertension adhered with significantly ($p<0.001$) greater avidity to endothelium than did MNCs from a matched control group with normal blood pressure.[35] However, the enhanced binding of MNCs isolated from patients with hypertension to endothelium appeared to be more closely related to the degree of insulin resistance than blood pressure, per se, and the relationship between insulin-mediated glucose disposal and MNC binding was highly correlated in both normotensive ($r=0.86$; $p<0.001$) and hypertensive ($r=0.74$; $p<0.001$) individuals.

The interaction between circulating MNCs and the endothelium is modulated by the activity of cellular adhesion molecules (CAMs) secreted by endothelial cells. CAMs can be identified in the circulation, and elevated plasma concentrations of CAMs have been noted in association with a variety of conditions associated with insulin resistance, including essential hypertension.[36,37] To explore the possibility that the insulin resistance commonly seen in patients with hypertension was responsible for the increased plasma concentration of CAMs, we[38] defined in a group of healthy volunteers the relationship between insulin-mediated glucose disposal and the plasma concentrations of three CAMs—E selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1). The results demonstrated that statistically significant relationships existed between degree of insulin resistance and E selectin ($r=0.54$; $p<0.05$), ICAM-I ($r=0.67$; $p<0.001$), and VCAM-1 ($r=0.41$; $p<0.05$). Furthermore, plasma concentration of MNC binding to cultured endothelium was significantly correlated with the plasma concentrations of E selectin ($r=0.5$; $p<0.05$), ICAM-1 ($r=0.47$; $p<0.01$), and VCAM-1 ($r=0.21$; $p<0.30$). Thus, it appears that the subset of patients with essential hypertension who are insulin resistant have an increase in the endothelial production of CAMs, thereby increasing the likelihood that circulating MNCs will bind to endothelium and initiate the process of atherogenesis.

Table II. Mean (±SE) Lipid and Lipoprotein Concentrations in Hypertensive Subjects With and Without ECG Evidence of Ischemic Changes

Group	Cholesterol (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Cholesterol/ HDL-C (ratio)	Triglyceride (mmol/L)
Control (n=25)	5.05±0.24	3.11±0.22	1.36±0.08	3.95±0.31	1.16±0.12
Normal ECG (n=24)	4.79±0.19	3.03±0.18	1.28±0.07	4.00±0.25	1.21±0.14
Abnormal ECG (n=29)	5.36±0.18	3.39±0.17	1.10±0.06*	5.04±0.23**	1.81±0.13**

ECG=electrocardiogram; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; *different from control ($p<0.01$); **different from control and normal ECG ($p<0.02$)

Another abnormality of endothelial function that may contribute to increased CHD risk in insulin-resistant individuals with hypertension is the dysregulation of asymmetric dimethylarginine (ADMA). ADMA is an endogenous inhibitor of nitric oxide synthase, recently shown to be elevated in patients with essential hypertension,[39] which has also received considerable attention as an important CHD risk factor.[40] Given this background, we thought it important to measure insulin-mediated glucose disposal, the plasma-insulin response to oral glucose, and plasma ADMA concentrations in normal volunteers and patients with essential hypertension.[41] The results indicated that plasma ADMA concentrations and degree of insulin resistance were significantly correlated in both healthy volunteers (r=0.73; p<0.001) and patients with essential hypertension (r=0.70; p<0.003). Furthermore, plasma ADMA concentrations were similar in normotensive individuals and hypertensive patients when the two diagnostic groups were stratified into insulin-resistant or insulin-sensitive subgroups. Thus, as with the MNC binding and the plasma concentration of CAMs, the reported increase in plasma ADMA concentrations in patients with essential hypertension seems to be more a matter of insulin resistance than the increase in blood pressure.

CONCLUSION

Patients with high blood pressure, as a group, are insulin resistant, glucose intolerant, hyperinsulinemic, and dyslipidemic, with evidence of endothelial dysfunction. There is substantial evidence supporting the view that insulin resistance and/or compensatory hyperinsulinemia have a role in blood pressure regulation and may predispose a substantial number of individuals to develop high blood pressure. Of greater immediate clinical import is the fact that the abnormalities of glucose, insulin, lipid metabolism, and endothelial dysfunction that exist in substantial numbers of patients with high blood pressure seem to be a consequence of their insulin resistance. These insulin-resistance–associated changes are mainly responsible for the increased CHD morbidity and mortality that characterizes patients with essential hypertension. Given this information, it seems prudent to enlarge the scope of our therapeutic approach to patients with hypertension and to realize that blood pressure lowering is necessary, but not sufficient, if the goal is to reduce CHD in patients with essential hypertension. More succinctly, efforts at global CHD risk reduction must be implemented.

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