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Insulin resistance and upper-normal glucose levels in hypertension: a review

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Reduced insulin-mediated glucose disposal, indicative of insulin resistance, has been demonstrated in lean male hypertensives both with the hyperinsulinaemic euglycaemic clamp and the insulin suppression test. In lean hypertensives, insulin resistance was not accompanied by increases in fasting plasma insulin and glucose levels; but with modest hyperglycaemia and hyperinsulinaemia after a glucose load. Population studies (no stratification) reveal that: (1) insulin sensitivities vary widely in normotensives and hypertensives, (2) there are hypertensives and normotensives with similar degrees of insulin resistance, (3) not all hypertensives are insulin resistant, and (4) insulin resistance does not contribute to the blood pressure level of the hypertensive population. In large cross-sectional studies, the clustering of obesity, dyslipidaemia and type 2 diabetes is largely responsible for the observed associations between insulin or insulin resistance and hypertension. Recent studies indicate a role of glucose in blood pressure control. Glucose has been shown to elevate blood pressure in the presence of endothelial dysfunction and glucose values in the upper-normal range have been shown to be associated with increased cardiovascular mortality. Since endothelial dysfunction is present in hypertensives, dyslipidaemic, obese and in glucose intolerant individuals, lowering of high-normal glucose levels becomes a new, additional therapeutic target in the management of these patients. Hyperglycaemia together with endothelial dysfunction may account for the increased incidence of hypertension in obesity and diabetes mellitus. Because of the strong association between insulin resistance, hyperglycaemia and endothelial dysfunction, and the clustering of risk factors in these subjects, we propose the lowering of high normal glucose levels as part of the therapeutic strategy to prevent cardiovascular and metabolic disease.
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Insulin resistance in hypertension

Assessment of insulin resistance

Direct evaluation of insulin resistance has been achieved with the euglycaemic hyperinsulinaemic clamp and the insulin suppression test.[1–3] The euglycaemic hyperinsulinaemic clamp, also known as the euglycaemic insulin clamp, is considered to be the gold standard for evaluating insulin resistance as it measures insulin-mediated glucose disposal. The procedure employs a 2-h constant insulin infusion (1 mU/kg/min) to achieve plasma insulin levels around 60 μU/ml. Plasma glucose levels, obtained from arterialised venous blood, are held constant at approximately 80 mg/dl by means of a glucose infusion at a variable rate.[1] Serial blood samples are obtained during the procedure. The glucose infusion rate is expressed as mg/min/kg, and is commonly referred to as the M value. Low M values (low glucose infusion rates) indicate reduced insulin-mediated glucose disposal and are thus indicative of insulin resistance. The test can be performed at different levels of plasma insulin. If higher insulin levels are desired then the glucose infusion rate is adjusted to maintain euglycaemic levels. Employing the euglycaemic insulin clamp[1,2] in healthy, non-diabetic, lean normotensive and hypertensive males, it was demonstrated that hypertension is associated with a decrease in insulin-mediated glucose disposal. The studies revealed that hypertension *per se*, in the absence of obesity and/or of diabetes mellitus, is associated with insulin resistance.[1,2] Obesity and type 2 diabetes mellitus are conditions characterised by the presence of insulin resistance[4–6] and additive effects on insulin resistance have been shown for hypertension, obesity and type 2 diabetes mellitus.[7]

The insulin suppression test has also been employed to test for the presence of insulin resistance in hypertension.[3,8–10] The procedure requires the use of three simultaneous intravenous infusions. Commonly, somatostatin is infused at a rate of 250 μg/h, insulin at 25 mU/m^2/min and glucose at 320 mg/m^2/min.[10] Somatostatin is employed to

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inhibit endogenous production of insulin and other glucose-regulating hormones. Serial blood samples are obtained during the test. Samples obtained from 150 to 180 min of infusion are used to calculate steady-state levels of glucose and insulin. Steady-state plasma glucose (SSPG) is indicative of the level of insulin sensitivity. The higher the SSPG level the lesser the amount of glucose being metabolised by a fixed concentration of insulin. High SSPG levels is suggestive of insulin resistance. Employing the insulin suppression test, Swislocky and colleagues[9] demonstrated that compared with lean normotensives, lean hypertensives have higher SSPG values. These results support the view that hypertension *per se* is associated with insulin resistance.

Fasting and post-load plasma insulin and glucose, and insulin/glucose ratios have been employed to infer the presence of insulin resistance. Its use is based on the observed presence of compensatory hyperinsulinaemia associated or not with hyperglycaemia, in subjects with insulin resistance. In addition, if hyperinsulinaemia goes hand in hand with insulin resistance, and insulin resistance is linked to hypertension, it is expected that hypertensives would have higher insulin levels than normotensives. Therefore, insulin concentrations may be correlated with blood pressure (BP) levels. However the results are controversial. Both, positive significant relationships and lack of associations between fasting or post-load insulin levels and BP have been reported.[5,11–14] For example, in a cross-sectional study, Muller and colleagues[14] demonstrated in 649 white, healthy subjects, a strong association between age, body mass index and waist to hip ratio with systolic BP. No association was observed between the log of fasting insulin or the AUC for the log of insulin levels after a glucose load and systolic BP. Similarly, no association was found between fasting or post-load insulin and systolic or diastolic BP in a healthy Hispanic population under low and high salt intake conditions.[15]

A major problem with most of these studies is the poor stratification of the study patients.[5,11–14] The presence of confounding variables such as older age, obesity, visceral or abdominal fat accumulation, salt sensitivity, dyslipidaemia and others, complicates the interpretation of the results. Statistical dissection of the data by multiple regression analysis often eliminates most of the observed associations between insulin and BP.

In addition to insulin, glucose levels, either fasting or post-load, have also been employed to infer about the presence or absence of insulin resistance. It is expected that in the presence of insulin resistance, glucose levels may be increased despite the presence of compensatory hyperinsulinaemia. Accordingly, higher glucose levels are expected in insulin-resistant individuals, and if insulin resistance is linked to hypertension, then hypertensives could have higher glucose levels than normotensives. In healthy, glucose tolerant subjects, we found no associations between fasting or post-load (75 g of glucose) plasma glucose and BP. In these subjects, similar plasma glucose levels were encountered in normotensives and hypertensives. Further, in small studies where insulin resistance has been detected by direct methods, fasting plasma glucose and insulin levels and insulin/glucose ratios of lean, male hypertensives were not significantly different from those of lean, male normotensives.[1–3,9,10] However, the glucose levels and occasionally the insulin levels, following a glucose load, were in general higher in hypertensives than in normotensive subjects. This is consistent with reports of postprandial hyperglycaemia in patients with mild essential hypertension.[16]

In summary, these findings indicate that insulin resistance may be observed in lean hypertensives. This state of insulin resistance commonly manifests with greater increases in plasma glucose and insulin after a glucose load, but with normal fasting levels of these substances. The existence of associations between insulin levels and BP is questionable, and when found it seems determined by the presence of associated variables, such as, abdominal obesity, older age, dyslipidaemia, sedentarism, salt sensitivity and others. When the contribution of these variables is taken into account, such a relationship is commonly lost.

Prevalence of insulin resistance in hypertension

Although the above described studies reported the presence of insulin resistance in hypertension,[1–4] the small number of subjects assessed did not allow to infer about the prevalence of insulin resistance in hypertensive subjects. The answer to this question could be found in the study of Lind and coworkers.[17] These authors performed the euglycaemic insulin clamp in 420 hypertensives and 51 normotensive (controls) individuals. Wide ranges of insulin sensitivities were found in hypertensives; although the mean M values were lower in hypertension than in normotension. Employing the mean M values for normotensives minus two standard deviations as the cut-off limit to define insulin resistance, only 27% of the hypertensives were undoubtedly more insulin-resistant than the normotensives. This study clearly indicates that: (1) insulin sensitivities vary largely in the normotensive and hypertensive subject population, (2) there are hypertensives and normotensives with similar degrees of insulin resistance, and (3) not all hypertensives are insulin resistant. Additionally in this study[17] insulin-resistant hypertensives had BP levels comparable to that of the non-insulin resistant hypertensives; suggesting, that insulin resistance may not contribute to the BP level of the hypertensive population. It should be emphasised that this study was conducted in Caucasian males, and that racial differences in the

relationship between insulin resistance and hypertension have been reported.[18]

Who are then the insulin resistant hypertensives?

Interestingly, of the hypertensives who were considered as insulin resistant one out of two subjects had in addition abdominal obesity, high triglyceride and low high-density lipoprotein cholesterol (dysmetabolic cardiovascular syndrome); whereas these conditions were present in only one out of five of the non-insulin resistant hypertensives.[17] Therefore, the increased incidence of insulin resistance in hypertensives and the higher insulin levels previously reported, could in addition to hypertension, be determined by co-morbid conditions commonly associated with hypertension. This cluster of risk factors further increases cardiovascular morbidity and mortality. Therefore, even if insulin resistance would not contribute to the severity of hypertension, the presence of additional cardiovascular risk factors mandates the use of aggressive therapy in this patient population. It would have been of interest to know whether the more insulin-resistant normotensives were also those with the dysmetabolic cardiovascular syndrome.

In summary, in highly stratified studies (healthy, young, lean males), where confounding variables are minimised, insulin-mediated glucose disposal is reduced in hypertensives compared with normotensives. The fact that in lean males, insulin resistance does not necessarily lead to high fasting plasma insulin levels, no association between BP and insulin levels are encountered. In population studies, the clustering of risk factors (obesity, sedentarism, dyslipidaemia, type 2 diabetes mellitus) becomes the major determinant of the reported association between insulin resistance and hypertension. Because of the wide range of insulin sensitivities in the normotensive and hypertensive population, it is likely to observe normotensives and hypertensives with similar degrees of insulin resistance. In fact, it is likely that not all-insulin resistant individuals have elevated BP. Many obese and type 2 diabetics have BP within the normotensive range. Both genetic, environmental and disease related factors play a role in the development of insulin resistance; hypertension being one of them.

Glucose and hypertension

Current studies indicate that high normal glucose levels may be an additional cardiovascular risk factor. High normal glucose levels and mild hyperglycaemia are more frequently observed in subjects with insulin resistance (older, sedentary, obese, hypertensive, dyslipidaemic). Presence of high-normal glucose levels has been shown to be associated with increases in cardiovascular mortality. A 22 follow-up study in healthy white men of 40–59 years of age, revealed that the presence of fasting plasma glucose levels of 86–109 mg/dl, were associated with a 53% increase in cardiovascular mortality.[19] This study suggests that blood glucose in the upper normal range appears to be an important independent predictor of cardiovascular death in non-diabetic apparently healthy, middle-aged white men. Additionally, salt-sensitive hypertensives when placed on a high salt diet become more hyperglycaemic and more hypertensive than salt-resistant individuals.[10] Feeding of rats with high sugar diets induces hypertension[20] and glucose infusion to rats induces BP elevations, particularly in the presence of endothelial dysfunction.[21,22] Because endothelial dysfunction has been linked to insulin resistance,[23–28] it is likely that even modest increases in blood glucose may exert detrimental effects in the insulin-resistant subject. In fact, hyperglycaemia and endothelial dysfunction coexists in type 2 diabetes, obesity, hypertension and dyslipidaemia, particularly in subjects with combined risk factors (ie, obese diabetic dyslipidaemic hypertensives). Hyperglycaemia together with endothelial dysfunction may account for the increased incidence of hypertension in obesity and diabetes mellitus. In conclusion, recent evidence suggests that glucose may play an important role in BP control, mainly in the presence of endothelial dysfunction. Since endothelial dysfunction is present in hypertensives, dyslipidaemic, obese and glucose intolerant individuals, lowering of high-normal glucose levels becomes a new, additional therapeutic target in the management of these patients.

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