Blood pressure and diabetes: a fatal attraction

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This editorial refers to ‘Hypertensive target organ damage predicts incident diabetes mellitus’, by R. Izzo et al., on page 3419

It is what we think we know already that often prevents us from learning

Claude Bernard, 1813–1878

The clinical management of two of the most important risk factors for cardiovascular disease, notably high blood pressure and diabetes, have evolved over many years as independent clinical disciplines, that have only in recent years begun to overlap. The overlap has in large part been due to recognition that the treatment of hypertension is one of the most effective therapeutic strategies to reduce the macrovascular and microvascular complications of diabetes and the associated premature morbidity and mortality.

Indeed, specialists working in the field of hypertension have long recognized that the high blood pressure associated with diabetes is often associated with the early development of recalcitrant systolic hypertension and invariably associated with disturbances to the 24 h circadian rhythm of blood pressure regulation, notably the common development of nocturnal hypertension and greater blood pressure variability. Thus, the link between diabetes and blood pressure is well established at a clinical practice level.

The epidemiological and pathophysiological link between hypertension and diabetes dates back many years. This, often subtle, elevation in pressure load, alongside characteristic but equally subtle disturbances to blood lipids (elevated LDL-cholesterol, reduced HDL-cholesterol, and increased triglycerides) is the most likely explanation for patients frequently exhibiting evidence of seemingly disproportionate cardiovascular structural damage and disease at the time of diagnosis of type 2 diabetes.

As well as impaired glucose metabolism predicting the likelihood of developing hypertension, elevated blood pressure levels also predict incident type 2 diabetes. Abnormalities in carbohydrate metabolism are common in people with hypertension who, as a consequence, are ∼2.5 times more likely to develop type 2 diabetes.

This cross-predictive nature of blood pressure and risk of type 2 diabetes is supported by findings from a 5-year follow-up study of 10 000 men from Israel in which baseline systolic blood pressure was a significant predictor of diabetes regardless of age or obesity. The risk of incident diabetes in hypertensive patients is further magnified by some commonly used blood pressure-lowering medications such as thiazide/thiazide-like diuretics and beta-blockers, especially when these agents are combined.

The enhanced risk of developing diabetes in people with hypertension appears to relate to hypertension being an insulin-resistant state.
In 1966, Welborn and colleagues noted that patients with hypertension had a heightened plasma insulin response to an oral glucose load, indicative of insulin resistance.9 This has subsequently been confirmed by many other studies.10,11 The relationship holds true even in lean individuals and appears to be associated with both the severity of hypertension and the deposition of ectopic fat, especially in the pericardium and mediastinum.12 This latter finding explains why classic indices of obesity are sometimes inadequate surrogates for body fat, especially in lean individuals with hypertension. More recently, the likelihood of developing diabetes in people with longstanding hypertension has been shown to be predictable on the basis of a positive relationship to baseline systolic blood pressure and the characteristic features of metabolic syndrome.13

Izzo and colleagues now extend and add intrigue to the aforementioned findings, in their analysis of a cohort of 4000 hypertensive non-diabetic patients (mean age 59 years), followed for at least 1 year (mean 3.6 years) using an observational registry from primary care and community hospitals in southern Italy.14 They used echocardiography to detect left ventricular hypertrophy (LVH) and carotid ultrasound to define carotid atherosclerosis, i.e. carotid intima-media thickness (CIMT) > 1.5 mm, at baseline. They make the novel observation that the extent of baseline cardiac and vascular damage, i.e. LVH and/or increased CIMT in otherwise seemingly health hypertensive patients, was associated with a markedly increased risk of incident diabetes, by > 60%, when compared with those without evidence of cardiac or vascular damage at baseline. This held true even after adjustment for potential confounders such as metabolic syndrome, obesity, antihypertensive medication, and baseline systolic blood pressure. These findings prompt consideration of the potential mechanism(s) underpinning this association.

The first potential explanation is that LVH and increased CIMT are the end result of more severe blood pressure and metabolic disturbances, tracking together, over a long duration, consistent with the tracking relationships between blood pressure and risk of incident diabetes as discussed above. Both LV mass and CIMT are sensitive barometers of pressure load, and it is likely that those developing these complications had previously experienced a greater and longer burden of systemic pressure elevation. This would be consistent with reports discussed above, that insulin resistance and thus the risk of developing diabetes is greater in those in whom blood pressure elevation is more severe. This hypothesis further suggests that the severity of the hypertension and associated metabolic syndrome most probably result from common antecedents, genetic and/or acquired (see Figure 1).

A second explanation is the more tantalizing possibility that hypertension is not simply associated with a greater risk of developing diabetes, but is the cause of incident diabetes in hypertensive patients. How could this be? One possibility is the inverse relationship between insulin sensitivity and muscle blood flow. The vascular remodelling process in the heart and large vessels is replicated throughout the vasculature, including small resistance arteries, where characteristic remodelling of the medial: lumen ratio results in an increased resistance to flow and reduced capacity to adapt to increased demands for flow.15 This could limit muscle glucose uptake and overall insulin-mediated glucose disposal, and thereby generate insulin resistance. Further work would be necessary to evaluate this hypothesis.

A third possibility is that subtle elevations in blood glucose or a reduced threshold for advanced glycation could be the cause of systolic hypertension. This would replicate an accelerated ageing process and early large artery stiffening due to advanced glycation of arterial wall collagen, thereby increasing characteristic impedance to flow. This would result in earlier development of LVH and increased CIMT, long before the blood glucose levels are sufficient to merit a diagnosis of diabetes. This, in turn, could explain the

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/34/44/3395/458816)  
**Figure 1** Hypertension is associated with a metabolic syndrome and genetic and lifestyle predisposition to a two-fold increased risk of developing diabetes. Elevated glucose levels and metabolic syndrome contribute to the development of accelerated vascular ageing (large artery atherosclerosis/stiffening and generalized atheroma). Arterial stiffening contributes to the development of systolic hypertension and cardiovascular structural damage. In parallel, hypertension-induced vascular structural damage is associated with an increased risk of developing diabetes. Hypertension in combination with diabetes greatly increases the risk of developing cardiovascular, cerebrovascular, peripheral, ocular, and renal disease.
strong link between systolic hypertension, cardiovascular structural changes, and an increased risk of incident diabetes reported by Izzo and colleagues. Together, any or all of these explanations would be sufficient to explain the marked amplification in cardiovascular disease risk when hypertension and diabetes co-exist.

So, what are the clinical implications of the link between hypertensive target organ damage and the increased risk of incident diabetes? First, the findings of Izzo and colleagues suggest that those with structural damage such as LVH and increased CIMT are more likely to have had a more severe metabolic diathesis contributing to the increased cardiovascular risk associated with cardiovascular structural damage. Secondly, these data provide a strong indication to consider the avoidance of metabolically unfriendly antihypertensive drugs in people with hypertension and established structural disease because of the markedly increased risk of incident diabetes in these patients. Thirdly, these data might provide a basis for revisiting the role of insulin-sensitizing drugs as part of a cardiovascular disease risk-reducing strategy in the treatment of hypertension, or the earlier treatment/lifestyle intervention for the pre-hypertensive phenotype to limit insulin resistance, if the latter is related to hypertensive vascular disease.

Finally, as the reference list indicates, this is a subject that has been discussed and debated for many years, consequently there is danger in the perception that we have learned all we need to know about the ‘fatal attraction’ between blood pressure and diabetes and that we should just get on and treat it. Whilst I agree with the need to better implement effective treatment, we should reflect on the pertinent words of Claude Bernard, who reportedly said ‘it is what we think we know already that often prevents us from learning.’ The work of Izzo and colleagues has shown that there is still much to be learned with regard to the link between blood pressure and diabetes. Indeed, we have only scratched the surface.

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References