Insulin and Blood Pressure Relationships

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Peter M. Nilsson and Andrea Natali

8.1 Observational Studies: Epidemiology

Already in 1987 a first report indicated that insulin sensitivity is impaired in subjects with essential hypertension and that hyperinsulinaemia is a consequence of this phenomenon [1], as later summarized [2]. In 1988, Gerald Reaven stated in his Banting Lecture that insulin resistance could be a unifying factor for impaired glucose metabolism, dyslipidaemia and elevated blood pressure [3], often considered together as representing the so-called metabolic syndrome and linked to (abdominal) obesity as the 'deadly quartet' [4]. Numerous studies later on reported that hyperinsulinaemia, as a marker of insulin resistance, in subjects with elevated blood pressure or hypertension [5–7] is a phenomenon that could also be influenced by the drugs used for the reduction of blood pressure. Some antihypertensive drugs seem to be beneficial for insulin sensitivity (RAS blockers, moxonidine, alpha-receptor blockers), others are mostly neutral (calcium antagonists), but some may even be detrimental, especially when used at higher dosages (thiazide diuretics, beta-receptor blockers) [8–10]. However, among beta-receptor blockers there exist also vasodilating drugs with less negative impact on glucose metabolism. The weight increase of a mean 2–4 kg induced by more traditional beta-receptor blockers could be a contributing factor for the concomitant decrease in insulin sensitivity (increased insulin resistance).

When epidemiological correlations have been studied between insulin and blood pressure, it was noted that such correlations are stronger when more

P. M. Nilsson (✉)
Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden
e-mail: Peter.Nilsson@med.lu.se

A. Natali
Department of Clinical and Experimental Medicine, Università di Pisa (UNIPI), Pisa, Italy

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sophisticated measures are used for reflecting glucose metabolism and blood pressure control than more simple methods. One example was then oral glucose tolerance testing (OGTT), and hyperinsulinaemic and euglycaemic clamp data for insulin sensitivity were used together with 24-h ambulatory blood pressure monitoring (ABPM), showing stronger correlations, in contrast to using only fasting insulin and office blood pressure correlations [11]. The study concluded that the apparent association between blood pressure and insulin resistance not only is obscured by measurement error, but is also affected by the particular measures of insulin resistance and blood pressure used. The study thus provided further evidence that a relationship exists between blood pressure levels and hyperinsulinaemia or insulin resistance [11]. Similar findings were also obtained from a cohort of patients with type 2 diabetes [12] and one cohort consisting only of middle-aged women [13].

The importance of sex differences for these associations have been discussed in two other studies as men are more prone to abdominal obesity and insulin resistance than women, at least before menopause [14, 15].

The problem of proving a causal link between insulin metabolism and blood pressure regulation can be addressed by applying genetic analyses via Mendelian randomization (causal inference) methodology. In a recent publication applying genetic methods, several biomarkers were found to be causally related to blood pressure, among them insulin-like growth factor binding protein 3 (IGF-BP3), but not the biomarker insulin itself [16]. However, insulin sensitivity is not a single biomarker like that, but more complex, and if impaired insulin sensitivity (insulin resistance) is causally related to blood pressure regulation, it might be a better choice to go for intervention studies directed towards insulin resistance and then follow the effects on blood pressure.

It could also be the other way around, i.e. that pathophysiological changes associated with hypertension increases the risk of insulin resistance. One study supported the hypothesis that genes in the blood pressure pathway may play a role in insulin resistance in Mexican-Americans, a population with a high prevalence of abdominal obesity and the metabolic syndrome [17].

Finally, it should be noted that patients with insulinoma do not in general have elevated blood pressure in spite of hyperinsulinaemia [18], indicating that it may be insulin resistance per se that after all is more important for blood pressure regulation than hyperinsulinaemia itself.

8.2 Mechanistic Studies Linking Insulin, Insulin Resistance and Blood Pressure Regulation

The precise mechanism linking insulin resistance to blood pressure is still unknown probably simply because there is not just one, but many, each not efficient enough either in terms of potency or prevalence, but all together they do justify the observed epidemiologic association. Classically these mechanisms can be divided in *three groups* according to the type of cause-effect relationship.

8.2.1 Insulin Resistance Facilitates Elevated Blood Pressure

Insulin resistance, observed at the whole-body level, is caused by a reduced liver, adipose and skeletal muscle tissues response to insulin, while it neither affects the kidney nor the sympathetic nervous system (SNS), which in insulin-resistant individuals respond normally to insulin. Therefore, the resulting compensatory day-long relative hyperinsulinemia—faced by insulin-resistant subjects—will produce an overstimulation of these two tissues with possible consequences on blood pressure control. Indeed, insulin directly acts on the kidney at the tubular level by promoting sodium reabsorption similarly in healthy subjects and in patients with essential hypertension and insulin resistance [19], while it increases the SNS tone similarly in lean and obese insulin-resistant subjects [20]. These effects, modest in quantitative terms and transient during the day (fed > fasting), are unlikely to be responsible of large blood pressure changes, but might become effective synergizing with others of similar nature, like environmental stress and a high-salt diet [21].

On the other hand, insulin also acts on the endothelium by facilitating nitric oxide release [22], but the endothelium in insulin-resistant individuals is also less responsive [23, 24]; therefore, this 'hypotensive' effect is lost. The direct link between insulin sensitivity and endothelial function has been shown also in an intervention study in which in subjects with type 2 diabetes the glucose control was improved with either metformin or rosiglitazone, but only the latter treatment was able to improve both mechanisms and to a similar extent [25].

8.2.2 Elevated Blood Pressure Facilitates Insulin Resistance

Essential hypertension and obesity are associated with variable degrees of endothelial dysfunction and microvascular rarefaction [26]. Insulin, in order to exert its full metabolic effect (glucose uptake), requires an optimal skeletal muscle perfusion, which in turn requires a normal endothelial function [27] and a normal microvascular recruitment [28]. It is thus possible to hypothesize that in the hypertensive subjects in whom either component is affected, there is also a blunted insulin function. In a series of experiments, a research group in Pisa, Italy, tried to verify this elegant hypothesis by first improving skeletal muscle capillary recruitment with adenosine [29] and subsequently by improving overall tissue perfusion with sodium nitroprusside (a nitric oxide donor) [30] in subjects with established essential hypertension, but neither intervention was associated with improvement in skeletal muscle insulin resistance. Possibly, the vasodilation induced through drugs does not reproduce the capillary recruitment of the nutritive network, as it occurs with insulin, or the network is structurally compromised due to capillary rarefaction [31]. Endothelial dysfunction per se probably is not effective on metabolism unless it is associated with other chronic metabolic stress. Indeed, in genetically manipulated mice the selective partial deletion of endothelial nitric oxide produced insulin resistance and hypertension only when the animals were submitted to a chronic high-fat diet [32].

A second mechanism through which hypertension might facilitate insulin resistance is through the negative effect on insulin action of some antihypertensive drugs and it will be addressed in the next paragraph. Nevertheless, this would only explain in part the observed epidemiologic association and does not shed light on the mechanism since insulin resistance has been demonstrated also in untreated lean subjects with essential hypertension [1].

8.2.3 Factors Able to Induce Simultaneously Insulin Resistance and Elevated Blood Pressure

At least four major factors are involved through distinct mechanisms in the simultaneous regulation of blood pressure and insulin action.

Stress hormones (catecholamines and glucocorticoids) induce insulin resistance and elevates blood rather effectively. This is clearly seen in conditions of abnormal secretion of either hormone or when glucocorticoids are given for therapeutic purposes or when voluptuary substances increasing the SNS adrenergic tone are consumed. A series of elegant studies in monkeys [33] has clearly demonstrated that social stress induces abdominal obesity, elevated blood pressure and insulin resistance, as well as coronary atherosclerosis. Whether also in humans the physiologic response to stress, when protracted, is able to achieve the hormone levels that are effective both on metabolism and on blood pressure in humans is uncertain. In an elegant nested case-control study, subjects with metabolic syndrome showed an enhanced cortisol and catecholamine 24-h urinary secretion when compared to healthy controls [34]. A peculiar condition of intermittent but rather persistent stress response activation is represented by obstructive sleep apnoea (OSA) and indeed this affection is known to be associated with both hypertension [35] and insulin resistance [36]. The treatment of OSA is beneficial for both conditions [37, 38].

Lack of physical activity is able to produce biochemical changes in the skeletal muscle cells that makes them less responsive to insulin [39] and is also able to modify the vascular network so as to reduce peripheral resistances [40]. Training programmes are indeed almost invariably associated with improvements in both insulin sensitivity [41] and reduced blood pressure [42].

Elevated free fatty acids (FFA) are able to induce impaired endothelial function and skeletal muscle insulin resistance when their concentration is raised through experimental manipulations [43]. Whether the mild FFA elevations observed in obese individuals and in stress conditions (beta adrenergic-induced lipolysis) are effective in this regards is uncertain and still to be demonstrated.

Low-grade inflammation induces insulin resistance [44], impairs endothelial function [45] and promotes arterial stiffness [46]. Plasma C reactive protein predicts both hypertension [47] and diabetes [48], and in a cohort of subjects with type 2 diabetes, we observed a clustering of inflammation, insulin resistance and endothelial dysfunction [49]. A poor diet, a poor hygiene, environmental pollution and smoking are all conditions of low-grade inflammation as well as factors predisposing to both type 2 diabetes and hypertension [50].

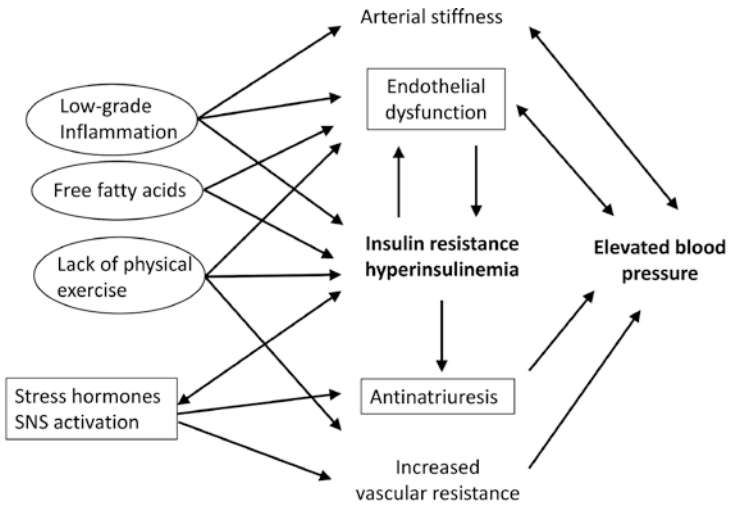

Fig. 8.1 The major mechanism directly linking IR and BP are in boxes, the circles represents factors that simultaneously induces IR and elevate BP through distinct and multiple mechanisms

In summary the mechanism directly linking blood pressure to insulin resistance are depicted in Fig. 8.1. These are based essentially on endothelial dysfunction, anti-natriuresis and the activity of stress hormones, as well as increased SNS activity [51]. Then there are a number of factors, mostly related to the environment that acts on one or more of these mechanism and reinforce the link.

8.3 Intervention Studies

8.3.1 Lifestyle Intervention: Weight Loss and Physical Exercise

There are different ways to reduce insulin resistance and hyperinsulinaemia in order to evaluate the effects on blood pressure regulation and levels.

First of all, different lifestyle modifications (diet, physical exercise) have been shown to be of special benefit to people with hyperinsulinaemia, as shown in a 1-year randomized, controlled study from Sweden when also office blood pressure was lowered [52]. As there were several metabolic effects induced by this multimodality lifestyle intervention, keeping a constant drug usage over the study period, it could be problematic to disentangle if the beneficial effect was due to weight loss, improved physical activity and muscle activation, or a more direct effect on insulin resistance causing hyperinsulinaemia by stress reduction, or unknown mechanisms linked to improved lifestyle [52].

Even calorie restriction alone, without the physical exercise component, may impact on insulin resistance and lower blood pressure [53].

8.3.2 Drug Effects on Insulin and Blood Pressure

As already mentioned, the various antihypertensive drugs commonly used may have shifting effects on body weight, insulin sensitivity, insulin levels and blood pressure regulation [8–10, 54]. Some of these drugs are of special relevance as they improve insulin sensitivity and reduce blood pressure levels at the same time, both measured as office blood pressure and 24-h ambulatory blood pressure. One of the drugs, moxonidine, seems to work via central nervous inhibition of the SNS via its interaction with imidazolidine receptors [10]. However, it is not enough to show these favourable metabolic and haemodynamic effects, but also the effect on cardiovascular endpoints must be evaluated. For example, even if alpha-receptor blockers have been shown to improve insulin sensitivity and lower blood pressure, the selective alpha-blocker doxazosin did not show special clinical benefits in the ALLHAT study when compared with the ACE-inhibitor lisinopril and the diuretic chlorthalidone; in fact congestive heart failure increased in the doxazosin arm [55].

Finally, also some anti-diabetic drugs have documented benefits for reducing insulin resistance and at the same time lower blood pressure levels. One such drug is rosiglitazone (a thiazolidinedione) with favourable metabolic and haemodynamic effects [56–58]. On the other hand, there was a tendency for volume retention and peripheral oedema that could increase the risk of congestive heart failure in susceptible patients with type 2 diabetes. In a randomized trial (RECORD), the risk of cardiovascular events in general was, however, not different between rosiglitazone treatment and other per-oral anti-diabetes drugs [59]. The lesson from this is that in the end it is the cardiovascular preventive effect of a specific drug that matters, not the different ways (mechanisms) this is achieved. Even drugs that may increase body weight and worsen insulin sensitivity (but lower peripheral blood pressure) may show protective effects on the risk of re-infarction, for example, selective beta-receptor blockers in secondary prevention post-myocardial infarction.

Finally, also metformin has been investigated for blood pressure-lowering properties but with conflicting results even if this drug may increase hepatic insulin sensitivity and stabilize glucose metabolism [60]. The newer anti-diabetes drugs (SGLT-2 inhibitors, GLP-1 receptor agonists, RA) may reduce body weight and blood pressure [61], but the effect on hyperinsulinaemia and insulin resistance is less clear. In fact, incretin-active drugs such as DPP-4 inhibitors and GLP-1 RA may in fact increase insulin secretion, but blood pressure is at least not elevated by this influence. Experimental studies have indicated a role of GLP-1 receptor signalling for blood pressure regulation. In one study in rodents, endogenous GLP-1R signalling exerted a physiologically relevant effect on BP control, which may be attributable, in part, to its tonic actions on the proximal tubule NHE3-mediated sodium reabsorption, intrarenal renin-angiotensin system and insulin sensitivity [62].

8.4 Summary

There are many observational studies to show associations between insulin levels, or insulin sensitivity, with blood pressure levels, and with more sophisticated methods stronger associations can be shown as compared to the use of more simple methods. Several mechanisms have been described to mediate these effects of insulin regulation on blood pressure levels, most importantly involving the endothelium [63], sodium retention, SNS activation and vascular remodelling. It is possible to favourably reduce hyperinsulinaemia and insulin resistance, either by lifestyle alone (weight loss, physical exercise, smoking cessation) or by some antihypertensive and anti-diabetic drugs.

Future studies may shed more light on these associations, including determination of causality by genetic methods [16, 17], and newer drugs may be designed to better target insulin resistance without side effects. Blood pressure and central haemodynamics should then be evaluated by more sophisticated methods such as 24-h ABPM and measurement of central blood pressure, as well as aortic stiffness by use of pulse wave velocity and pulse wave analyses.

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