Insulin resistance, obesity and hypertension: is the link waist circumference?

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Obesity, insulin resistance and systemic hypertension are risk factors for cardiovascular diseases, and are clearly inter-related. However, the exact nature of their relationship remains unclear. A review of evidence from epidemiological and experimental studies, emphasizing a link between these three determinants of cardiometabolic abnormalities, suggests that obesity (particularly abdominal obesity) may play a central role in the association between insulin resistance and hypertension. This concept remains to be confirmed by future research.

Obesity, insulin resistance and dysglycemia are common features in patients with systemic hypertension. Even if the relationship between these leading factors of cardiovascular disease is well known, the pathophysiology process is not clear. Recently, waist circumference has been recognized as a cornerstone of the metabolic syndrome [1]. Therefore, one may speculate that abdominal obesity plays a role in pathophysiologic events that link insulin resistance to hypertension. In this review, we summarize available evidence from epidemiological and experimental studies that emphasize the potential link between these three major determinants of cardiovascular diseases (i.e., obesity, elevated blood pressure and insulin resistance).

Does insulin resistance lead to hypertension or the inverse?

Since the first description of hyperinsulinemia in hypertensive patients [2], numerous investigations have been performed to clarify the link between insulin abnormalities (i.e., hypersinsulinemia or insulin resistance) and hypertension [3–5]. Despite apparently conflicting results reported in the literature, a meta-analysis supported the role of hyperinsulinemia in the pathogenesis of essential hypertension [6]. Since then, this role was corroborated by results from the San Antonio Heart study, in which it was reported that elevated fasting insulin was among metabolic changes that may precede the development of hypertension [7]. Insulin concentrations have also been associated with the incidence of hypertension in other large cohorts, such as the Atherosclerosis Risk in Communities (ARIC) study [8], the Coronary Artery Risk Development in Young Adults (CARDIA) study [9], and the eastern Finland cohort [10]. Recently, insulin resistance was also prospectively linked to incident hypertension. Interestingly, the Insulin Resistance Atherosclerosis Study (IRAS) observed an inverse association between insulin sensitivity (SI) and incident hypertension (10% decrease for every increase of SI unit) [11]. A large cross-sectional study in a healthy population (normotensive without diabetes) has shown that each increase of 10 units of insulin resistance corresponded with an increment of 1.7 mmHg of systolic and 2.3 mmHg of diastolic blood pressure [12]. In young normotensive Americans, Falkner and colleagues reported a similar association [13]. Finally, these results were recently confirmed in individuals without diabetes [4], as well as those with diabetes [14]. Interestingly, the latter retrospective study in patients with Type 2 diabetes showed that exogenous insulin use increased the risk for the development of hypertension compared with nonusers [14]. The pathogenesis through which insulin potentially induces hypertension has not been clearly identified, since there are most certainly numerous mechanisms involved. Except for a mild vasodilator effect encountered in insulin-sensitive individuals, it has been shown that insulin stimulates numerous processes (**Figure 1**). All of the potential pathophysiological mechanisms linking insulin to hypertension have been investigated in experimental studies, which were exhaustively summarized in a recent review [15]. Nevertheless, the link between insulin resistance and blood pressure suffers from a lack of consistency from one study to another. Ferrannini commented on the large differences in the strength of the association reported in several studies and suggested that confounders and sample size are primarily responsible for this discrepancy [12]. Adding to this concept, one could include

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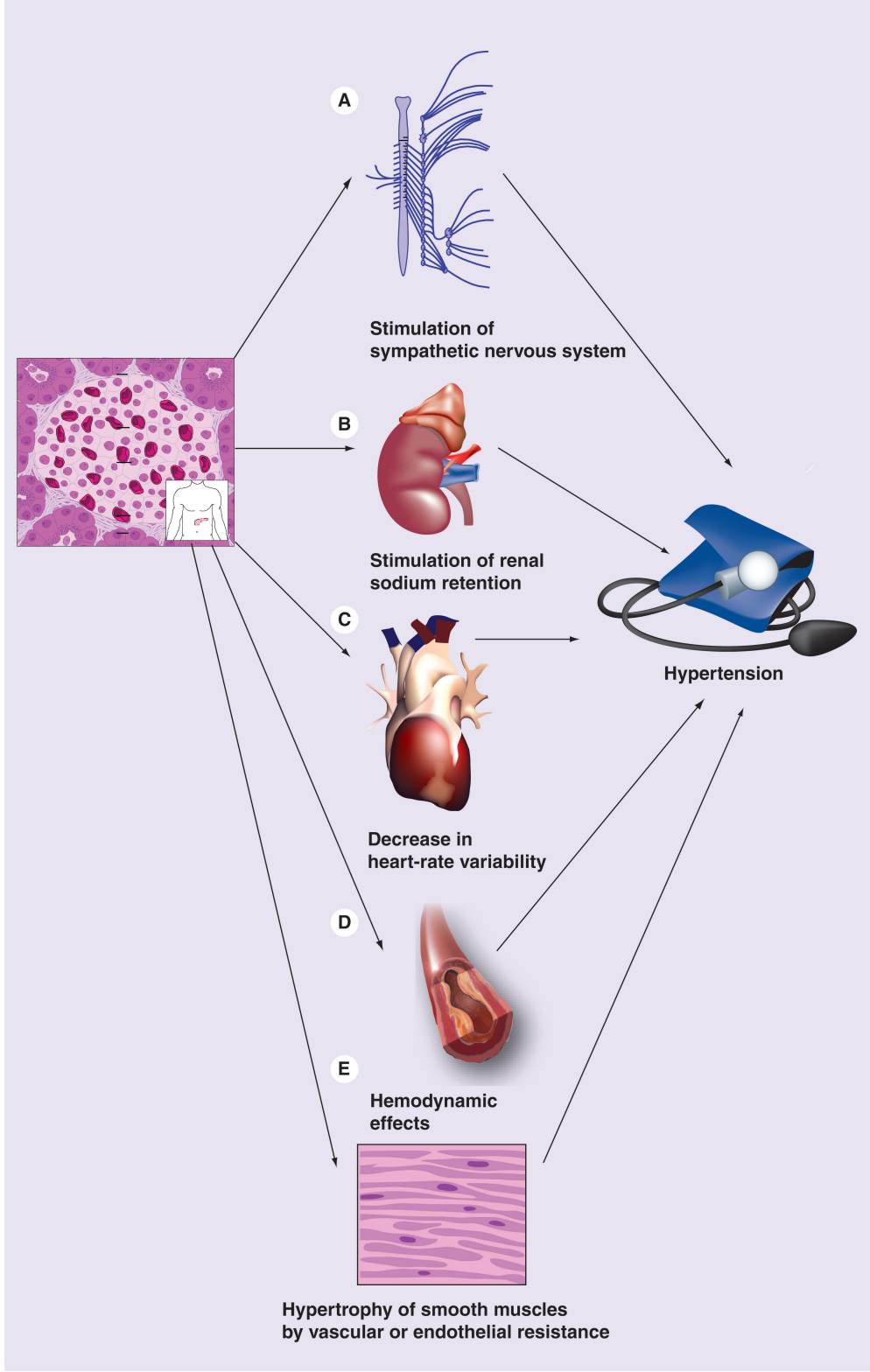
Figure 1. Potential pathophysiological pathways of insulin leading to hypertension.



Adapted from: **(A)** [50,84,85]; **(B)** [86–88]; **(C)** [50]; **(D)** [89–92]; and **(E)** [13].

ethnicity as an important potential confounder. Indeed, the strength of the relationship between insulinemia, insulin resistance and hypertension varies widely according to ethnic groups:

- Showing no racial difference in the IRAS study [11]
- Weak associations in African–Americans as compared with white Americans in the ARIC [8] and the CARDIA studies [9]
- Strong relationship observed in European individuals [12]

Without reviewing all causative criteria in order to establish the causality of insulin with respect to hypertension enumerated by Hill in 1965 [16], we cannot ignore that this link is seriously challenged in terms of biological plausibility, strength, consistency and temporality. Even if reviewed studies support the biological plausibility of an etiological link, this concept is challenged by animal studies. Chronic infusion of insulin did not affect blood pressure [17]. The strength of the association also varies among studies, but this is probably related to the assessment, design and population, which differ between studies. The third important criteria for establishing the causality is the temporality. In humans, the temporal sequence is insulin resistance then hypertension. However, there are always patients with insulinoma who are free of hypertension [18,19].

The presence of different clinical phenotypes may have led to discrepancy in the field. For example, as described above, some subjects with insulin resistance may depict abnormal regulation of blood pressure. However, it is not rare for hypertensive patients to develop Type 2 diabetes. A recent prospective study provides interesting results in favor of the hypothesis that blood pressure precedes the development of insulin resistance [20]. In a cohort of 1152 men, a greater risk of developing diabetes in individuals with hypertension was observed. They also found that these two pathological states were separated by approximately 25 years [20]. Smaller cross-sectional studies also showed that hypertensive subjects have a higher risk of insulin resistance compared with normotensive subjects [21,22], but this was not observed in all studies [23]. As for the previous association, the strength varies owing to different sample characteristics, such as size, severity and/or duration of hypertension, as well as study design (i.e., rest vs exercise condition) and different methods in the assessment of insulin sensitivity.

Metabolic pathways through which elevated blood pressure induces insulin resistance are not clearly understood. It has been hypothesized that insulin resistance is caused by attenuated insulin-mediated skeletal blood flow. In other words, insulin resistance in hypertensive patients may have a hemodynamic basis [24,25]. Hyperinsulinemia may be related to resistance to insulin-mediated glucose disposal [3,21]. Blood pressure and insulin sensitivity may be linked by the renin–angiotensin system (RAS) [26,27], or by the stimulation of nitric oxide (NO) synthesis [28]. However, the exact mechanisms, as well as the etiological role, of hypertension are hyperinsulinemia is still debated [26].

In light of these findings and theories, the link between insulin abnormalities and blood pressure has now been clearly accepted; however, the controversy of the direction of the link remains. This is mainly owing to the etiological heterogeneity of hypertension [3,29]. Consequently, insulin may be viewed as an etiologic component of hypertension. Within this multifactorial framework of the etiology of hypertension, one must consider obesity as another major determinant.

Is obesity a confounder or an etiologic factor in the insulin resistance–hypertension relationship?

In a population of hypertensive subjects without diabetes, it has recently been shown that obesity and insulin resistance have an additive effect, which explains a significant variance of the model (38%) [5]. In other words, obesity, insulin resistance and hypertension are highly interrelated and there is colinearity among these parameters [26]. Indeed, the Baltimore Longitudinal Study of Aging reported, in a Caucasian population of 649 patients, that the simple correlation between fasting insulin and blood pressure was secondary to the confounding effects of age and obesity [30]. The correlation of blood pressure was considerably stronger with BMI, percentage body fat, and waist:hip ratio than with insulin levels in both sexes [30]. The strength of the relationship between insulin resistance, obesity and hypertension was largely described in adults, as well as in children and adolescents, as reviewed by Rocchini 12 years ago [31].

Obesity is recognized as a major cause of hypertension in humans [32] and is also strongly associated with insulin resistance [33–35]. For both associations, mechanisms are not fully understood.

Many pathways are suspected, such as an activation of the RAS, increment in sympathetic nervous system activity, which mediates an increase in leptin secretion [36–38], as well as an involvement of microvascular dysfunction [39]. These mechanisms may contribute to the increase in blood pressure resulting from increasing levels of adiposity independently of insulin resistance. Sympathetic nervous system activation associated with obesity [40] and molecules released by hypertrophied fat cells are two factors with the potential to promote the formation of angiotensin II (Ang II) and aldosterone. These have a direct vasopressor and antinatriuretic effect [41]. A local RAS is present in human adipose tissue and may act as a distinct system from the plasma RAS [42,43]. Interestingly, in a recent study in rodents overexpressing 11β-hydroxysteroid dehydrogenase type 1 in fat cells, an activated circulating RAS has been observed along with hyperinsulinemia and hyperleptinemia. The authors suggest a causal role of circulating RAS in salt-sensitive hypertension observed in their mice model [44]. Nevertheless, the involvement of RAS in hypertension needs to be confirmed in humans. Secondary to the liver, white adipose tissue is an important production site of angiotensinogen (AGT). This hormone is secreted into the circulation and it is conceivable that it increases cardiometabolic complications [45–47]. It has been demonstrated, in transgenic mice that either overexpress adipose AGT or restrict AGT expression to adipose tissue, that these animals exhibit higher blood pressure than their controls [45]. Interestingly, there are also data suggesting a trophic role of Ang II in adipose tissue development [45,48]. Accordingly, expression of adipose AGT compared with AGT-deficient mice increases fat mass by 1.5-fold and results in the normalization of systolic blood pressure [45]. In accordance, several studies have demonstrated that weight loss induced concomitant reduction in blood pressure and insulin resistance [37,49]. In light of these findings, obesity may appear to be an essential yet complex factor in the insulin resistance–hypertension relationship. Again, by its strong association to both hypertension and insulin resistance, obesity may be viewed as either a confounder, an intermediate or an etiological factor in this relation.

Numerous patient phenotypes support all three of the above interpretations; however, the etiological role of obesity is heavily supported in human studies. For example, a cross-sectional study by Ferrannini found an inverse association between insulin sensitivity and blood pressure. This association was stronger in nonobese than in obese subjects [12]. This was confirmed by Muscelli and colleagues, who investigated the acute effects of insulin on autonomic control of cardiac function in obese and lean subjects [50]. They suggested that obesity could be linked to hyperinsulinemia, in turn acting on both the sympathetic and the parasympathetic systems, which are known to modulate blood pressure [50]. Moreover, in obese subjects, a slight over reactivity of the sympathetic nervous system was observed, depicting obesity as a state of chronic desensitization with impairment of autonomic modulation of the sino-atrial activity [37]. Even if these results need to be prospectively confirmed, this supports obesity as an etiological factor of hypertension via increased insulin resistance. In addition, a gene–environment interaction should be considered when looking at different populations. Concordance rates of 15% for dizygotic and 31% for monozygotic twins have been reported in those with both obesity and hypertension [51].

The abdominal region: a strategic deposit site for deleterious fat

Whatever the true extent of the influence of obesity, body fat distribution is a crucial determinant of insulin resistance and hypertension. Since the late 1950s, it has been established that abdominal obesity, or android obesity, is an important constituent of insulin resistance, hypertension, Type 2 diabetes and cardiovascular disease [27,32,52–57]. The abdominal adipose tissue is divided into subcutaneous and visceral tissue (VAT). Evidence from experimental studies suggested that the VAT mediates the detrimental effects of obesity. VAT secretes numerous biologically active substances (adipokines), which act on insulin resistance and vasculature [58–60]. Its central physiological and anatomical positioning allows for high selective release of substances in the portal system. All components of the RAS system (AGT, AT_1 receptor and ACE, but not renin or AT_2 receptor) are found in both visceral and subcutaneous adipose tissue [61]. Specifically, AGT mRNA and AT_1 receptor mRNA levels have been shown to be higher in visceral than in subcutaneous adipose tissue [61]. Therefore, one could speculate that the contribution of adipose tissue to plasma AGT levels is significant in overweight or obese subjects. AGT expression is known to be upregulated by glucocorticoids in mouse cells, and insulin resistance

leads to increased AGT levels [62]. It is also noteworthy that the hypothalamo–pituitary–adrenal axis is activated in abdominal obesity [63]. Since plasma AGT levels correlate with blood pressure and are associated with BMI [64], it is tempting to speculate that hypertension is associated with overweight and/or obesity, which may be mediated by AGT produced by the enlarged adipose tissue mass [65]. This model implies adipose tissue RAS in the pathogenic alterations of metabolism and hypertension. The physiological significance of the hormonal regulation of adipose tissue AGT with respect to increased Ang II production, leading to elevated blood pressure, warrants further investigation. However, previous data are in favor of such a hypothesis. Finally, it was also postulated that the detrimental effect of VAT was exerted by an increased liberation of free fatty acids, which consequently decrease hepatic insulin clearance and increase gluconeogenesis and dyslipidemia [66–68].

There is increasing evidence from small and large human epidemiological studies that abdominal fat may be highly implicated in the link between insulin resistance and hypertension [4,57,69–73]. For instance, VAT, insulin resistance and blood pressure are quantitatively inter-related (r = 0.39–0.47) in men [71]. It was reported that a 1-kg increment in visceral fat predicts a 10-mmHg increase in blood pressure [71]. VAT was also associated with blood pressure and hyperinsulinemia in children [74]. In postmenopausal women, VAT was strongly associated with insulin resistance and dyslipidemia [70,75]. Furthermore, in postmenopausal women, a negative correlation was observed between blood pressure, or insulin and fat leg mass, suggesting, to some degree, a protection of peripheral adiposity compared with adipose tissue stored in the visceral region [75]. Clinical data showed that visceral fat reduction improves the metabolic profile [76], whereas removal of subcutaneous fat tissues produced contradictory results (i.e. no effect [77], or a weak positive influence [78,79], on the metabolic profile).

The aforementioned studies share a similar sophisticated measurement method of abdominal fat: scanner imaging. Unfortunately, this powerful tool cannot be easily used in large epidemiological studies. Nevertheless, in each of these studies, simple clinical measures such as waist circumference were also significantly associated

Executive summary

- Obesity, insulin resistance and hypertension are closely inter-related. However, their relationship remains unclear.
- Does insulin resistance precede hypertension or is it the reverse? There is as much evidence as inconsistencies in the first assumption as there are for the second. Thus, even if the link becomes clearly established, the sequence of events remains to be determined.
- Obesity (particularly abdominal obesity) appears to be an important yet complex marker in the insulin resistance–hypertension relationship.

Does insulin resistance lead to hypertension or the inverse?

- Numerous epidemiological studies supported by experimental evidence suggest an impact of insulin resistance on hypertension. Moreover, there are also several studies supporting the inverse. To date, both positions are still strongly debated. However, causative criteria suggest that insulin resistance should be viewed as an etiologic component of hypertension.

Is obesity a modulator or an etiologic factor in the insulin resistance–hypertension relationship?

- The influence of obesity on insulin resistance and hypertension is well known and heavily supported by epidemiological evidence. It has been suggested that the influence could be related to joint modulation of both the sympathetic and the parasympathetic systems.

The abdominal region: a strategic deposit site for deleterious fat

- Visceral adipose tissue (VAT) secretes adipokines that act on insulin resistance and vasculature, and the renin–angiotensin system may be more active in VAT than other adipose tissue.
- Removal of subcutaneous fat does not markedly improve metabolic or cardiovascular functions in obese individuals, whereas reduction of VAT does improve it.
- Waist circumference appears to be a valid clinical measure of abdominal obesity.

Expert commentary & future perspective

- To the question: 'Does a link between obesity, insulin resistance and hypertension exist?', the answer is likely positive, with the link between these entities being waist circumference. Nevertheless, as underlined here, this still remains to be confirmed by future research.

with hypertension [71] and correlated with sophisticated measures of VAT [4,70–72]. Moreover, waist circumference (above and beyond BMI), showed a great ability to predict hypertension in a large population [69]. Indeed, waist circumference has been reported as the strongest independent predictor (age, gender, BMI and insulin resistance included) of both systolic and diastolic blood pressure in 413 normoglycemic Chinese individuals [72]. In this study, waist circumference was found to be the major determinant of blood pressure, accounting for more than 20% of the variance [72]. A similar association, in a cohort of 563 Japanese–Americans, has been recently reported between the prevalence of hypertension and intra-abdominal fat accumulation, but not with waist circumference [80]. Recently, a comparative study on different abdominal fat measurement showed that waist circumference correlated better than BMI or percent fat measured by dual energy X-ray absorptiometry (with insulin and blood pressure, as well as glucose concentration, triglycerides and high density lipoprotein levels in healthy white and African–American men and women [81].

Expert commentary & future perspective

Waist circumference may be central in the association between insulin resistance and hypertension; however, further research is needed to confirm this concept [82]. It is plausible that cross-talks exist between visceral adipose tissue, Ang II and insulin in the overweight/obesity state in humans, in an independent and facilitative manner, depending on a permissive genetic background. This process may contribute to conditions such as the development of cardiovascular diseases and metabolic complications. Central obesity, assessed by waist circumference, has a predominant role, compared with insulin levels, in explaining individual differences in blood pressure, at least in a Caucasian [69], Chinese [72] and Japanese [80] populations.

In the late 1990s, Brands and colleagues, ended their elegant review on the link between insulin resistance and hypertension, writing: "The only clear way to view insulin resistance as a cause of hypertension is in obesity" [17]. Nearly a decade later, more data supports their statement; excess visceral adipose tissue significantly contributes to this association, whereas waist circumference is a simple clinical marker of this fat deposit. Consequently, to the question: "Does a link between obesity, insulin resistance and hypertension exist?", the answer is likely positive, with the clinical easily recognizable link between these entities being waist circumference. Nevertheless, as underlined here, this still remains to be confirmed by future research [83].

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