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# Link between Insulin Resistance and Hypertension: What Have We Learned from Our Ancestors?

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Insulin resistance is typically defined as decreased sensitivity and/or responsiveness to the metabolic actions of insulin that promote glucose disposal. Obesity, physical inactivity, hypertension, hyperlipidemia and aging, which are independent risk factors for cardiovascular disease, contribute to the complex interaction between genetic and environmental factors required for impaired insulin signaling [1]. Clinical studies have shown that hypertension and insulin resistance often coexist and their association increases cardiovascular risk and the incidence of new onset type 2 diabetes [2,3]. Although the association between insulin resistance and hypertension has long been recognized, a direct relationship between insulin resistance and blood pressure remains controversial.

Medical research is generally concerned with mechanistic questions pertaining to how diseases develop, particularly cellular signaling pathways of disease production. In contrast, evolutionary research addresses why diseases develop by studying the ancestral origins of modern diseases, particularly the evolutionary advantage of certain genotypes that now are maladaptive and promote disease. Evolutionary medicine may provide some important clues for medical research to unravel novel mechanisms of disease. Hypertension and insulin resistance are considered prototypical "diseases of civilization" that are only manifested in modern world environments where food is plentiful and people are sedentary; these diseases did not exist in pre-modern times [4]. The following is a review of evolutionary aspects of insulin resistance and hypertension.

Obesity is a common cause of insulin resistance. The epidemic-like rise in the prevalence of obesity constitutes an undoubted and serious global health problem [5,6]. Importantly, hypertension and diabetes are associated with obesity and together, constitute a significant burden in terms of patient morbidity and mortality as well as escalating health care costs [7]. Stocking up on food was key to survival in pre-modern times, but now with energy dense and cheap foods, labor-saving devices, motorized transport and sedentary work, obesity is rapidly becoming a consequence of modern life.

Many studies suggest that obesity is associated with a systemic chronic inflammatory response characterized by altered proinflammatory cytokine production and activation of inflammatory signaling pathways in adipose tissue [8,9]. Clinical and experimental studies have provided ample evidence showing a close link between chronic inflammation and insulin resistance in obesity [10]. However, insulin resistance also exists in malnourished populations and is mechanistically linked to inflammation [11].

Evolution by natural selection is a central organizing concept in biology. For millions of years, living beings from lower-level organisms to human beings have been faced with survival stresses, including malnutrition and infection. Survival of multicellular organisms depends on the ability to store energy for times of low nutrient availability or high energy need and the ability to fight infections [12]. The metabolic and immune systems are therefore among the most basic requirements across the animal kingdom [13]. It is not surprising then that metabolic and immune pathways have evolved to be closely linked and interdependent, and that the genes that control metabolic and pathogen-sensing systems have been highly conserved from lower-level organisms to mammals [11]. Under normal conditions, the integration of the metabolic and immune systems is fundamental for the maintenance of good health. It has been well recognized that there is a link between infection and poor nutrition. The basic inflammatory response favors a catabolic state and inhibits anabolic pathways, such as the highly conserved insulin signaling pathway, and consequently results in insulin resistance. As a result of insulin resistance, plasma levels of glucose are elevated to provide energy sources to maintain the function of vital organs, such as the heart and brain, and of immune cells, such as leukocytes, to combat infection, since the heart, brain and leukocytes are dependent on plasma levels of glucose for energy. Therefore, insulin resistance resulting from inflammation may represent a feedback mechanism for poor nutrient organisms to fight against infection.

Natural selection shapes organisms to function within a particular set of environmental conditions [14]. Because organisms adapt to the totality of their environment, or ecological niche, it is hypothetically possible that natural selection favors organisms harboring the genotype for a metabolic system (such as the insulin signaling pathway) that has an increased response to inflammation. The modern environment has been shown to promote the development of the metabolic syndrome [14], and it is not surprising that overnutrition initiates inflammation that results in insulin resistance. We now understand that many inflammatory cytokines, such as tumor necrosis factor (TNF) α, interleukin-6 and NFκB, can inhibit the insulin-stimulated phosphorylation of insulin receptor substrate-1 at the tyrosine residue [15,16], which is key signaling molecule for insulin-mediated metabolic effects and vasorelaxation.

Hypertension is also associated with an increase in systemic and vascular inflammatory responses, which contributes to vascular dysfunction [17]. Although the genetic causes of essential hypertension remain elusive, studies in Dahl salt-sensitive (DS) rats, a paradigm

of salt-sensitive hypertension in humans, have suggested that chromosome 2 contains quantitative trait loci for blood pressure and genes encoding for inflammatory mediators with biological effects on T lymphocytes [18]. DS rats exhibit elevation of blood pressure, vascular inflammation, and endothelial dysfunction that is reduced in the SSBN2 rat, a consomic rat in which chromosome 2 of the DS rat is replaced by that of the normotensive Brown Norway rat [18]. Our studies [17-19] in DS rats have shown that inflammation is linked not only to elevation of blood pressure and vascular dysfunction, but also to insulin resistance, because inhibition of the NFκB inflammatory pathway significantly reduced blood pressure and vascular inflammation and improved endothelial function as well as systemic and vascular insulin resistance. These studies support the notion that inflammation is a link between hypertension and insulin resistance.

Salt-sensitivity may be another link between insulin resistance and hypertension. High salt diet impairs insulin sensitivity in hypertensive patients with salt-sensitivity but not in those with salt-resistance [1]. Clinical studies have demonstrated that salt sensitive hypertension is more prevalent among populations of patients that are obese, aging, postmenopausal, and/or manifest the metabolic syndrome [20,21]. In these populations, the risk of diabetes and cardiovascular disease is increased. A recent clinical study has shown that insulin resistance enhances the blood pressure response to sodium intake [21]. Therefore, reduction in sodium intake may be an especially important component in reducing blood pressure in patients with multiple risk factors for insulin resistance and the metabolic syndrome [21].

The role of sodium in the regulation of blood pressure has been well demonstrated. Excess dietary salt and caloric intake, as commonly found in western diets, has been shown to promote hypertensive and metabolic diseases [1]. However, in pre-modern times, sodium deprivation threatened human survival, particularly in hot and dry climates such as the African savannah. The principle of natural selection may have allowed the ancestral sodium-conserving genotype to persist [22], which may be maladaptive to the modern environment of sodium abundance, and results in hypertension. Experimental evidence from trials of dietary sodium restriction generally supports the hypothesis of a sodium-hypertension link, particularly among salt-sensitive populations. That African Americans have a higher prevalence of salt sensitivity than White Americans is another evidence to support the hypothesis.

Interestingly, insulin has been shown to reduce urinary sodium excretion by increased renal tubular sodium reabsorption [23]. It is unknown whether this antinatriuretic effect of insulin enhanced survival in our malnourished ancestors by promoting sodium preservation. On the other hand, it has been postulated that the antinatriuretic effects of insulin promotes hypertension in insulin resistance and hyperinsulinemic conditions [24].

In summary, abundant clinical and epidemiologic evidence demonstrates a close linkage between insulin resistance and hypertension. The coexistence of insulin resistance and hypertension results in a substantial increase in risk of developing cardiovascular disease and type II diabetes. The driving force linking insulin resistance and hypertension remains to be fully elucidated due to the complex and multifactorial nature of the associated conditions, which involve environmental, genetic, and behavioral confounders, all of which should be addressed in future studies. However, evolutionary medicine may help us understand why we are susceptible to hypertension, insulin resistance and other "diseases of civilization". We can learn from our ancestors how to combat these diseases.

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