Diet-Induced Hyperinsulinemia as a Key Factor in the Etiology of Both Benign Prostatic Hyperplasia and Essential Hypertension?

Wolfgang Kopp

Former head of the Diagnostikzentrum Graz, Graz, Austria.

ABSTRACT: Benign prostatic hyperplasia and hypertension are common age-related comorbidities. Although the etiology of benign prostatic hyperplasia (BPH) is still largely unresolved and poorly understood, a significant age-independent association was found between BPH and hypertension, indicating a common pathophysiological factor for both diseases. It has previously been suggested that the development of essential hypertension may be related to diet-induced hyperinsulinemia. This study follows the question, whether BPH may develop due to the same mechanism, thereby explaining the well-known comorbidity of these 2 disorders. The scientific evidence presented shows that BPH and hypertension share the same pathophysiological changes, with hyperinsulinemia as the driving force. It further shows that significant dietary changes during human history cause disruption of a finely tuned metabolic balance that has evolved over millions of years of evolution: high-insulinemic food, typical of current "Western" diets, has the potential to cause hyperinsulinemia and insulin resistance, as well as an abnormally increased activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, alterations that play a pivotal role in the pathogenesis of BPH and hypertension.

KEYWORDS: BPH, hypertension, diet, pathomechanism, etiology, insulin resistance hyperinsulinemia, SNS, RAAS

Introduction

Benign prostatic hyperplasia (BPH) is the most common hyperplastic disorder in men and the most influential factor for the development of lower urinary tract symptoms (LUTS).[1] Its incidence is age-related: it is estimated that nearly 50% of men at the age of 60 and almost 90% by the ninth decade develop histological BPH.[2] It is well established that BPH and hypertension are common age-related comorbidities; approximately 25% to 30% of men older than 60 years have concomitant BPH and hypertension.[3] Although the etiology of BPH is still largely unresolved and poorly understood, a significant age-independent association was found between BPH and hypertension, indicating a common pathophysiological factor for both diseases.[4] It has previously been suggested that the development of essential hypertension may be related to diet-induced hyperinsulinemia.[5] This study follows the question, whether BPH may develop due to the same mechanism, thereby explaining the well-known comorbidity of these 2 disorders.

Etiological Aspects of BPH

Benign prostatic hyperplasia is characterized by increased cellular proliferation of epithelial and stromal cells and enhanced sympathetic smooth muscle tone in the periurethral region.[1,2,6,7] Several etiologic factors for the development of BPH have been proposed. Most interest has been focused on hormones, especially testosterone. The role of androgens in the development of BPH has been intensively studied. Androgens seem to play a permissive rather than a causative role in the development of

human BPH. Their influence appears to be nonspecific: basically, androgens (particularly dihydrotestosterone [DHT]) are necessary for the development and maintenance of prostatic epithelial and stromal growth and also for the development of BPH.[2] This is underlined by the fact that BPH never occurs in men castrated before puberty who received no androgen supplement.[8] Androgen withdrawal causes not only regression of BPH but also atrophy of the normal gland.[9] Although serum testosterone levels decrease with age (by about 2%-3% per year), development of BPH continues with increasing age. In a study on 148 men (mean age: 59.8 years), no significant correlation of testosterone levels in the serum with prostate volume could be detected.[10] Also, the finding that BPH in humans is not associated with elevated tissue levels of DHT questions the role of DHT as a causative factor in the etiology of BPH: in a study by Walsh et al,[11] the DHT content of normal peripheral and benign hyperplastic tissues obtained at open surgery procedures was the same. Furthermore, while testosterone or DHT increases prostate weight in animal models of BPH (reviewed in Li et al[12]), no influence on prostate growth was found in a randomized, placebo-controlled study in which 114 healthy men underwent 24-month DHT treatment.[13] Also, supplementation of men with androgens does not increase the incident risk of BPH or LUTS; when hormonally deficient men are treated, prostate volume increases but only to the size expected for eugonadal men of the same age.[14] The paradox of continuing prostatic growth with declining androgen levels suggests that other growth-stimulating factors must come into play. Several

metabolic factors have been suggested to be causally related to the development of BPH, such as the metabolic syndrome (MetS),[15–18] hyperinsulinemia,[19–22] the chemical transmitter norepinephrine (NE),[23] angiotensin II (ANG II),[24] and various growth factors, such as insulin-like growth factors (IGFs).[15,25]

Insulin and BPH

Hyperinsulinemia has been suggested to be causally related to the development of BPH.[19–22] Several studies demonstrated that fasting serum insulin levels were significantly higher in men with BPH than in controls without BPH[20,21] and correlated with the annual BPH growth rate.[21] In a stepwise regression analysis, Nandeesha et al[22] found that insulin levels were an independent predictor of prostate volume in symptomatic BPH. Hyperinsulinemia and insulin resistance (IR) are critical features of the MetS.[26] The MetS involves a constellation of abnormalities, including central adiposity, impaired glucose metabolism, dyslipidemia, endothelial dysfunction, arterial hypertension, atherosclerotic disease, low-grade inflammation, and in men, low testosterone levels. Several definitions of MetS have been proposed by various organizations.[27] In recent decades, an increasing body of evidence points to a significant association between MetS and BPH/LUTS. The syndrome itself, as well as individual components such as hypertension, abdominal obesity, and dyslipidemia, has been associated with an increased risk of developing BPH and LUTS, thus supporting an important role for hyperinsulinemia in the development of BPH.[4,15–18,28–30] The close relationship between Mets and BPH is also underlined by a large cross-sectional study based on the UK Clinical Practice Research Datalink. The authors reported that men with clinical BPH have substantially greater odds of also having MetS or individual components of the syndrome than matched controls without BPH.[16]

Clinical and epidemiologic research suggests that type 2 diabetes[31,32] and hypertension[33–35] also significantly increase the risks of BPH and LUTS. Hammarsten et al[33] reported that individuals with treated hypertension had a larger prostate volume and higher annual BPH growth rate than did controls. Similarly, Joseph et al[34] reported that men with a history of hypertension had a 1.5-fold higher risk of moderate-to-severe LUTS compared with their counterparts without a history of hypertension. Furthermore, in a retrospective study of 9857 patients with BPH, Michel et al[4] found a significant, age-independent relationship between hypertension and BPH symptoms, and a prospective study on 212 men confirmed a significant correlation between mean blood pressure (BP) and prostate size in all subjects.[35]

Animal models of hypertension likewise support an association between hypertension and the development of BPH. Spontaneously hypertensive rats (SHR), a commonly used model of genetic hypertension, were shown to develop rapid prostatic proliferation and BPH, whereas their normotensive counterparts did not develop such features.[36–38] The SHR is not only genetically hypertensive but also has increased fasting levels of insulin consistent with IR.[39] In another animal study in rats, IR with compensatory hyperinsulinemia was induced by a high-fat diet; the hyperinsulinemic condition caused enlargement, increased proliferation, and cellular hyperplasia of the prostate gland. The pioglitazone-mediated reversal of hyperinsulinemia resulted in improved insulin sensitivity, decreased plasma insulin levels, and reduced prostate weight.[40] These animal studies further support the role of hyperinsulinemia in prostate growth.

Hyperinsulinemia may directly affect prostate gland growth through insulin receptor–mediated growth-promoting effects and/or through enhancing IGF-1 receptor signaling. Because of its structural similarity to IGF, insulin can bind to the IGF receptor[41] and activate the IGF signaling pathway to promote prostatic growth. In addition, elevated circulating levels of insulin may lead to increased IGF-1 bioavailability as a result of insulin-mediated changes in insulin-like growth factor–binding protein (IGFBP).[42] The IGF-1 has been associated with BPH risk in several epidemiological studies.[43–45]

Equally or perhaps even more important to the developmental process itself is the fact that insulin activates the sympathetic nervous system (SNS) in a dose-dependent manner,[46] and insulin and IGF-1 promote activation of the renin-angiotensin-aldosterone system (RAAS).[47]

SNS and BPH

Prostate smooth muscle cells represent a significant proportion of the prostate gland. Active smooth muscle tone in the gland is regulated by the adrenergic nervous system. The prostate is innervated by sympathetic nerves that, upon stimulation, release NE and evoke smooth muscle contractions, mediated by α-1-adrenergic receptors.[48] Increased local sympathetic activity and enhanced sympathetic smooth muscle tone are characteristic features of BPH.[1,2,7,49] It has been suggested that NE is involved in the pathogenesis of BPH by stimulating the proliferation of nonepithelial prostate cells and thereby affecting prostate growth.[1,2,23,49,50] Furthermore, overactivity of the autonomic nervous system results in a dynamic increase in prostatic urethral resistance.[2] Of particular note, the SNS can interact with the RAAS in the form of a positive feedback loop: NE activates ANG II production through stimulation of renin secretion, whereas circulating ANG II interacts with the SNS at various sites and amplifies the response to sympathetic stimulation by presynaptic facilitatory modulation of NE release.[51,52]

RAAS and BPH

All components of the RAAS in the human prostate, including angiotensinogen, renin, angiotensin-converting enzyme, angiotensin II receptor type 1 (AT1), and ANG II itself, were identified and localized to the glandular epithelium.[53] Angiotensin

II as the major effector peptide of the RAAS interacts with at least 2 receptors, denoted AT1 and AT2. In addition to the "classic" hormonal circulating system, a local, tissue-specific RAAS exists also in the prostate with autocrine and paracrine effects.[53,54] Increasing evidence has accumulated showing that the RAAS plays an important role in the development of BPH.[24,53,55,56] The expression of ANG II and angiotensin-converting enzyme, a key component of the RAAS, is aberrantly increased in BPH.[24,56] Angiotensin II is well known to stimulate cellular proliferation and growth in vascular smooth muscle cells and to enhance smooth muscle tone.[57] Similar to its effect on vascular smooth muscle cells, a mitogenic and proliferative effect of ANG II on the stromal compartment of human prostate tissue has been demonstrated, mediated by AT1 receptors.[58] In the normal human prostate, ANG II receptors, consisting mainly of the AT1 subtype, are located predominantly on stromal smooth muscle cells[24] and are densely populated in the periurethral region, which is precisely the region most affected by BPH.[55]

In summary, hyperinsulinemia with increased activation of the IGF system, the SNS, and the (local) RAAS may cause proliferation of the stromal compartment and enhance smooth muscle tone. As AT1 receptors are localized predominantly to periurethral stromal smooth muscle, the proliferative effect will be greatest in this area, explaining one of the unique pathologic-anatomic features of BPH.

The next section shows that—concordant with these findings—the same metabolic factors involved in the development of BPH may play a pivotal role in the development of hypertension, explaining the well-known comorbidities of the 2 disorders.

Etiological Aspects of Essential Hypertension

Physiological mechanisms to maintain normal BP

Basically, arterial BP is the product of cardiac output and peripheral vascular resistance (PVR). Cardiac output is the product of stroke volume and heart rate, whereas PVR is primarily determined by the contractile state of small arteries and arterioles. Factors affecting cardiac output include sodium intake, renal function, and mineralocorticoids. Peripheral vascular resistance is dependent on the SNS and humoral factors such as ANG II, nitric oxide (NO), and endothelin. A finely tuned balance of various mechanisms serves to adjust and maintain BP in the short and long term, most importantly neural mechanism, renal endocrine-hormonal mechanisms, and local endothelium-derived factors.[59]

The SNS and the RAAS play important roles in arterial pressure control by modifying cardiac output, PVR, and renal function. Activation of the SNS not only causes an increased heart rate and systemic vasoconstriction, which increases the BP in the short term,[60] but also plays an important role in long-term regulation through stimulation of renin release in the juxtaglomerular apparatus, with

activation of the RAAS.[59] The RAAS plays a crucial role in regulation of BP and cardiovascular homeostasis by affecting renal function and by modulating vascular tone.[61] In addition to the "classic" hormonal circulatory system, a local RAAS exists in the kidneys, the heart, and the arterial tree, with autocrine and paracrine effects.[48] Angiotensin II as the main effector of the RAAS is a potent vasoconstrictor that causes an increase in mean arterial pressure and the direct stimulation of sodium retention via the increased synthesis of aldosterone.[59,62]

In addition, the most important method for long-term BP monitoring is the renal fluid system, which increases or decreases blood volume in response to changes in BP through pressure diuresis and pressure natriuresis.[59,62] Thus, short-term changes in BP are regulated by SNS and RAAS, whereas long-term changes in BP are controlled by the kidney.[59,62,63] Among the local endothelial-derived factors, endothelin-1 (one of the most potent vasoconstrictor ever isolated) and NO, a major vasodilator, are most important. Interactions between all these physiological mechanisms are autoregulated to maintain normal BP according to specific needs.[60,62,63]

The last century recognized a dramatic increase in the prevalence of BP; in the United States, the prevalence rose from almost absence in the early 1900s to rates of 30% and more at present,[64] despite the absence of a significant temporal rise in sodium intake over this period.[65] The most likely reason for the dramatic increase in the incidence of hypertension has been attributed to the marked increase in obesity. Obesity, an important risk factor for hypertension, has increased from about 5% of the US population in 1900 to more than 30% today.[66,67] Hypertension is now also common in the pediatric population, frequently associated with obesity and the MetS.[64,67] The dramatic increase in obesity and hypertension may be attributed to significant alterations in dietary habits, especially the significant increase in the consumption of sugars and high-insulinemic nutrition during the second half of the 20th century (see below).

Development of hypertension

Essential, primary, or idiopathic hypertension (EH) is defined as high BP, in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or Mendelian forms (monogenic) are not present.[68] Basically, hypertension is caused by a disruption of the autoregulatory mechanism described above. Not surprisingly, the same mechanisms, responsible for maintenance of normal BP, in especially the SNS, the RAAS, and the kidney, are also involved in the development of EH.[60,62,63,68]

Increased insulin production (hyperinsulinemia) appears to play a crucial role in disrupting the fine balance of BP regulation, as most of the changes related to hypertension development are due to increased insulin levels.

Insulin and hypertension

High BP is a classical feature of the MetS, and the MetS is present in up to one-third of hypertensive patients. Abundant clinical and epidemiologic evidence demonstrates a close linkage between IR and hypertension.[69–73] Obese as well as lean individuals with EH display IR and hyperinsulinemia.[72,73] Fasting insulinemia and IGF-1 levels were significantly higher in patients with EH compared with normotensive patients and patients with secondary hypertension,[74] and several prospective studies have shown that baseline hyperinsulinemia predicts the development of EH.[75,76] As an example, a prospective study of 1865 children and adolescents over a 6-year period showed that the higher the fasting serum insulin concentration at baseline, the greater the increase in BP over a 6-year observation period.[76]

Several physiological mechanisms connect IR and hyperinsulinemia with EH:

- Hyperinsulinemia leads to increased IGF-1 expression.[41,42,77]
- Insulin and IGF-1 cause activation of the vascular RAAS in both vascular smooth muscle cells and endothelial cells.[47]
- Insulin activates the SNS in a dose-dependent fashion in normal individuals, indicated by increased plasma NE levels and microneurographic studies.[46,78,79]
- Insulin stimulates renal sodium reabsorption, favoring expansion of extracellular fluid volume.[70,80]
- Insulin stimulates both endothelin-1 production and its action on the vascular wall.[81]
- Prolonged hyperinsulinemia stimulates leptin release, which has been implicated in the pathomechanism of hypertension.[82]
- Even modest hyperinsulinemia causes severe endothelial dysfunction in large conduit arteries, probably by increasing oxidative stress.[83]

A pivotal role of IR and hyperinsulinemia is also supported by family studies. It is well established that persons with a family history (at least 1 first-degree relative with hypertension) are at significant increased risk of also developing hypertension.[73,84,85] Insulin resistance seems to be the determining link; several studies showed that young healthy offspring of hypertensive parents are more insulin resistant and have higher BP, heart rate, and plasma insulin levels compared with matched healthy individuals with negative family history of hypertension.[85,86]

SNS and hypertension

Essential, primary, or idiopathic hypertension is characterized not only by an impaired parasympathetic tone but also by marked sympathetic overdrive.[87,88] Increased SNS activity causes peripheral and renal vasoconstriction, increases renin secretion and tubular sodium reabsorption, and thereby contributes to the development and maintenance of hypertension and organ damage.[60,62,87] As mentioned before, hyperinsulinemia induces systemic activation of the SNS.[46,78,79] This has been attributed to the fact that insulin causes vasodilation and increased regional blood flow, which would lower BP. Activation of SNS causes vasoconstriction, thereby antagonizing the vasodilatory effect of insulin and avoiding a fall in BP.[89] However, not all persons with IR and hyperinsulinemia develop hypertension. The difference between insulin-resistant individuals with and without hypertension may be related (at least in part) to a hypersensitivity to NE. In individuals prone to EH, insulin evokes an abnormal muscle sympathetic overactivity; the increase in insulin-induced NE release was found to be 3-fold greater in hypertensive patients than that observed in normotensive subjects.[90] Furthermore, hypertensive patients were characterized by a significantly increased vasoconstrictor response to infused NE. Microneurographic studies also demonstrated that sympathetic nerve traffic is potentiated in established hypertension.[79] Similarly, an exaggerated pressor responsiveness to exogenous NE (in the presence of normal endogenous plasma NE concentrations) was found in normotensive offspring of hypertensive individuals compared with normotensive controls without a family history,[91] indicating a genetic origin. As mentioned before, the SNS can interact with the RAAS in the form of a positive feedback loop.[51,52]

RAAS and hypertension

To date, the central role of the RAAS in the acceleration and maintenance of EH is well established. Overproduction of ANG II increases arterial pressure, produces oxidative stress, and impairs endothelium-dependent relaxation. In addition, it stimulates the release of aldosterone from the zona glomerulosa of the adrenal gland, which results in a further rise in BP related to sodium and water retention.[51,63,92] Chronic activation of the RAAS promotes vascular remodeling and inflammation of resistance vessels of the systemic circulation[93] and of renal vessels,[94] causes cardiac hypertrophy and promotes salt and water retention, consistent features of established hypertension.[51,63,92]

Vascular remodeling

Very early hypertension is characterized by increased heart rate and cardiac output and normal PVR, while most patients with established EH have normal cardiac output but increased PVR.[59,60,62] The morphological substrate of this transition from low to high PVR are progressive trophic changes in the vascular wall ("vascular remodeling") of resistance vessels of the systemic circulation[90,93,95] and of renal vessels, with gradual involvement of the kidney.[94] Metabolic agents responsible for these trophic changes are NE, ANG II, and insulin.[93–95] Narrowing (with diminished perfusion of the kidney) and a

decreased dispensability (sensed by stretch receptors in the granular cells) of preglomerular kidney vessels cause chronic activation of the RAAS,[96] with generalized vasoconstriction and increased PVR, cardiac hypertrophy, and alterations in cardiac and renal function—consistent features of established hypertension.[62,63,96–98] A central role of the kidney in the pathogenesis and maintenance of EH[98] is directly supported by the finding that "BP goes with the kidney": transplantation studies, both in animals and humans, have documented that a normotensive recipient of a kidney of a genetically hypertension-prone donor will develop hypertension, whereas in hypertensive patients who were recipients of kidneys from normotensive donors, the BP returns to normal levels.[99,100]

Endothelial dysfunction and hypertension

Endothelial dysfunction, a hallmark of hypertension, is characterized by impaired endothelium-dependent vascular relaxation due to decreased vascular NO bioavailability and signaling. Reactive oxygen species play a pivotal role in controlling the endothelial function. Increased levels of oxygen reactive species and decreased antioxidant capacity (characterized as oxidative stress) may directly impair endothelium-dependent vasodilation through inactivation of NO.[101] Insulin resistance and hyperinsulinemia,[83,102] as well as ANG II,[103] are well known to produce oxidative stress and endothelial dysfunction.

In summary, BPH and hypertension share the same pathophysiological alterations, with hyperinsulinemia as the driving force. High-insulinemic diets may play a key role in the development of hyperinsulinemia and IR[104] and therefore in the etiology of EH and BPH, as the following sections show.

Dietary Considerations

Although the development of BPH and an increase in BP are usually considered an inevitable consequence of aging in industrialized societies[105,106] studies on hunter-gatherer (HG) populations and rural populations[107] report fewer LUTS as well as a smaller anatomical prostate size and reduced prostate growth with age. The Tsimane, an indigenous population living in the lowland Amazonian region of Bolivia, rely on hunting, fishing, foraging, and small-scale horticulture for subsistence.[107] The authors report that

> Tsimane men have significantly smaller prostate volumes and a reduced rate of prostate growth with age, compared to men in industrial populations. The Tsimane prevalence of BPH between the ages of 40-80 is less than half of what is seen in U.S. and British men [. . .], while more advanced cases of BPH (>40 cc) were almost non-existent (<1% of Tsimane men).[107]

Similarly, scattered throughout the world, in the arctic, the savanna, the desert, and the rainforests, are HG communities whose members do not develop EH, and the age-related increase in the average BP that characterizes populations living in industrialized countries is absent.[108–112] However, HG are not genetically immune to hypertension, because with acculturation and transition to a westernized lifestyle, especially to Western diets, they develop an increasing incidence of EH and a tendency for their BP to rise with age.[109,113] As an explanation for the lack of development of hypertension, it has been suggested that these normotensive cultures share diets that contain little sodium and lots of potassium.[109,113] Recently published studies, however, doubt the importance of high salt intake in the pathogenesis of hypertension.[114–117] In addition, it has to be considered that, for instance, in the United States, the prevalence of EH increased from almost absence in the early 1900s to rates of 30% and more[64] despite the absence of a significant increase in sodium uptake during that time.[65] A similar trend has been recognized in virtually all Western populations in recent decades.[118] The most likely reason for the dramatic increase in the incidence of hypertension has been attributed to the marked increase in obesity and associated IR. Obesity, an important risk factor for hypertension, has increased from about 5% of the US population in 1900 to more than 30% today.[66,67] Hypertension is now also common in the pediatric population, frequently associated with obesity and the MetS.[64,67]

In addition to the low salt intake, however, there is another similarity in the diet of these cultures: in contrast to current "Western-style" high-glycemic/high-insulinogenic diets (HGHIDs), these ethnic groups subsist on Paleolithic low-glycemic/low-insulinogenic diets (LGLIDs).[119–125]

The fundamental differences between these diets are associated with significant metabolic disturbances that may induce the development of hyperinsulinemia and IR, as the following sections will show.

Significant dietary changes during human history related to the development of hypertension and BPH

The metabolism of each species has adapted genetically to a particular type of diet over a very long period of evolution. This specific diet guaranties health and survival.[126] Humans are no exception in this regard. But what is the specific diet to which human metabolism has adapted?

During the Paleolithic Period, from approximately 2.5 million years ago until the Agricultural Revolution about 10 000 years ago, our ancestors subsisted on diets containing large amounts of protein and varying amounts of fat (depending on the latitude) and relatively small amounts of (digestible) carbohydrate. Their diet was based mainly on wild game, fish, and uncultivated plant food, such as roots, tubers, wild herbs, berries, nuts, vegetables, and fruits. Wild plants are high in fiber and are digested slowly, much of the carbohydrate is unavailable, and their carbohydrate content is therefore lower than their cultured equivalents.[127] Hence, carbohydrates, consumed during this long period were low-glycemic and low-insulinogenic in effect.[128] As the effect of protein and fat on insulin production is relatively small too,[129] postprandial

glucose and insulin levels were low during a very long time of human evolution.

The Agricultural Revolution about 10 000 years ago resulted in a significant increase in dietary carbohydrates, especially in the form of grains, yet all of the carbohydrate foodstuff consumed during this period was low-glycemic in effect.[128] Progress in food processing during the Industrial Revolution about 250 years ago, however, resulted in a significant increase in the glycemic and insulinemic index[130] of refined cereals, sugars, and (peeled) rice.[131] In addition, cow milk and other dairy products also produce high postprandial insulin levels (despite a low-glycemic index), not significantly different from the insulinemic index of the reference bread.[132,133] The current high-insulinemic "Western" nutrition, with large amounts of refined cereals, potatoes, corn, and extreme amounts of sugars (up to 69 kg/person/year),[117,134] is the culmination of this development.

As mentioned before, living organisms thrive best on the diet to which they are evolutionarily adapted. The human genome has formed during a period of several million years and has remained largely unchanged during the past 10 000 years.[126] Dietary changes brought about by the Agricultural and the Industrial Revolution occurred far too recently on an evolutionary time scale for the human genome to adjust.[131] A period of a few hundred or even a couple of thousand years is not nearly sufficient to ensure an adequate adaptation of the human metabolism.[126] Hence, human metabolism is still adapted to the low-glycemic and low-insulinemic diet of our Paleolithic ancestors.

Diseases of civilization, including coronary heart disease, obesity, hypertension, diabetes, and other more diseases, are rare or absent among HG societies,[121–125,135] and low serum insulin levels and a persistently excellent insulin sensitivity are characteristic of HG,[121–125,135] but only as long as these people adhere to their traditional "Paleolithic" LGLID. The transition to a "Western-style" HGHID, whether by migration or acculturation, invariably leads to a dramatic increase in IR and hyperinsulinemia,[136,137] obesity and the MetS,[119,121,136,138] and cancer.[104] On the contrary, a return to a traditional, low-insulinemic diet is associated with marked improvement in IR and fasting insulin levels.[121,139,140]

The notion that Stone Agers usually do not live long enough to develop degenerative diseases is not accurate. *Average* life expectancy in HG societies is lower than in most acculturated societies today, which largely is attributed to higher rates of infant and child mortality and a lack of medical assistance. But once these people reach adulthood, their life expectancy is comparable to that of affluent nations. A conspectus of data on HG societies suggests that *modal age* of adult death is about 7 decades (adaptive life span of 68-78 years). In contrast to most westerners, these people tend to be healthy up to old age. Causes of death are predominantly infectious diseases, whereas chronic degenerative disorders are rare.[141]

With the transition from LGLIDs to HGHIDs, insulin has gained a dominant position in human metabolism, resulting in a disruption of a finely tuned metabolic balance that has evolved over millions of years of evolution. As a result, hyperinsulinemia and IR may develop, accompanied by an abnormal activation of several metabolic systems, like the SNS and the RAAS[104,142] alterations that are deeply involved in the development of several diseases, including hypertension and BPH, as shown above.

Development of hyperinsulinemia and IR: diet matters!

Traditionally, obesity is considered to be the cause of IR and (compensatory) hyperinsulinemia, based on the idea that increased adipose tissue mass causes increased release of free fatty acids into the portal system, which in turn promotes IR in target tissues, but this assumption is not convincing for several reasons (for details, see Karpe et al[143]). In addition, not all obese individuals are insulin resistant, while IR has been shown to exist in a significant proportion of the normal weight population.[144] Furthermore, several studies in humans and animals have shown that hyperinsulinemia and IR precede the development of obesity.[133,145–148] Meanwhile, substantial evidence has accumulated indicating that hyperinsulinemia represents the driving force in the development of IR.[133,147–153] As shown by a series of experimental studies in animals[148,150,151] and humans,[133,152–155] persistent elevated insulin levels, regardless of their origin, are critical for the development of IR.[156] Hyperinsulinemia was shown to impair insulin-stimulated glucose uptake and its cellular signaling in a dose-dependent manner.[157,158] Activation of the SNS may play an important role in this process: as noted before, insulin increases plasma NE levels in a dose-dependent fashion.[46] In turn, increased sympathetic vasoconstriction has been shown to decrease glucose uptake in skeletal muscle, thereby promoting IR and compensatory hyperinsulinemia, indicating that the SNS interaction with insulin sensitivity is a 2-way street.[79,159,160] Also, a decrease in cellular insulin receptor numbers,[158] an (insulin-induced) increased gene expression of proinflammatory cytokines in adipocytes,[161] metabolic inflexibility and ectopic lipid accumulation,[162] upregulation of the RAAS,[163] and increased reactive oxygen species production[162–164] have also been implicated in the development of IR.

High-glycemic/high-insulinogenic diets may play a key role in the development of hyperinsulinemia.[104,145,165] These diets elicit a high postprandial insulin response. Along with a "Western dietary pattern" of frequent snacking and frequent consumption of sucrose-containing soft drinks, insulin levels are elevated most of the day.[166] The high insulin requirement associated with HGHIDs severely strains pancreatic β-cells. β-cells, genetically not adapted to this high insulin demand, may react with hypertrophy, functional dysregulation, and finally overresponsiveness and hyperinsulinemia.[104,167] Depending on the individual

texture of the β-cells, hyperinsulinemia and IR may develop rapidly or increase gradually with increasing age.

Sucrose and fructose appear to play a particularly important role in the pathogenic process.[117] Most recent estimates suggest that the intake of sugars, for instance by the US population, ranges between 35 and 69 kg/person/year.[117,134] Not only sugar in beverages and sweets but also sugar added in most ready meals (often in the form of fructose) contributes to these enormous amounts.[117] Based on evidence from epidemiological studies and experimental trials in animals and humans, DiNicolantonio and Lucan[117] suggested that "sugars, particularly fructose, may increase BP and BP variability, increase heart rate and myocardial oxygen demand, and contribute to inflammation, IR and broader metabolic dysfunction."

Feeding studies in rats[145,165] using high-fat, refined-sugar (HFS) diets, similar to the typical US diet, clearly showed that these diets cause IR prior to weight gain and that sucrose, not fat, is the determining factor for development of IR. Insulin resistance developed, regardless of whether dietary fat was high (39.5%) or low (9%).[165] In addition, HFS diets cause hypertension, associated with significant endothelial dysfunction.[168] Otherwise, a high-fat diet/low-carbohydrate reduced BP in SHR without producing signs of IR or altering insulin-mediated signaling in the heart, skeletal muscle, or vasculature.[169] Consistent with this, it has been shown that high-fat/low-carbohydrate diets, such as ketogenic diets, lower BP in humans.[170] Also, evidence of epidemiological studies and experimental trials in animals and humans shows that high glycemic index food,[171] sucrose,[172] and fructose[173] may increase BP (reviewed in DiNicolantonio and Lucan[117]).

Hyperinsulinemia not only precedes the development of obesity but also seems to be its cause: postprandial hyperinsulinemia has been shown to be the very first metabolic abnormality in developing obesity, while fasting insulin levels and insulin sensitivity are still normal.[133,146–148] It is well known that insulin promotes the transport of nutrients (glucose, fatty acids, and amino acids) across the cell membrane for oxidation or storage. Furthermore, hyperinsulinemia downregulates skeletal muscle lipoprotein lipase and upregulates lipoprotein lipase of adipose tissue, reducing the ability of the muscle to absorb fat and force it into fat cells.[174] Hence, hyperinsulinemia, together with overnutrition as described above, causes excessive storage of nutrients and weight gain—as long as insulin sensitivity is preserved. This is supported by a study of Pima Indians that showed that the most insulin-sensitive individuals had a greater tendency toward weight gain than the most insulin-resistant ones.[175] Similarly, high rates of weight gain occurred in individuals who presented with a high acute insulin response to glucose, and this effect was particularly manifested in insulin-sensitive individuals.[176] Insulin resistance (with compensatory hyperinsulinemia) develops later during the course of chronic obesity[146,176] and limits further weight gain.[146,177] Rapid development of IR prior to significant weight gain may

thus account for the well-known existence of IR in lean individuals.[144]

High-glycemic/high-insulinogenic diets also influence SNS activity: among dietary substrates, carbohydrate (starch and sugars) ingestion significantly increases SNS activity, whereas protein or fat ingestion has no significant sympathoexcitatory effect.[178–180] Insulin has been shown to be the link between carbohydrate intake and SNS activity.[46] Hence, diet composition plays a major role in determining the level of SNS activity. High-glycemic/high-insulinogenic diets elicit a high insulin response, with significant activation of the SNS, whereas LGLIDs are not associated with a significant sympathoexcitatory effect.[179–181]

High-fat diets have been implicated in the development of BPH (although the number of related reports is rather limited), possibly involving oxidative stress and inflammation.[182–187] In a large prospective study, Arnold et al[182] examined dietary risk factors for the occurrence of BPH in 4770 Prostate Cancer Prevention Trial placebo-arm participants. The authors found evidence that high consumption of red meat and a high-fat diet increased the risk of BPH.

Obviously, the focus of these studies is on the fat content of diets. However, the typical US "Western-style" diet not only contains relatively high amounts of fat but also substantial amounts of refined carbohydrates, especially in the form of sucrose and fructose, which also applies to diets of animal studies.[134,185–187] As mentioned earlier, HFS diets cause IR and hyperinsulinemia in animal models[145,165,188] and were shown to cause enlargement, increased proliferation, and cellular hyperplasia of the prostate gland.[40]

Although it is quite possible that dietary fat may be involved in the development of BPH, it should also be considered that the high sucrose content of such diets could also play an important role by producing a hyperinsulinemic condition.

The authors of the aforementioned Prostate Cancer Prevention Trial[182] conclude that "a dietary pattern high in vegetables and protein, moderate in alcohol, and low in fat and red meat may protect men from developing symptomatic BPH." This dietary pattern largely corresponds to a Paleolithic diet, described above.

Age, BPH, and hypertension

Aging as a risk factor of BPH and hypertension is associated with metabolic changes related to the development of BPH and hypertension, such as IR and hyperinsulinemia, including the activation of the IGF system[189] and an increased SNS activity.[190] All of these metabolic changes can be attributed to HGHIDs as described above.

Summary and Conclusions

Although hypertension and BPH are considered to be multifactorial diseases, involving environment, lifestyle, and genetic

components, HGIDs may play a crucial role in the pathogenesis of both diseases. It is suggested that development of BPH and hypertension is not an inevitable consequence of aging, but rather a consequence of diet: due to the dramatic shift from LGLIDs to HGHIDs only 250 years ago, insulin has gained a dominant position in human metabolism, resulting in disruption of a finely tuned metabolic balance that has evolved over millions of years of evolution, with development of hyperinsulinemia and IR as well as an abnormally increased activation of the SNS and the RAAS—metabolic alterations that play a pivotal role in the pathomechanism of both disorders. A restriction of high-insulinemic food may help to limit the development of these diseases.

Author Contributions

WK conceived the concept, analyzed the data, wrote the first draft of the manuscript, developed the structure and arguments for the paper, made critical revisions and reviewed and approved of the final manuscript.

REFERENCES

1. Lee CL, Kuo HC. Pathophysiology of benign prostate enlargement and lower urinary tract symptoms: current concepts. *Ci Ji Yi Xue Za Zhi*. 2017;29:79–83. doi:10.4103/tcmj.tcmj_20_17.
2. Roehrborn CG. Benign prostatic hyperplasia: etiology, pathophysiology, epidemiology, and natural history. In: McDougal WS, Wein AJ, Kavoussi LR, Partin AW, Peters CA, eds. *Campbell-Walsh Urology (11th Edition Review)*. 2nd ed. Philadelphia, PA: Elsevier; 2016:411–415.
3. Boyle P, Napalkov P. The epidemiology of benign prostatic hyperplasia and observations on concomitant hypertension. *Scand J Urol Nephrol Suppl*. 1995;168:7–12.
4. Michel MC, Heemann U, Schumacher H, Mehlburger L, Goepel M. Association of hypertension with symptoms of benign prostatic hyperplasia. *J Urol*. 2004;172:1390–1393.
5. Kopp W. Pathogenesis and etiology of essential hypertension: role of dietary carbohydrate. *Med Hypotheses*. 2005;64:782–787.
6. McNeal JG. The prostate gland: morphology and pathobiology. *Monogr Urol*. 1983;4:3–33.
7. Patel ND, Parsons JK. Epidemiology and etiology of benign prostatic hyperplasia and bladder outlet obstruction. *Indian J Urol*. 2014;30:170–176. doi:10.4103/0970-1591.126900.
8. Wu JP, Gu FL. The prostate 41–65 years post castration: an analysis of 26 eunuchs. *Chin Med J (Engl)*. 1987;100:271–272.
9. Zeng QS, Xu CL, Liu ZY, et al. Relationship between serum sex hormones levels and degree of benign prostate hyperplasia in Chinese aging men. *Asian J Androl*. 2012;14:773–777. doi:10.1038/aja.2012.32.
10. Liu CC, Huang SP, Li WM, et al. Relationship between serum testosterone and measures of benign prostatic hyperplasia in aging men. *Urology*. 2007;70:677–680.
11. Walsh PC, Hutchins GM, Ewing LL. Tissue content of dihydrotestosterone in human prostatic hyperplasis is not supranormal. *J Clin Invest*. 1983;72:1772–1777. doi:10.1172/JCI111137.
12. Li J, Tian Y, Guo S, Gu H, Yuan Q, Xie X. Testosterone-induced benign prostatic hyperplasia rat and dog as facile models to assess drugs targeting lower urinary tract symptoms. *PLoS ONE*. 2018;13:e0191469. doi:10.1371/journal.pone.0191469.
13. Idan A, Griffiths KA, Harwood DT, et al. Long-term effects of dihydrotestosterone treatment on prostate growth in healthy, middle-aged men without prostate disease: a randomized, placebo-controlled trial. *Ann Intern Med*. 2010;153:621–632. doi:10.7326/0003-4819-153-10-201011160-00004.
14. Morales A. Androgen replacement therapy and prostate safety. *Eur Urol*. 2002;41:113–120.
15. Ngai HY, Yuen KS, Ng CM, Cheng CH, Chu SP. Metabolic syndrome and benign prostatic hyperplasia: an update. *J Urol*. 2017;4:164–173. doi:10.1016/j.ajur.2017.05.001.
16. DiBello JR, Ioannou C, Rees J, et al. Prevalence of metabolic syndrome and its components among men with and without clinical benign prostatic hyperplasia:

a large, cross-sectional, UK epidemiological study. *BJU Int*. 2016;117:801–808. doi:10.1111/bju.13334.
17. Gacci M, Corona G, Vignozzi L, et al. Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. *BJU Int*. 2015;115:24–31. doi:10.1111/bju.12728.
18. De Nunzio C, Aronson W, Freedland SJ, Giovannucci E, Parsons JK. The correlation between metabolic syndrome and prostatic diseases. *Eur Urol*. 2012;61:560–570. doi:10.1016/j.eururo.2011.11.013.
19. Vikram A, Jena G, Ramarao P. Insulin-resistance and benign prostatic hyperplasia: the connection. *Eur J Pharmacol*. 2010;641:75–81. doi:10.1016/j.ejphar.
20. Dahle SE, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. *J Urol*. 2002;168:599–604. https://doi.org/10.1016/S0022-5347(05)64687-3.
21. Hammarsten J, Hogstedt B. Hyperinsulinemia as a risk factor for developing benign prostatic hyperplasia. *Eur Urol*. 2001;39:151–158. doi:10.1159/000052430.
22. Nandeesha H, Koner BC, Dorairajan LN, Sen SK. Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia. *Clin Chim Acta*. 2006;370:89–93. doi:10.1016/j.cca.2006.01.019.
23. Kanagawa K, Sugimura K, Kuratsukuri K, Ikemoto S, Kishimoto T, Nakatani T. Norepinephrine activates P44 and P42 MAPK in human prostatic stromal and smooth muscle cells but not in epithelial cells. *Prostate*. 2003;56:313–318.
24. Dinh DT, Frauman AG, Somers GR, et al. Evidence for activation of the Renin-angiotensin system in the human prostate: increased angiotensin II and reduced AT(1) receptor expression in benign prostatic hyperplasia. *J Pathol*. 2002;196:213–219.
25. Hennenberg M, Schreiber A, Ciotkowska A, et al. Cooperative effects of EGF, FGF, and TGF-ß1 in prostate stromal cells are different from responses to single growth factors. *Life Sci*. 2015;123:18–24.
26. Landsberg L. Insulin resistance and the metabolic syndrome. *Diabetologia*. 2005;48:1244–1246. doi:10.1007/s00125-005-1818-z.
27. Gorbachinsky I, Akpinar HMD Assimos DG. Metabolic syndrome and urologic diseases. *J Urol*. 2010;12:e157–e180.
28. Abdollah F, Briganti A, Suardi N, et al. Metabolic syndrome and benign prostatic hyperplasia: evidence of a potential relationship, hypothesized etiology, and prevention. *J Urol*. 2011;52:507–516. doi:10.4111/kju.2011.52.8.507.
29. Gacci M, Corona G, Sebastianelli A, et al. Male lower urinary tract symptoms and cardiovascular events: a systematic review and meta-analysis. *J Urol*. 2016;70:788–796. doi:10.1016/j.eururo.2016.07.007.
30. Kwon H, Kang HC, Lee JH. Relationship between predictors of the risk of clinical progression of benign prostatic hyperplasia and metabolic syndrome in men with moderate to severe lower urinary tract symptoms. *Urology*. 2013;81:1325–1329. doi:10.1016/j.urology.2013.01.042.
31. Sarma AV, Kellogg Parsons J. Diabetes and benign prostatic hyperplasia: emerging clinical connections. *Curr Urol Rep*. 2009;10:267–275.
32. Breyer BN, Sarma AV. Hyperglycemia and insulin resistance and the risk of BPH/LUTS: an update of recent literature. *Curr Urol Rep*. 2014;15:462. doi:10.1007/s11934-014-0462-x.
33. Hammarsten J, Högstedt B. Clinical, anthropometric, metabolic and insulin profile of men with fast annual growth rates of benign prostatic hyperplasia. *Blood Press*. 1999;8:29–36.
34. Joseph MA, Harlow SD, Wei JT, et al. Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. *Am J Epidemiol*. 2003;157:906–914.
35. Tran HV, Nguyen TN. P-175: relation between the hypertension and benign prostatic hyperplasia in the elderly. *Am J Hypertens*. 2003;16:102A. doi:10.1016/S0895-7061(03)00340-6.
36. Golomb E, Rosenzweig N, Eilam R, Abramovici A. Spontaneous hyperplasia of the ventral lobe of the prostate in aging genetically hypertensive rats. *J Androl*. 2000;21:58–64.
37. Rosenzweig N, Matityahou A, Golomb E. Rapid proliferation of prostatic epithelial cells in spontaneously hypertensive rats: a model of spontaneous hypertension and prostate hyperplasia. *J Androl*. 2003;24:263–269.
38. Yamashita M, Zhang X, Shiraishi T, Uetsuki H, Kakehi Y. Determination of percent area density of epithelial and stromal components in development of prostatic hyperplasia in spontaneously hypertensive rats. *Urology*. 2003;61:484–489.
39. Reaven GM, Chang H. Relationship between blood pressure, plasma insulin and triglyceride concentration, and insulin action in spontaneous hypertensive and Wistar-Kyoto rats. *Am J Hypertens*. 1991;4:34–38.
40. Vikram A, Jena GB, Ramarao P. Increased cell proliferation and contractility of prostate in insulin resistant rats: linking hyperinsulinemia with benign prostate hyperplasia. *Prostate*. 2010;70:79–89. doi:10.1002/pros.21041.
41. Werner H, Weinstein D, Bentov I. Similarities and differences between insulin and IGF-I: structures, receptors, and signaling pathways. *Biochem*. 2008;114:17–22. doi:10.1080/13813450801900694.

42. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst*. 2002;94:972–980. doi:10.1016/j.diff.2011.04.004.

43. Chokkalingam AP, Gao YT, Deng J, et al. Insulin-like growth factors and risk of benign prostatic hyperplasia. *Prostate*. 2002;52:98–105. doi:10.1002/pros.10096.

44. Stattin P, Kaaks R, Riboli E, Ferrari P, Dechaud H, Hallmans G. Circulating insulin-like growth factor-I and benign prostatic hyperplasia: a prospective study. *Scand J Urol Nephrol*. 2001;35:122–126.

45. Neuhouser ML, Schenk J, Song YJ, et al. Insulin-like growth factor-I, insulin-like growth factor binding protein-3 and risk of benign prostate hyperplasia in the prostate cancer prevention trial. *Prostate*. 2008;68:1477–1486. doi:10.1002/pros.20819.

46. Rowe JW, Young JB, Minaker KL, et al. Effect of insulin and glucose infusions on sympathetic nervous activity in normal man. *Diabetes*. 1981;30:219–225.

47. Kamide K, Hori MT, Zhu JH, et al. Insulin and insulin-like growth factor-I promotes angiotensinogen production and growth in vascular smooth muscle cells. *J Hypertens*. 2000;18:1051–1056.

48. Marshall I, Burt RP, Chapple CR. Noradrenaline contractions of human prostate mediated by alpha 1A-(alpha 1c-) adrenoceptor subtype. *Br J Pharmacol*. 1995;115:781–786.

49. Fabiani ME, Sourial M, Thomas WG, et al. Angiotensin enhances noradrenaline release from sympathetic nerves of the rat prostate via a novel angiotensin receptor: implications for the pathophysiology of benign prostatic hyperplasia. *J Endocrinol*. 2001;171:97–108.

50. McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the prostate gland is facilitated by the autonomic system. *Biol Reprod*. 1994;51:99–107.

51. Grassi G. Renin-angiotensin-sympathetic crosstalks in hypertension: reappraising the relevance of peripheral interactions. *J Hypertens*. 2001;19:1713–1716. doi:10.1097/00004872-200110000-00003.

52. Saxena PR. Interaction between the renin–angiotensin–aldosterone and sympathetic nervous systems. *J Cardiovasc Pharmacol*. 1992;19:S80–S88.

53. Leung PS, Sernia C. The renin–angiotensin system and male reproduction: new functions for old hormones. *J Mol Endocrinol*. 2003;30:263–270.

54. Lazartigues E, Feng Y, Lavoie JL. The two fACEs of the tissue renin-angiotensin system: implication in cardiovascular diseases. *Curr Pharm Des*. 2007;13:1231–1245.

55. Dinh DT, Frauman AG, Sourial M, Casley DJ, Johnston CI, Fabiani ME. Identification, distribution and expression of angiotensin II receptors in the normal human prostate and benign prostate hyperplasia. *Endocrinology*. 2001;142:1349–1356.

56. Nassis L, Frauman AG, Ohishi M, et al. Localization of angiotensin-converting enzyme in human prostate: pathological expression in benign prostatic hyperplasia. *J Pathol*. 2001;195:571–579.

57. Dzau VJ. Theodore Cooper Lecture: tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension*. 2001;37:1047–1052.

58. Wennemuth G, Aumuller G. Angiotensin II-mediated calcium signals and mitogenesis in human prostate stromal cell line hPCPs. *Br J Pharmacol*. 2005;144:3–10.

59. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. *Ind J Endocrinol Metab*. 2011;15:S281–S288. doi:10.4103/2230-8210.86860.

60. Bolivar JJ. Essential hypertension: an approach to its etiology and neurogenic pathophysiology. *Hypertens*. 2013;2013:547809. doi:10.1155/2013/547809.

61. Paul M, Mehr AP, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev*. 2006;86:747–803. doi:10.1152/physrev.00036.2005.

62. Hall JE, Granger JP, do Carmo JM, et al. Hypertension: physiology and pathophysiology. *Physiol*. 2012;2:2393–2442. doi:10.1002/cphy.c110058.

63. Takahashi H, Yoshika M, Komiyama Y, Nishimura M. The central mechanism underlying hypertension: a review of the roles of sodium ions, epithelial sodium channels, the renin-angiotensin-aldosterone system, oxidative stress and endogenous digitalis in the brain. *Hypertens Res*. 2011;34:1147–1160. doi:10.1038/hr.2011.105.

64. Province MA, Kardia SL, Ranade K, et al. A meta-analysis of genome-wide linkage scans for hypertension: the national heart, lung and blood institute family blood pressure program. *Am J Hypertens*. 2003;16:144–147.

65. Bernstein AM, Willett WC. Trends in 24-h urinary sodium excretion in the United States, 1957–2003: a systematic review. *Am J Clin Nutr*. 2010;92:1172–1180. doi:10.3945/ajcn.2010.29367.

66. Helmchen LA, Henderson RM. Changes in the distribution of body mass index of white US men, 1890–2000. *Ann Hum Biol*. 2004;31:174–118.

67. Johnson RJ, Feig DI, Nakagawa T, et al. Pathogenesis of essential hypertension: historical paradigms and modern insights. *J Hypertens*. 2008;26:381–391. doi:10.1097/HJH.0b013e3282f29876.

68. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation*. 2000;101:329–335. doi: 10.1161/01.CIR.101.3.329.

69. Yanai H, Tomono Y, Ito K, et al. The underlying mechanisms for development of hypertension in the metabolic syndrome. *Nutr J*. 2008;7:10. doi:10.1186/1475-2891-7-10.

70. Horita S, Seki G, Yamada H, Suzuki M, Koike K, Fujita T. Insulin resistance, obesity, hypertension, and renal sodium transport. *Int J Hypertens*. 2011;2011:391762. doi:10.4061/2011/391762.

71. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996;334:374–381.

72. Bonora E, Zavaroni I, Alpi O, et al. Relationship between blood pressure and plasma in insulin in non-obese and obese nondiabetic subjects. *Diabetologia*. 1987;30:719–723.

73. Penesova A, Cizmarova E, Belan V, et al. Insulin resistance in young, lean male subjects with essential hypertension. *J Human Hypertens*. 2011;25:391–400. doi:10.1038/jhh.2010.72.

74. Marigliano A, Tedde R, Sechi LA, Pala A, Pisanu G, Pacifico A. Insulinemia and blood pressure: relationships in patients with primary and secondary hypertension, and with or without glucose metabolism impairment. *Am J Hypertens*. 1990;3:521–526.

75. Jung JY, Choi WJ, Park SK, et al. Elevated fasting serum insulin level predicts future development of hypertension. *Int J Cardiol*. 2014;172:450–455. doi:10.1016/j.ijcard.2014.01.087.

76. Raitakari OT, Porkka KVK, Rönnemaa T, et al. The role of insulin in clustering of serum lipids and blood pressure in children and adolescents. *Diabetologia*. 1995;38:1042–1050.

77. Gallagher EH, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol Metab*. 2010;21:610–618. doi:10.1016/j.tem.2010.06.007.

78. Muntzel MS, Anderson EA, Johnson AK, Mark AL. Mechanisms of insulin action on sympathetic nerve activity. *Clin Exp Hypertens*. 1995;17:39–50.

79. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. *Circ Res*. 2015;116:976–990. doi:10.1161/CIRCRESAHA.116.303604.

80. Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJM, Gans ROB. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci*. 1997;92:51–58.

81. Sarafidis PA, Bakris GL. Insulin and endothelin: an interplay contributing to hypertension development? *J Clin Endocrinol Metab*. 2007;92:379–385. doi:10.1210/jc.2006-1819.

82. Boden G, Chen X, Kolaczynski JW, Polansky M. Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. *Invest*. 1997;100:1107–1113.

83. Arcaro G, Cretti A, Balzano S, et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. *Circulation*. 2002;105:576–582.

84. Ferrari P, Weidmann P, Shaw S, et al. Altered insulin sensitivity, hyperinsulinemia, and dyslipidemia in individuals with a hypertensive parent. *Am J Med*. 1991;91:589–596.

85. Grunfeld B, Balzareti M, Romo M, Gimenez M, Gutman R. Hyperinsulinemia in normotensive offspring of hypertensive parents. *Hypertension*. 1994;23:I12–I15.

86. Vlasáková Z, Pelikánová T, Karasová L, Skibová J. Insulin secretion, sensitivity, and metabolic profile of young healthy offspring of hypertensive parents. *Metabolism*. 2004;53:469–475.

87. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res*. 2014;114:1804–1814. doi:10.1161/CIRCRESAHA.114.30252.

88. Joyner MJ, Charkoudian N, Wallin BG. Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. *Hypertension*. 2010;56:10–16. doi:10.1161/HYPERTENSIONAHA.109.140186.

89. Anderson E, Hoffman P, Balon T, Sinkey C, Mark A. Hyperinsulinemia produces both sympathetic neural activation and vasodilatation in normal humans. *J Clin Invest*. 1991;87:2246–2252.

90. Lembo G, Napoli R, Capaldo B, et al. Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with hypertension. *J Clin Invest*. 1992;90:24–29.

91. Bianchetti MG, Weidmann P, Beretta-Piccoli C, et al. Disturbed noradrenergic blood pressure control in normotensive members of hypertensive families. *Br Heart J*. 1984;51:306–311.

92. Johnston CI. Franz Volhard Lecture. Renin Angiotensin system: a dual tissue and hormonal system for cardiovascular control. *J Hypertens Suppl*. 1992;10:S13–S26.

93. Watanabe T, Pakala R, Katagiri T, Benedict CR. Angiotensin II and serotonin potentiate endothelin-1-induced vascular smooth muscle cell proliferation. *J Hypertens*. 2001;19:731–739.

94. Edgeley AJ, Kett MM, Anderson WP. Evidence for renal vascular remodeling in angiotensin II-induced hypertension. *J Hypertens*. 2003;21:1401–1406.

95. Rizzoni D, Rosei EA. Small artery remodeling in hypertension and diabetes. *Curr Hypertens Rep*. 2006;8:90–95.

96. Giebisch G, Windhager E. Integration of salt and water balance. In: Boron WF, Boulpaep EL, eds. *Medical Physiology*. Philadelphia, PA; London, England; New York, NY; St. Louis, MI; Sydney, NSW, Australia; Toronto, ON, Canada: WB Saunders; 2003:861–877.

97. Ashley E, Cain AE, Khalil RA. Pathophysiology of essential hypertension: role of the pump, the vessel, and the kidney. *Semin Nephrol*. 2002;22:3–16.

98. Coffman TM, Crowley SD. Kidney in hypertension: guyton redux. *Hypertension*. 2008;51:811–816. doi:10.1161/HYPERTENSIONAHA.105.063636.

99. Bianchi G, Fox U, DiFrancesco GF, Giovanni AM, Pagetti D. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive and normotensive rats. *Clin Sci Mol Med*. 1974;47:435–438.

100. Curtis JJ, Luke RG, Dustan HP, et al. Remission of hypertension after renal transplantation. *N Engl J Med*. 1983;309:1009–1015.

101. Silva BR, Pernomian L, Bendhack LM. Contribution of oxidative stress to endothelial dysfunction in hypertension. *Front Physiol*. 2012;3:441. doi:10.3389/fphys.2012.00441.

102. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006;113:1888–1904.

103. Gomolak JR, Didion SP. Angiotensin II-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation. *Front Physiol*. 2014;5:396. doi:10.3389/fphys.2014.00396.

104. Kopp W. Significant dietary changes during human evolution and the development of cancer: from cells in trouble to cells causing trouble. *J Carcinog Mutagen*. 2017;8:303. doi:10.4172/2157-2518.1000303.

105. Pinto E. Blood pressure and ageing. *Postgrad Med J*. 2007;83:109–114. doi:10.1136/pgmj.2006.048371.

106. Oesterling JE. Benign prostatic hyperplasia: medical and minimally invasive treatment options. *N Engl J Med*. 1995;332:99–109. doi:10.1056/NEJM199501123320207.

107. Trumble BC, Stieglitz J, Rodriguez DE, et al. Challenging the inevitability of prostate enlargement: low levels of benign prostatic hyperplasia among Tsimane Forager-Horticulturalists. *J Gerontol A Biol Sci Med Sci*. 2015;70:1262–1268. doi:10.1093/gerona/glv051.

108. Trowell HC. From normotension to hypertension in Kenyans and Ugandans 1928–1978. *East Afr Med J*. 1980;57:167–173.

109. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med*. 1988;84:739–749.

110. Ekoé JM, Foggin PM, Thouez JP, et al. Obesity, hypertension, hyperuricemia and diabetes mellitus among the Cree and Inuit of northern Québec. *Arctic Med Res*. 1990;49:180–188.

111. Gurven M, Blackwell AD, Rodríguez DE, Stieglitz J, Kaplan H. Does blood pressure inevitably rise with age? longitudinal evidence among forager-horticulturalists. *Hypertension*. 2012;60:25–33.

112. Damon A, Page LB, Moellering RC Jr. Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation*. 1974;49:1132–1146.

113. Blackburn H, Prineas R. Diet and hypertension: anthropology, epidemiology, and public health implications. *Prog Biochem Pharmacol*. 1983;19:31–79.

114. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). *J Hypertens*. 2011;24:843–853. doi:10.1038/ajh.2011.115.

115. Georgiopoulou VV, Murphy RA, Kalogeropoulos AP, et al. Dietary sodium content, mortality, and risk for cardiovascular events in older adults: the health, aging, and body composition (Health ABC) study. *JAMA Intern Med*. 2015;175:410–419. doi:10.1001/jamainternmed.2014.6278.

116. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Investigators Fatal and nonfatal outcomes, incidence of hypertension and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305:1777–1785. doi:10.1001/jama.2011.574.

117. DiNicolantonio JJ, Lucan SC. The wrong white crystals: not salt but sugar as aetiological in hypertension and cardiometabolic disease. *Open Heart*. 2014;1:e000167. doi:10.1136/openhrt-2014-000167.

118. Sorrentino MJ. Implications of the metabolic syndrome: the new epidemic. *Am J Cardiol*. 2005;96:3E-7E.

119. Thorburn AW, Brand JC, O'Dea K, et al. Plasma glucose and insulin responses to starchy foods in Australian aborigines: a population now at high risk of diabetes. *Am J Clin Nutr*. 1987;46:282–285.

120. Thorburn AW, Brand JC, Truswell AS. Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes? *Am J Clin Nutr*. 1987;45:98–106.

121. O'Dea K, White NG, Sinclair AJ. An investigation of nutrition-related risk factors in an isolated aboriginal community in northern Australia: advantages of a traditionally-orientated life-style. *Med J Aust*. 1988;148:177–180.

122. Brand JC, Snow BJ, Nabhan GP, Truswell AS. Plasma glucose and insulin responses to traditional pima Indian meals. *Am J Clin Nutr*. 1990;51:416–420.

123. Carrera-Bastos P, Fontes-Villalba M, O'Keefe JH. The western diet and lifestyle and diseases of civilization. *Res Rep Clin Cardiol*. 2011;2:15–35.

124. Lindeberg S, Eliasson M, Lindahl B, Ahrén B. Low serum insulin in traditional Pacific Islanders—the Kitava study. *Metabolism*. 1999;4:1216–1219.

125. Lindgärde F, Widén I, Gebb M, Ahrén B. Traditional versus agricultural lifestyle among Shuar women of the Ecuadorian Amazon: effects on leptin levels. *Metabolism*. 2004;53:1355–1358.

126. Rendel JM. The time scale of genetic changes. In: Boyden SV, ed. *The Impact of Civilisation on the Biology of Man*. Canberra, ACT, Australia: Australian National University Press; 1970:27–47.

127. Eaton SB, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. *N Engl J Med*. 1985;312:283–289.

128. Björk I, Liljeberg H, Östan E. Low-glycemic index foods. *Br J Nutr*. 2000;83:S149–S155.

129. Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH. The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. *Am J Clin Nutr*. 1986;44:847–855.

130. Ray KS, Singhania PR. Glycemic and insulinemic responses to carbohydrate rich whole foods. *J Food Sci Technol*. 2014;51:347–352.

131. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81:341–354.

132. Ostman EM, Elmståhl HGL, Björck IM. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr*. 2001;74:96–100.

133. Hoppe C, Mølgaard C, Vaag A, et al. High intakes of milk, but not meat, increases insulin and insulin resistance in 8-year-old boys. *Eur J Clin Nutr*. 2005;59:393–398.

134. Strom S. U.S. cuts estimate of sugar intake. *The New York Times*. October 26, 2012. https://www.nytimes.com/2012/10/27/business/us-cuts-estimate-of-sugar-intake-of-typical-american.html

135. Sinnett PF, Whyte HM. Epidemiological studies in a total highland population, Tukisenta, New Guinea: cardiovascular disease and relevant clinical, electrocardiographic, radiological and biochemical findings. *J Chronic Dis*. 1973;26:265–290.

136. Wise PH, Edwards FM, Thomas DW, et al. Diabetes and associated variables in the south Australian aborigines. *Aust N Z J Med*. 1976;6:191–196.

137. King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care*. 1993;16:157–177.

138. Rowley KG, Best JD, McDermott R, et al. Insulin resistance syndrome in Australian aboriginal people. *Clin Exp Pharmacol Physiol*. 1997;24:776–781.

139. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian aborigines after temporary reversion to traditional lifestyle. *Diabetes*. 1984;33:596–603.

140. Rave K, Roggen K, Dellweg S, et al. Improvement of insulin resistance after diet with a whole-grain based dietary product: results of a randomized, controlled cross-over study in obese subjects with elevated fasting blood glucose. *Br J Nutr*. 2007;98:929–936.

141. Gurven M, Kaplan H. Longevity among hunter-gatherers: a cross-cultural examination. *Popul Dev Rev*. 2007;33:321–365.

142. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham offspring cohort. *Diabetes Care*. 2004;27:538–546.

143. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes*. 2011;60:2441–2449.

144. Reaven G. All obese individuals are not created equal: insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. *Diab Vasc Dis Res*. 2005;2:105–112.

145. Barnard RJ, Roberts CK, Varon SM, Berger JJ. Diet-induced insulin resistance precedes other aspects of the metabolic syndrome. *J Appl Physiol (1985)*. 1998;84:1311–1315.

146. Cusin I, Rohner-Jeanrenaud F, Terrettaz J, Jeanrenaud B. Hyperinsulinemia and its impact on obesity and insulin resistance. *Int J Obes*. 1992;16:S1–S11.

147. Le Stunff C, Bougneres P. Early changes in postprandial insulin secretion, not in insulin sensitivity, characterize juvenile obesity. *Diabetes*. 1994;43:696–702.

148. Pécinaud J, Kinebanyan MF, Ferré P, et al. Development of VMH obesity: in vivo insulin secretion and tissue insulin sensitivity. *Am J Physiol*. 1989;257:E255–E260.

149. Corkey BE. Banting lecture: hyperinsulinemia: cause or consequence? Diabetes. 2012;61:4–13.

150. Juan CC, Fang VS, Kwok CF, et al. Exogenous hyperinsulinemia causes insulin resistance, hyperendothelinemia, and subsequent hypertension in rats. *Metab Clin Exp*. 1999;48:465–471.

151. Ng Y, Ramm G, James DE. Dissecting the mechanism of insulin resistance using a novel heterodimerization strategy to activate Akt. *J Biol Chem*. 2010;285:232–239.

152. Rizza RA, Mandarino LJ, Genest J, et al. Production of insulin resistance by hyperinsulinemia in man. *Diabetologia*. 1985;28:70–75.

153. Del Prato S, Leonetti F, Simonson DC, et al. Effect of sustained physiologic hyperinsulinemia and hyperglycemia on insulin secretion and insulin sensitivity in man. *Diabetologia*. 1994;37:1025–1035.

154. Clark MG, Rattigan S, Clark DG. Obesity with insulin resistance: experimental insights. *Lancet*. 1983;26:1236–1240.

155. Ge X, Yu Q, Qi W, et al. Chronic insulin treatment causes insulin resistance in 3T3-L1 adipocytes through oxidative stress. *Free Radic Res*. 2008;42:582–591.

156. Shanik MH, Xu Y, Škrha J, et al. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? *Diabetes Care*. 2008;31:S262–S268.

157. Posa JK, Selvaraj S, Sangeetha KN, et al. p53 mediates impaired insulin signaling in 3T3-L1 adipocytes during hyperinsulinemia. *Cell Biol Int*. 2014;38:818–824.

158. Olefsky JM, Kolterman OG. Mechanisms of insulin resistance in obesity and noninsulin-dependent (type II) diabetes. *Am J Med*. 1981;7:151–168.

159. Gamboa A, Okamoto LE, Arnold AC, et al. Autonomic blockade improves insulin sensitivity in obese subjects. *Hypertension*. 2014;64:867–874.

160. Lembo G, Capaldo B, Rendina V, et al. Acute noradrenergic activation induces insulin resistance in human skeletal muscle. *Am J Physiol Endo Met*. 1994;266:E242–E247.

161. Pedersen DJ, Guilherme A, Danai LV, et al. A major role of insulin in promoting obesity-associated adipose tissue inflammation. *Mol Metab*. 2015;4:507–518.

162. Muoio DM, Neufer DP. Lipid-induced mitochondrial stress and insulin action in muscle. *Cell Metab*. 2012;15:595–605.

163. Ramalingam L, Menikdiwela K, LeMieux M, et al. The renin angiotensin system, oxidative stress and mitochondrial function in obesity and insulin resistance. *Biochim Biophys Acta*. 2017;1863:1106–1114. doi:10.1016/j.bbadis.2016.07.019.

164. Montgomery MK, Turner N. Mitochondrial dysfunction and insulin resistance: an update. *Endocr Connect*. 2015;4:R1–R15.

165. Grimditch GK, Barnard RJ, Hendricks L, Weitzman D. Peripheral insulin sensitivity as modified by diet and exercise training. *Am J Clin Nutr*. 1988;48:38–43.

166. Esmaillzadeh A, Kimiagar M, Mehrabi Y, et al. Dietary patterns, insulin resistance, and prevalence of the metabolic syndrome in women. *Am J Clin Nutr*. 2007;85:910–918.

167. Paris M, Bernard-Kargar C, Berthault MF, Bouwens L, Ktorza A. Specific and combined effects of insulin and glucose on functional pancreatic beta-cell mass in vivo in adult rats. *Endocrinology*. 2003;144:2717–2727.

168. Reil TD, Barnard RJ, Kashyap VS, Roberts CK, Gelabert HA. Diet-induced changes in endothelial-dependent relaxation of the rat aorta. *J Surg Res*. 1999;85:96–100.

169. Lin HY, Sloan C, Bosse JD, et al. A low-carbohydrate/high-fat diet reduces blood pressure in spontaneously hypertensive rats without deleterious changes in insulin resistance. *Am J Physiol Heart Circ Physiol*. 2013;304:H1733–H1742. doi:10.1152/ajpheart.00631.2012

170. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. *Br J Nutr*. 2013;110:1178–1187. doi:10.1017/S0007114513000548.

171. Fournier RD, Chiueh CC, Kopin IJ, Knapka JJ, DiPette D, Preuss HG. Refined carbohydrate increases blood pressure and catecholamine excretion in SHR and WKY. *Am J Physiol*. 1986;250:E381–E385.

172. Malik AH, Akram Y, Shetty S, et al. Impact of sugar-sweetened beverages on blood pressure. *Am J Cardiol*. 2014;113:1574–1580.

173. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol*. 2010;21:1543–1549. doi:10.1681/ASN.2009111111.

174. Farese RV, Yost TJ, Eckel RH. Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. *Metabolism*. 1991;40:214–216.

175. Swinburn BA, Nyomba BL, Saad MF, et al. Insulin resistance associated with lower rates of weight gain in pima Indians. *J Clin Invest*. 1991;88:168–173.

176. Sigal RJ, EI-Hashimy M, Martin BC, Soeldner S, Krolewski AS, Warram JH. Acute post-challenge hyperinsulinemia predicts weight gain: a prospective study. *Diabetes*. 1997;46:1025–1029.

177. Eckel RA. Insulin resistance: an adaptation for weight maintenance. *Lancet*. 1992;340:1452–1453.

178. Welle SL, Lilavivathana U Campell RG. Increased plasma norepinephrine concentrations and metabolic rates following glucose ingestion in man. *Metabolism*. 1980;29:806–809.

179. Welle S, Ulavivat U, Campell G. Thermic effect of feeding in men: increased plasma norepinephrine levels following glucose but not protein or fat consumption. *Metabolism*. 1981;30:953–958.

180. Tentolouris N, Tsigos D, Perea E, et al. Differential effect of high-fat and high carbohydrate isoenergetic meals on cardiac autonomic nervous system activity in lean and obese women. *Metabolism*. 2003;52:1426–1432.

181. Kopp W. Chronically increased activity of the sympathetic nervous system: our diet-related "evolutionary" inheritance. *J Nutr Health Aging*. 2009;13:27–29.

182. Arnold KB, Schenk JM, Kristal AR, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol*. 2008;167:925–934. doi:10.1093/aje/kwm389.

183. Shankar E, Bhaskaran N, MacLennan GT, Liu G, Daneshgari F, Gupta S. Inflammatory signaling involved in high-Fat diet induced prostate diseases. *J Urol Res*. 2015;2:1018.

184. Parsons JK. Lifestyle factors, benign prostatic hyperplasia, and lower urinary tract symptoms. *Curr Opin Urol*. 2011;21:1–4. doi:10.1097/MOU.0b013e32834100c9.

185. Vykhovanets EV, Shankar E, Vykhovanets OV, Shukla S, Gupta S. High-fat diet increases NF-κB signaling in the prostate of reporter mice. *Prostate*. 2011;71:147–156. doi:10.1002/pros.21230.

186. Ribeiro DL, Pinto ME, Rafacho A, et al. High-fat diet obesity associated with insulin resistance increases cell proliferation, estrogen receptor, and PI3K proteins in rat ventral prostate. *J Androl*. 2012;33:854–865. doi:10.2164/jandrol.111.016089.

187. Mizoguchi S, Mori K, Yamanaka N, Sato F, Mimata H. Prostatic enlargement associated with inflammation in high fat diet induced obesity rat model. Paper presented at: International Continence Society 2017; September 15, 2017; Oita, Japan. https://www.ics.org/2017/abstract/535

188. Marwitz SE, Woodie LN, Blythe SN. Western-style diet induces insulin insensitivity and hyperactivity in adolescent male rats. *Physiol Behav*. 2015;151:147–154. doi:10.1016/j.physbeh.2015.07.023.

189. Fink RL, Kolterman OG, Griffin J, Olefsky JM. Mechanism of insulin resistance in aging. *J Clin Invest*. 1983;71:1523–1535.

190. Seals DR, Esler MD. Human ageing and the sympathoadrenal system. *J Physiol*. 2000;528:407–417. doi:10.1111/j.1469-7793.2000.00407.x.