The Metabolic Syndrome and Kidney Disease

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ABSTRACT

The prevalence of obesity and the metabolic syndrome are increasing worldwide and reaching epidemic proportions in industrialised and developing countries. Obesity is the major driver of type 2 diabetes and it is the phenotypic hallmark of the metabolic syndrome. The global increasing prevalence of obesity has to a large extent mirrored the increase in cardiovascular diseases as well as chronic kidney disease (CKD) and its progression to end-stage renal disease (ESRD). End-stage renal disease is a devastating condition not only for the patient but also imposes a huge economic demand on the society. Several multi-ethnic societies have reported a higher prevalence of CKD and ESRD in blacks compared to whites or individuals of other ethnic groups and data from renal registries often reveal hypertension as cause of ESRD in blacks. Reasons given for this include misdiagnosis, socioeconomic status, poor access to health care and genetic differences, however, the worldwide increasing prevalence of obesity and the metabolic syndrome may contribute significantly to the high prevalence of CKD and ESRD seen in black Africans.

Keywords: *Hypertension, metabolic syndrome, obesity, kidney disease, Africans*

INTRODUCTION

The prevalence of obesity is increasing worldwide and is reaching epidemic proportions. Increasing urbanisation, unhealthy dietary patterns and sedentary lifestyles have all added to the obesity epidemic. Obesity is the major driver and phenotypic hallmark of the metabolic syndrome and has increased at a dramatic rate over the last three decades in industrialised countries. In the United States, the National Health and Nutrition Examination Surveys (NHANES) show that the prevalence of obesity rose gradually from 14.5% to 22.5%[1]. Also in Canada, the prevalence of obesity between 1985 and 1998, more than doubled from 5.6% to 14.8%[2]. This increase was not only confined to the adult population but also children and adolescents[3]. Data from the adult health section of the 1998 South African demographic and health survey (SADHS)[4] showed that the malnutrition pattern seen in adult South African population, is one of predominantly over-nutrition rather than under-nutrition with a concomitant high prevalence of obesity among the blacks of South Africa. The survey revealed that the prevalence of overweight and obesity in South African men and women was 29.2 % and 56.6 % respectively[4].

The metabolic syndrome is common but often under-diagnosed and has had different definitions since its first description[5-8]. However, the guideline of the 2001 National Cholesterol Education Program—Adult Treatment Panel III (NCEP – ATP III) (Table 1) is widely used to identify it. Generally, it is characterized by a clustering of abdominal obesity, insulin resistance / hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein cholesterol, hypertension, chronic inflammation, and prothrombotic status[5, 9-10] all of which confer higher risks of incident diabetes, cardiovascular events, cardiovascular mortality and overall mortality. There are few national surveys reporting the

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prevalence of the metabolic syndrome. However, available data suggest a wide variation from one population to another[11-15]. For instance, data from the United States and Finland reported a prevalence of 27% and 14.2% respectively [13,12] while two studies from Nigeria reported a prevalence of 25.2% and 59.1% in type 2 diabetics[16,17]. Reported prevalence tends to be dependent on the sub-population studied within a given population (diabetics, specific gender, ethnicity/race, age groups). There are few studies that have reported on the prevalence of the metabolic syndrome in African countries.

A common false impression is that non-communicable diseases (NCDs) are of lesser importance than communicable diseases in most African countries. The Global Burden of Disease (GBD) study report of 1990 suggested that NCDs accounted for only 14% of the total burden of diseases in sub-Saharan Africa but that the probability of death from NCDs is higher in sub-Saharan Africa than in developed nations[18]. Studies from Tanzania have shown that the probabilities of death from a non-communicable cause are higher than that from a communicable cause[19]. As chronic kidney disease (CKD) contributes to approximately 850,000 deaths every year[20], the consequences of the increasing epidemiology of CKD continues to devastate, patients and the society. Chronic Kidney Disease is characterized by progression to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). African Americans have been shown to have a higher prevalence of incident ESRD (988 / million population) compared to Caucasians (254 / million population) and an excess risk of CKD from hypertension, diabetes mellitus and obesity[21]. Hypertensive nephrosclerosis is considered one of the most common causes of ESRD[22] and in the US, was reported as cause of ESRD in 30% of all new cases in 2002 and was found to be five times as frequent in blacks compared with Caucasians[23]. In South Africa, hypertension accounted for 45.6% of all ESRD, second only to glomerulonephritis (52.1%) from the 1994 South Africa Dialysis and Transplant Registry (SADTR) data [24]. In Nigeria, hypertension accounted for 61% of cases of CRF followed by diabetes mellitus (11%) and chronic glomerulonephritis (5.9%) [25]. The frequent "labelling" of black Africans with the diagnosis of hypertensive nephrosclerosis as cause of ESRD without histological proof by many nephrologists and in many dialysis registries has led some authors to investigate if other factors could explain the difference in hypertension - related ESRD between black Africans and Caucasians. Seedat, in a review, pointed out that improvement in treatment of hypertension over a ten-year period had led to a decline of major complications of hypertension such as stroke and myocardial infarction by about 25% but that the incidence of hypertension - related ESRD continued to increase over that same period [26]. He suggested factors such as misdiagnosis, socioeconomic status, severity of hypertension, inadequate blood pressure control and genetic differences in the black race as possible explanation for the higher diagnosis of hypertension related ESRD.

In the light of the increasing world wide prevalence of obesity and the metabolic syndrome, we sought to summarize findings from relevant clinical and experimental studies of the association between the metabolic syndrome, obesity and CKD and explore the role that each diagnostic criterion of the metabolic syndrome plays in the development and progression of CKD especially as it relates to black Africans. However the review is hampered by a paucity of data from Africa.

Kidney Disease and Metabolic Syndrome

Microalbuminuria marks the initiation of kidney disease and is believed to reflect endothelial dysfunction within the glomerulus. Several clinical studies have linked microalbuminuria / CKD with the metabolic syndrome[27,28] and a number of mechanisms have been proposed to explain this association.

(A) *Insulin Resistance*

Evidence for the central role of insulin resistance in the development of the metabolic syndrome is supported by the Bruneck Study in which the degree of insulin resistance correlated with the number and clustering of metabolic abnormalities[29]. Proposed mechanisms linking insulin resistance to the metabolic syndrome centre on three major areas:

(1) Tissue and cellular effects of mild to moderate hyperglycaemia,

(2) tissue and cellular effects of compensatory hyperinsulinemia, and

(3) the unbalanced pathways of insulin action.

Molecular studies have shown that the 2 major pathways for insulin signalling are: the Phosphatidyl Inositol-3 (PI-3) Kinase pathway which leads to the

metabolic effects of insulin and the Mitogen-activated Protein Kinase (MAPK) pathway which leads to the inflammatory effects of excess insulin[30]. In metabolic syndrome and type 2 diabetes mellitus, the pathways leading to activation of PI-3K are blocked while the MAPK pathway remains open and may even be hypersensitive[30]. This pathway can be activated by angiotensin II and leptin among others. (Figure 1) In obesity and insulin resistance there is an excess of circulating angiotensin II, leptin and insulin which means the MAPK pathway will be in an overdrive state leading to excess inflammation, endothelial damage and microalbuminuria or proteinuria as a consequence. Although other mechanisms could be involved in the initiation of microalbuminuria in metabolic syndrome patients, the MAPK pathway could be very important as insulin resistance may have been present well before the recognised phenotypic manifestations of the metabolic syndrome.

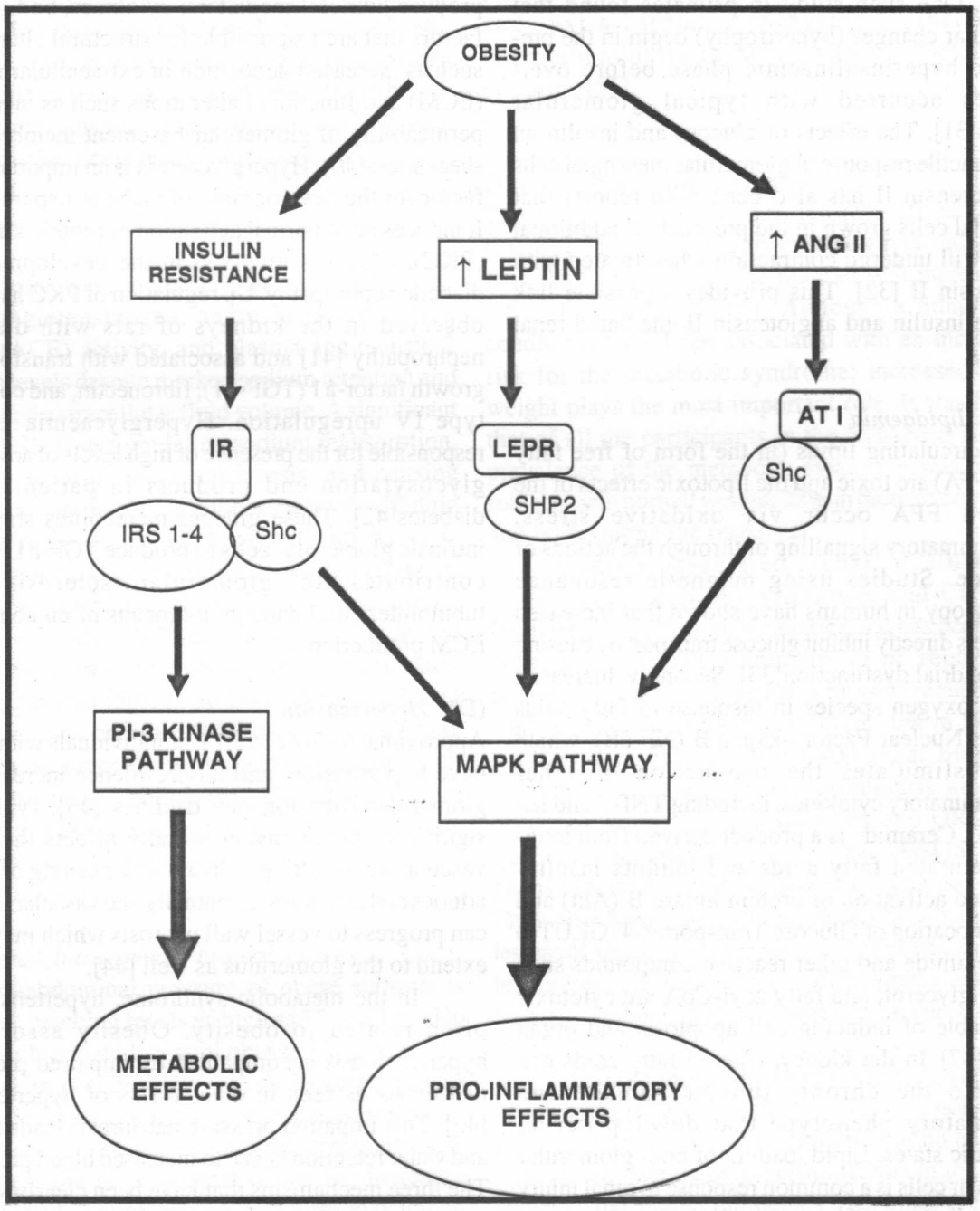

Fig. 1: The MAPK signalling pathway. Insulin, Leptin and Angiotensin II through their receptors can activate the MAPK pathway leading to the proinflammatory effects of these molecules which include endothelial dysfunction and microalbuminuria. IR – Insulin receptor, IRS 1-4 – Insulin receptor substrate protein, LEPR – Leptin receptor, AT I – Angiotensin receptor. The upstream mediators of MAPK pathway are Shc and SHP2

IRS 1-4 – Insulin receptor substrate protein, LEPR – Leptin receptor, AT I – Angiotensin receptor. The upstream mediators of MAPK pathway are Shc and SHP2.

There are studies that have reported the association between insulin resistance and kidney dysfunction both experimentally and clinically. Animal studies have shown that alterations in glomerular structure are seen very early in the metabolic syndrome and are mediated by hyperinsulinaemia and obesity. One such study in primates found that glomerular changes (hypertrophy) begin in the pre-diabetic hyperinsulinaemic phase before overt diabetes occurred with typical glomerular features[31]. The effects of glucose and insulin on the contractile response of glomerular mesangial cells to angiotensin II has also been with reports that mesangial cells grown in the presence of additional insulin will undergo contraction when treated with angiotensin II [32]. This provides a possible link between insulin and angiotensin II–mediated renal injury.

(B) *Dyslipidaemia*

Excess circulating lipids (in the form of free fatty acids - FFA) are toxic and the lipotoxic effects of the elevated FFA occur via oxidative stress, proinflammatory signalling or through the actions of ceramide. Studies using magnetic resonance spectroscopy in humans have shown that increased FFA levels directly inhibit glucose transport by causing mitochondrial dysfunction[33]. Secondly, increased reactive oxygen species in response to fatty acids activates Nuclear Factor –kappa B (NF-κB), which further stimulates the production of other proinflammatory cytokines, including TNF-α and IL-6 [34,35]. Ceramide is a product derived from long-chain saturated fatty acids and inhibits insulin-stimulated activation of protein kinase B (Akt) and the translocation of Glucose Transporter-4 (GLUT4) [36]. Ceramide and other reactive compounds such as diacylglycerol, and fatty acyl-CoA are cytotoxic and capable of inducing cell apoptosis and organ damage[37]. In the kidney, filtered fatty acids can aggravate the chronic tubular damage and inflammatory phenotype that develop during proteinuric states. Lipid loading of both glomerular and tubular cells is a common response to renal injury that contributes to the progression of nephropathy. Hunsicker *et al* [38] have reported six factors, including low serum HDL cholesterol, that independently predict a faster decline in GFR while reports from the Atherosclerosis Risk in Communities (ARIC) study[39] found high triglycerides and low HDL cholesterol, but not low-density lipoprotein cholesterol, to predict an increased risk of renal dysfunction.

(C) *Dysglycaemia*

Renal cells are stimulated by hyperglycaemia to produce humoral mediators, cytokines, and growth factors that are responsible for structural alterations such as increased deposition of extracellular matrix (ECM) and functional alterations such as increased permeability of glomerular basement membrane or shear stress[40]. Hyperglycaemia is an important risk factor for the development of diabetic nephropathy. It induces an abnormal activation of protein kinase C (PKC), which is involved in the development of diabetic nephropathy. Up regulation of PKC has been observed in the kidneys of rats with diabetic nephropathy [41] and associated with transforming growth factor-β1 (TGF-β1), fibronectin, and collagen type IV upregulation. Hyperglycaemia is also responsible for the presence of high levels of advanced glycosylation end products in patients with diabetes[42]. These glucose metabolites stimulate intrinsic glomerular cells to produce TGF-β1, which contributes to glomerular sclerosis and tubulointerstitial damage by means of an abnormal ECM production.

(D) *Hypertension*

Approximately 70% to 80% of individuals with CKD have hypertension, and its prevalence increases as glomerular filtration rate declines [43]. Typically, significant hypertension initially affects the renal vasculature, resulting in hyaline thickening of small arteries and arterioles. Eventually, the vascular lesions can progress to vessel wall necrosis which may then extend to the glomerulus as well [44].

In the metabolic syndrome, hypertension is often related to obesity. Obesity associated hypertension is accompanied by impaired pressure natriuresis as seen in other forms of hypertension [45]. This impaired pressure natriuresis leads to salt and water retention hence to increased blood pressure. The three mechanisms that have been clearly shown to mediate the increased reabsorption of sodium in the kidneys in obesity-related hypertension are:

(i) *Increased Renal Sympathetic Activity*

Excess weight gain is associated with increased sympathetic activity, especially in the kidney [46]. In experimental dogs for instance, it has been shown that increased sympathetic activity appears to raise blood pressure mainly through the renal sympathetic nerves [46]. Hyperleptinaemia has been proposed as one of the most promising mechanisms through which obesity may increase sympathetic activity. Both acute and chronic infusions of leptin have been demonstrated to cause sympathetic activation and to chronically sustain elevated blood pressure [47, 48]. However, the mechanisms of leptin-induced sympathetic activation are still unclear, although recent studies suggest important interactions with other neurochemicals in the hypothalamus.

(ii) *Activation of the Renin-Angiotensin System (RAS)*

Obese subjects have increased plasma renin activity, plasma angiotensinogen, angiotensin-converting enzyme (ACE) activity, and plasma angiotensin-2 (ANG II) levels despite marked sodium retention and an expanded extracellular fluid volume. A significant role for ANG II in stimulating sodium reabsorption, impairing renal-pressure natriuresis, and causing hypertension in obesity is supported by the finding that treatment of obese dogs with an ANG II antagonist or ACE inhibitor blunts sodium retention and volume expansion, as well as increased arterial pressure [49]. Also, ACE inhibitors are effective in reducing blood pressure in obese humans, particularly in young patients [50]. In addition to raising blood pressure, activation of the RAS may also contribute to glomerular injury and nephron loss associated with obesity because increased ANG II formation constricts the efferent arterioles and exacerbates the rise in glomerular hydrostatic pressure caused by systemic arterial hypertension [51].

(iii) *Altered Intra-renal Physical Forces*

The intra-abdominal pressure of obese subjects is increased, reaching levels as high as 35 to 40 mmHg in some subjects with central obesity [52]. Also, the kidney is almost completely covered by adipose tissue that also penetrates into the medullary sinuses causing compression and increased intrarenal pressures[53]. It has therefore been suggested that the increased intrarenal and intra-abdominal pressures may impair pressure natriuresis in the kidneys and contribute to obesity-associated hypertension[53].

An analysis of the influence of metabolic syndrome on target organ damage (cardiac, renal and retinal) in a group of non-diabetic patients with essential hypertension has shown that the presence of the metabolic syndrome may amplify hypertension-related cardiac and renal changes, over and above the potential contribution of each single component of this syndrome[54]. Cuspidi *et al* in a cohort of hypertensive subjects reported about equal values of ambulatory blood pressures in those with and without the metabolic syndrome but found increased cardiac and extra-cardiac involvement including microalbuminuria in those with the metabolic syndrome[55].

Obesity and Kidney Disease

The World Health Organization (WHO) estimates that over 1 billion people are overweight globally, and with the current trend, the number will increase to 1.5 billion by 2015 [56]. Although a number of conditions have been associated with an increased risk for the metabolic syndrome; increased body weight plays the most important role. It was found that of all the participants in the NHANES III, the prevalence of the metabolic syndrome was 5% in subjects with normal weight, 22% in those overweight, and 60% among the obese [2].

Obesity-associated renal dysfunction (proteinuria, nephrotic syndrome, and CKD) is frequently seen in clinical practice and has been well described [57, 58]. Kambham *et al*. reported a progressive 10-fold increase in biopsy frequency of ORG from 0.2% in 1986 to 1990 to 2.0% in 1996 to 2000 in a review of over 6800 renal biopsies. Indications for biopsy were proteinuria alone or occurring with renal insufficiency and ORG was defined morphologically as FSGS and glomerulomegaly or glomerulomegaly occurring alone. They also found that patients with ORG had fewer lesions of segmental sclerosis, more glomerulomegaly, less extensive foot process effacement and less frequent doubling of serum creatinine and progression to ESRD [58].

A comparison of biopsy proven FSGS from 15 obese patients and idiopathic FSGS in 15 non-obese patients revealed heavy proteinuria but no oedema, hypoalbuminaemia or hyperlipidaemia in the obese subjects and glomerulomegaly was observed in all renal biopsies from the obese patients (mean glomerular diameter 256 ± 24 µm in obesity-FSGS vs 199 ± 26 µm in idiopathic-FSGS, $P<0.001$) [78]. With

Fig. 2: TGF-β pathways between glomerular endothelial and mesangial cells mediated by leptin. Whas lereeptin increases TGF-β1 synthesis in endothelial cells, it upregulates TGF-β type II receptor expression in mesangial cells without influencing TGF-β1 synthesis. Leptin also stimulates the synthesis of type I collagen

a mean follow-up of 82months, 50% of obese FSGS patients had developed advanced renal insufficiency or end-stage renal disease. The risk of developing progressive renal failure among obesity-FSGS patients was statistically correlated with serum creatinine and creatinine clearance at presentation [59].

Although the exact mechanisms that link obesity and renal damage have not yet been fully clarified, it can be speculated that at least some of the many inflammatory cytokines that are secreted by adipose tissue may be involved in promoting renal impairment[51]. Leptin is one of the many cytokines produced by fat cells and serum leptin levels and overall fat mass are positively correlated [62]. Massively obese patients with hyperleptinaemia tend to develop focal glomerulosclerosis [63, 64]. In the glomerular endothelial cells, leptin increases TGF-β1 synthesis and upregulates TGF-β type II receptor expression without influencing TGF-β1 synthesis in mesangial cells. TGF-β produced by endothelial cells may reach neighbouring mesangial cells and induce an amplified response because of upregulated TGF-β type II receptors (Figure 2). Leptin also stimulates the synthesis of type I collagen in mesangial cells and type IV collagen in glomerular endothelial cells. Activation of the TGF-β system by leptin eventually contributes to extracellular matrix deposition, glomerulosclerosis, and proteinuria [65].

CONCLUSION

Hypertension remains one of the most important cardiovascular diseases in the world today and major complications of hypertension such as myocardial infarction, stroke, heart failure and especially ESRD have impacted hugely on patients and the society. With the current global epidemic of obesity, the prevalence of metabolic syndrome and its associated consequences, especially those related to renal and cardiovascular diseases will continue to increase and the real challenge will be to prevent the occurrence of these consequences rather than diagnose and treat established and irreversible damages.

As obesity and the metabolic syndrome are partly responsible for the several cases of so called "hypertension- related ESRD", measures addressing the prevention and treatment of these conditions should therefore be priority for physicians who treat black hypertensives. Finally, although the components of the metabolic syndrome have been reported to be associated with kidney disease, the specific cellular pathways that lead to these associations are still

unclear. Studies on obesity, insulin resistance and inflammation and how these are associated with CKD still have to be extensively researched.

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