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Abstract: The prevalence of metabolic syndrome is increasing worldwide and has become a risk factor for the development of chronic kidney disease. The complex linkage between metabolic syndrome and chronic kidney disease is under research and the factors involved beyond the biological background include demographic, sociological and psychological factors that are related to the metabolic syndrome prevalence. The social context of disease causation is as relevant to today's clinical scientist and practitioner as biomarker-directed risk stratification and therapy. The aim of this review is to compare the criteria for diagnosis among different international health organizations, identifying all factors that contribute to the development of this association between metabolic syndrome and chronic kidney disease, and categorizing them by those that could be useful for preventive strategies. In addition, patients with metabolic syndrome have microvascular disease characterized by microalbuminuria, decreased glomerular filtration rate, tubular atrophy, interstitial fibrosis, and glomerulosclerosis. These effects may be due to insulin resistance, hypertension, dyslipidemias, activation of inflammatory processes, fibrotic, dysbiosis and generation of oxidative stress; which cause an imbalance in the main vasoactive factors and thus endothelial dysfunction, deteriorating the renal function. Furthermore, since unhealthy eating habits and a sedentary lifestyle are among the strongest risk factors related to these diseases, lifestyle interventions programs have been recommended for facilitating positive changes in behavior at the individual level. However, further research is needed to promote multiple social, economic and political transformations, shifting the intervention emphasis from individual education, counseling, regimens and medications to community, national and global institutions.

Renal damage in the metabolic syndrome (MetSx): Disorders implicated

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Abbreviations

AHA: American Heart Association; ~~**AMPK:** Adenosine monophosphate (AMP)-activated protein kinase;~~ **CKD:** Chronic kidney disease; **CTGF:** Connective tissue growth factor; **EGIR:** European Group for the study of Insulin Resistance; ~~**EMT:** Epithelial-mesenchymal transdifferentiation;~~ **FIZZ:** Found in inflammatory zone; **GFR:** Glomerular filtration rate; **HDL-C:** High density lipoprotein-cholesterol; **HOMA-IR:** Homeostatic model assessment of insulin resistance; **IDF:** International Diabetes Federation; **IGF-1:** Insulin-like growth factor-1; **ICAM:** Intercellular adhesion molecules-1; **LDL-C**: Low-density lipoprotein-Cholesterol; **MCP-1:** Macrophage chemoattractant protein-1 ~~(MCP-1)~~; **MetSx**: Metabolic syndrome; **NADPH:** Nicotinamide adenine dinucleotide phosphate oxidase; **NCEP-ATPIII:** National Cholesterol Education/Adult Treatment Panel III; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; ~~**$O_2^{\bullet-}$:** Superoxide anion;~~ **PAI-1:** Plasminogen activator inhibitor-1; ~~**p-CS:** p-Cresyl sulfate;~~ ~~**PPARs:** Peroxisome proliferator-activated receptors;~~ **RAAS:** Renin–angiotensin–aldosterone system; ~~**REGARDS:** Reasons for Geographic and Racial Differences in Stroke;~~ **ROS:** Reactive oxygen species; **SBP:** Systolic blood pressure; **TGF-β:** Transforming growth factor-beta; **TNF-α:** Tumor necrosis factor-alpha; ~~**US:** United States;~~ **VCAM-1:** Vascular cell adhesion molecule and **WHO:** World Health Organization.

Abstract

The prevalence of metabolic syndrome is increasing worldwide and has become a risk factor for the development of chronic kidney disease. The complex linkage between metabolic syndrome and chronic kidney disease is under research and the factors involved beyond the biological pathogenesis include demographic, sociological and psychological factors that are related to the metabolic syndrome prevalence. The social context of disease causation is as relevant to today's clinical scientist and practitioner as biomarker-directed risk stratification and therapy. The aim of this review is to compare the criteria for diagnosis among different international health organizations, identifying all factors that contribute to the development of this association between metabolic syndrome and chronic kidney disease, and categorizing them by those that could be useful for preventive strategies. In addition, patients with metabolic syndrome have microvascular disease characterized by microalbuminuria, decreased glomerular filtration rate, tubular atrophy, interstitial fibrosis, and glomerulosclerosis. These effects may be due to insulin resistance, hypertension, dyslipidemias, activation of inflammatory processes, fibrotic, dysbiosis and generation of oxidative stress; which cause an imbalance in the main vasoactive factors and thus endothelial dysfunction, deteriorating the renal function. Furthermore, since unhealthy eating habits and a sedentary lifestyle are among the strongest risk factors related to these diseases, lifestyle interventions programs have been recommended for facilitating positive changes in behavior at the individual level. However, further research is needed to promote multiple social, economic and political transformations, shifting the intervention emphasis from individual education, counseling, regimens and medications to community, national and global institutions.

Keywords: metabolic syndrome; chronic kidney disease; insulin resistance; dysbiosis; sociological aspects.

1. Introduction

Metabolic syndrome (MetSx) is a set of metabolic abnormalities that Avogaro et al. described for the first time as an association between obesity, hyperlipidemia, hypertension, diabetes and cardiovascular diseases defined as a plurimetabolic syndrome (Avogaro et al. 1967). Haller described MetSx ~~in 1977~~ (Haller, 1977), called "Syndrome X" ~~in 1988~~ (Reaven, 1995, 2004), and included insulin resistance as a central player. Multiple international health organizations define the presence of MetSx in individuals with insulin resistance, plus another two out of four following conditions: 1) visceral obesity, 2) elevated levels of triglycerides and/or low-density lipoprotein-Cholesterol (LDL-C), 3) hypertension and 4) elevated serum glucose levels (hyperglycemia) on fasting (Table 1). Numerous studies reported that the distribution of visceral fat is a major risk factor for cardiovascular diseases (Masson et al. 2017) and chronic kidney disease (CKD) (Huh et al. 2016); also obesity by itself is considered an independent risk factor for the development of the CKD (Panwar et al. 2015; Prasad, 2014) and breast, ovary, testicular and bladder cancers (Bogefors et al. 2017; Esposito et al., 2012). Thereby, MetSx is a specific set of abnormalities that contribute to cardiovascular morbimortality and type 2 diabetes mellitus (Reaven, 2004; Xanthakis et al. 2015). More recently, a group of researchers ~~Mazidi et al.~~ reported that the MetSx is a multifactorial disease caused by a complex interaction of genetics and environmental factors ~~(Mazidi et al. 2016)~~, and contributes to the deterioration of the disorders related to this syndrome (Mazidi et al. 2016).

Recently, CKD has gained attention because kidney function deteriorates rapidly in those patients with MetSx. The mechanisms by which MetSx is associated with a decrease in kidney function have been described, and while some literature attributes it more to metabolic dysfunction, for instance insulin resistance, there is also literature that has identified adipokine disturbances and lately, dysbiosis as important contributors. However, the current definition of both diseases

depends on the criteria of health organizations or institutions in each country or region, leading to the question of whether the criteria for diagnosis can be compared around the world. Additionally, one of the main concerns about the association between MetSx and CKD is the deterioration of the patients' health, which in severe cases might end up in disabilities beyond the economic impact not only for the patients themselves but for the health system of each country. Chronic diseases affect the quality of life and functional status of patients, thus substantially increasing the use of healthcare services and the costs of secondary health care (Anderson, 2009). Yet at the same time the economic and political forces of globalization are responsible for the changed living conditions and behaviors leading to the risk factors for chronic diseases (Manderson, 2010; Wiedman, 2010).

In this review, we first compare the criteria for diagnosis among different international health organizations. Secondly, we identify all factors that contribute to the development of the association between MetSx and CKD and then we categorize them by those that could be useful for preventive strategies for early detection or potential targets for treatment.

2. Prevalence of Metabolic Syndrome in the world

MetSx constitutes an economic and public health problem that adversely affects life quality (measured by 36 items that explore eight dimensions of health (Donini et al. 2016)) and is associated with risk factors such as gender, age, ethnicity[*] (Gravlee and Sweet, 2008), sedentism[†] (Ricciardi, 2005), lifestyle and diet (Donini et al., 2016). Also, in the last decade, intestinal microbiota has been identified as a significant player (Bischoff et al., 2016; Org et al., 2017). However, prevalence statistics depend on the criteria for clinical diagnosis of the World Health Organization (WHO, 1998), the European Group for the study of Insulin Resistance (EGIR, 1999), the National Cholesterol Education/Adult Treatment Panel III (NCEP-ATPIII, 2004), the American

[*] See ~~Gravlee and Sweet et al.~~ (Gravlee and Sweet, 2008) for a discussion about the use of the concepts 'race' and 'ethnicity' and the importance of identifying the sociocultural processes that generate health inequalities.

[†] See ~~Ricciardi et al.~~ (Ricciardi, 2005) for a thorough discussion on this concept and its implications for identifying effective intervention strategies and public policy changes to promote a physically active lifestyle.

Heart Association (AHA, 2005) and the International Diabetes Federation (IDF, 2005) (Lopes et al. 2016; Pucci et al. 2017) (Table 1).

An updated study from 2003 to 2012 showed a MetSx prevalence of 33% in the United States~~US~~ (Aguilar et al. 2015), 26.6% in Europe (Vishram et al. 2014), 49.5% in the Middle East (Hajat and Shather, 2012), 24% in China (Pan, et al. 2016), 32% in Brazil (De Carvalho Vidigal et al. 2013) and 36.8% in Mexico (Rojas et al. 2010); all countries indicated significant variable impact by gender and age (Table 2). According to NCEP-ATPIII, the MetSx is present in 82% of cases with type 2 diabetes mellitus, 64.7% of hypertensive patients, 54.5% of hypertriglyceridemic patients and 61.5% of individuals with microalbuminuria, defined as excretion of albumin in urine (González and Lavalle, 2009).

A homogenization in the definition adjusted to gender and ethnicity was carried out in 2009; however, the criteria mostly used in clinical studies are the NCEP-ATPIII and IDF, where a higher prevalence of MetSx associated to factors such as age and gender has generally been observed. There are also relative differences in the prevalence of the MetSx depending on the diagnosis criteria used in the different studies mentioned in Table 2 (Aguilar et al. 2015; De Carvalho Vidigal et al. 2013; Hajat and Shather, 2012; Lopes et al. 2016; Pan, 2016; Rojas et al. 2010; Vishram et al. 2014). The average MetSx prevalence is around 33.6% despite the different criteria to establish the diagnosis.

National surveys from different countries show a limited decrease on the prevalence of MetSx. In Mexico, there has been a significant increase in the last decade as shown by the National Institute of Public Health, which estimates for 2030 a cost of 1.2 billion dollars for the public health system, with a constant deterioration of quality of life (Rtveladze et al. 2014). Therefore, it is important to design therapeutic and preventive strategies to reduce the prevalence of MetSx (González and Lavalle, 2009; Rtveladze et al. 2014).

3. Pathophysiological aspects of Metabolic Syndrome

The pathophysiology of MetSx is complex and includes several metabolic alterations such as hyperglycemia, insulin resistance, dyslipidemia, hypertension, albuminuria, obesity (González and Lavalle, 2009) and intestinal microbiota (Mazidi et al., 2016; Org et al., 2017; Ussar et al., 2016). In recent years, visceral obesity and insulin resistance have been described as essential factors of MetSx. Also new factors have been identified including pro-inflammatory and prothrombotic processes, endothelial dysfunction, alterations in adipose tissue, and at the cellular level, mitochondrial defects and alterations in metabolic and cellular pathways (Ahirwar et al., 2014; Eirin et al. 2017; Hall et al. 2010; LeMieux et al. 2016; Lopes et al. 2016; Org et al. 2017; Steinberg et al. 1996), among others. And recently, new factors have identified like the outstanding effect of dysbiosis, which are changes in composition, localization and metabolic function of the intestinal microbiota (Nieuwdorp et al. 2014; Org et al. 2017). Particularly, intestinal microbiota have influence on the glucose homeostasis and the insulin secretion and resistance (Karlsson et al. 2013; Sekhar, 2015), modulating immune system activation and the renin–angiotensin–aldosterone system (RAAS) which regulates blood pressure (Ahren et al. 2014; Karbach et al. 2016).

At present, the therapeutic pharmacological management of MetSx cannot be treated with a single agent, so several pharmacological agents are indicated that deal with obesity, diabetes, hypertension, and dyslipidemia. These agents can be used alone or in combination: anti-obesity drugs, thiazolidinediones, metformin, statins, fibrates, renin-angiotensin system blockers, aspirin, diuretics, glucagon like peptide-1 agonists, sodium glucose transporter-2 inhibitors, and some antiplatelet (Lim and Eckel. 2014; Sherling et al. 2017).

More recently metabolites and/or natural nutraceuticals compounds are being researched for the treatment of various MetSx components with adequate doses. For example, the soluble fibers from psyllium and other sources; cinnamaldehyde, cinnamic acid and other cinnamon

phytochemicals; berberine and corosolic acid from lagerstroemia; charantin from bitter gourd; catechins and flavonols from green tea and cocoa; omega-3 polyunsaturated fatty acids and alliin from garlic; soy peptides; and curcumin from curcuma longa (Cicero et al. 2016; Cicero et al. 2017).

Therefore, the pathogenesis of MetSx is a multifaceted disorder that not only can lead to further health deterioration but can also end up in sociocultural disabilities with a vast impact on the economy.

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4. Metabolic syndrome association with social aspects.

MetSx has a direct relationship with an increase in sedentary lifestyle decreasing physical activity (Camhi et al. 2015)‡, unhealthy diets and overnutrition, and the use of harmful products like alcohol and cigarettes (Cardona Velásquez et al. 2017; Park et al. 2003; Villarini et al. 2015) . In addition, other socio-cultural attributes like marital status, occupational grade and education have also been used to explore their relationship (Vernay et al. 2013; Villarini et al. 2015). Furthermore, the gender-specific association between these attributes and the physiological factors like stress, depressive symptoms, and suicidal thoughts have also been studied (Cho et al. 2016). Several studies explore the effect of lifestyle intervention programs to decrease risk factors and MetSx prevalence in middle age population, reporting an inverse association between socioeconomic position (particularly education level and household income) and risk of MetSx in women only (Vernay et al. 2013; Villarini et al. 2015). Thus suggesting that gender-specific public heath interventions are needed to ensure appropriate MetSx prevention and treatment (Cho et al., 2016; Loucks et al. 2007) .

Lifestyle interventions delivered in community pharmacies have been suggested as one way to help patients (Villarini et al. 2015). In particular, diet education, physical activity, weight control, smoking cessation and their related behavior modification have been proposed as a high clinical

‡ See ~~Camhi et al.~~ (Camhi et al., 2015) for a discussion on how to objectively measure physical activity

priority (Park et al. 2003). Furthermore, in a systematic review designed to characterize the clinical trials related to the treatment of MetSx conducted from 1980 to 2015, the authors conclude that lifestyle interventions, in particular diet and physical activity, emerge as the most important for managing this multifactorial syndrome (Cardona Velásquez et al. 2017). An energy-prudent diet and moderate levels of physical activity ameliorate several parameters of MetSx and delay the onset of diabetic complications (Magkos et al. 2009). Physical exercise has been studied and proposed as an early prevention solution starting during childhood and adolescence; however, exercise programs should also consider patients from all ages (Misigoj-Duraković and Duraković, 2009). Furthermore, lifestyle modifications should also ameliorate sleep disorders, as they have been proposed as a risk factor for insulin resistance and type 2 diabetes (Spiegel et al. 2005).

However, it is important to consider that differences in lifestyle such as diet, physical activity, smoking, sensitivity to psychological stress and body image vary according to different socioeconomic levels of patients (Cardona Velásquez et al. 2017; Darmon and Drewnowski, 2008). In addition to limited access to medical care and effective educational approaches aimed at improving knowledge and lifestyle changes (Cardona Velásquez et al. 2017). It is worth mentioning that the determinants of socioeconomic differences in health behaviors are poorly understood but are likely to include characteristics of the physical environment, social norms, and the cost of health protective behaviors. Also, individual knowledge, attitudinal and motivational factors related to educational access, life experiences, and the general level of health consciousness expressed within the social environment should be also considered (Cardona Velásquez et al. 2017; Wardle and Steptoe, 2003). Therefore, greater research and public health efforts are needed that focus on strategies about how to facilitate the modification of behavior (Magkos et al. 2009).

5. Metabolic Syndrome as a risk factor for Chronic Kidney Disease

In 2002, the National Kidney Foundation of the United States ~~US~~ in K/DOQI Clinical Practice Guidelines for CKD ~~(National Kidney Foundation, 2002)~~ defined the disease as the presence of structural or functional damage in kidneys that last ≥ three months without reducing glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 (National Kidney Foundation, 2002). The CKD is a pathophysiological, progressive and multifactorial process, the GFR is the best method to determine renal function, which consists of measuring renal clearance of a substance, that is, the volume of plasma from which a substance can be completely removed per unit of time (Satlin et al. 2003).

The National Kidney Foundation of the United States ~~US~~ in K/DOQI Clinical Practice Guidelines for CKD has defined five stages based on the presence of renal damage and/or reduction in GFR. State 1: at least 90 ml/min/1.73 m^2, state 2: 60-89 ml/min/1.73 m^2, state 3-5: <60 ml/min/1.73 m^2 (National Kidney Foundation, 2002). States 3 to 5 are considered by some as a moderate to severe renal function reduction, the presence of microalbuminuria is sufficient to diagnose CKD in state 1 and 2 (Glassock and Winearls, 2008). Epidemiological studies have evaluated the impact of MetSx on CKD (Table 3). For instance, a 5,617-person cohort study in the United States ~~US~~ followed for 6 years' patients with normal renal function and a relationship was found between the development of CKD with MetSx compared with healthy individuals. This relationship persisted even when patients with diabetes mellitus were excluded (Chen et al. 2004). Recently in Taiwan, Ho and collaborators (2015) ~~(Ho et al. 2015)~~ evaluated the relation between risk factors for MetSx and CKD. An association between increased blood pressure levels and CKD development was established in 46,255 apparently healthy subjects (Ho et al. 2015). Also, two more cohort studies found that insulin resistance in CKD patients is frequently accompanied by hyperinsulinemia and glucose intolerance; as well as with abnormalities in insulin secretion (de Boer et al. 2016; Pham et al. 2012).

A positive association between hypertension, diabetes mellitus and hyperlipidemia with incidence and progression of CKD has been established with obesity as an independent risk factor for its development (Dai et al. 2016; Guyton and Hall, 2010; Zammit et al. 2016) (Table 3). In support of this study, it was previously found that massive obesity in the absence of diabetes mellitus may lead to the development of nephrotic syndrome, which is a kidney disease characterized by proteinuria and glomerulosclerosis (Wesson et al. 1985). In elderly adults, obesity measured by waist circumference was associated with higher end-stage renal disease risk (Kramer et al. 2016). In another study, in patients with a body mass index of 30 Kg/m^2 or more was associated with loss of kidney function, and for elderly patients with a body mass index higher than 35 kg/m^2 the association included a higher risk of mortality (Lu et al. 2015) (Table 3). Additional research on specific tissue complications has suggested that obesity is partly responsible for producing hemodynamics disturbances and alterations in the renal structure, for instance, increased mesangial matrix, glomerular sclerosis and mesangial cell proliferation, which are set up before the classic clinical manifestations such as microalbuminuria and/or proteinuria (Chen et al. 2017; Díaz, 2016; Guyton and Hall, 2010; Huh et al. 2017).

In a prospective study from 2001 to 2011 in Korea, from 6,065 patients with no history of CKD or cardiovascular disease, 14.7% developed CKD and from these, 42% were diagnosed with MetSx. This group also belongs to the upper age limit and had significantly higher body mass index, waist circumference, blood pressure, glucose and cholesterol levels (Huh et al. 2017). These patients regardless of age and sex showed significant association of MetSx with increased risk of incident CKD and rapid GFR decline (≤60 ml/min/1.73 m^2). In addition, CKD in those patients was associated with insulin resistance, suggesting that renal dysfunction is evident before the onset of hypertension or diabetes mellitus in MetSx patients (Huh et al. 2017). Preliminary data from a retrospective study from 2001 to 2015 described an alarming incidence of renal damage associated with obesity (D'Agati et al. 2016). In 146 patients with nephrectomy and 12 with MetSx,

the presence of histopathological lesions such as tubular atrophy, interstitial fibrosis and arterial sclerosis was observed, suggesting microvascular damage, and focal and segmental glomerulosclerosis (Alexander et al., 2009). Similar circumstances were observed in a cross-sectional study, in which 106 stable renal transplants had a 53% incidence of MetSx during the first year of transplantation (Hami et al. 2017). All these studies give greater solidity to the association of MetSx and CKD.

5.1 Disorders of chronic kidney disease development associated with metabolic syndrome

Many studies have evaluated disorders by which MetSx mediates pathophysiology of renal damage including obesity, hypertension, hyperglycemia, insulin resistance, activation of inflammatory factors (interleukin-6; tumor necrosis factor-alpha; TNF-α), increased adipokine expression, increased oxidative stress, endothelial dysfunction (Grundy et al. 2005) and dysbiosis (Bischoff et al. 2016; Shen et al. 2013). The above-mentioned alterations lead to glomerular hyperfiltration, activation of RAAS and abnormal secretion of growth factors, which in turn trigger microalbuminuria, renal vascular proliferation, mesangial cell proliferation and mesangial matrix expansion and finally CKD. These factors are described in detailed on the following sections.

5.1.1. Hypertension and obesity

Hypertension is one of two main causes of CKD and the prevalence is even greater if it is associated with overweight or obesity. Clinical studies have shown hypertension in obese subjects and excessive weight gain is a positive hypertension predictor (Hall et al. 2010; Jones et al. 2012). Obesity is a factor that promotes a greater sodium reabsorption, deterioration of natriuresis and an expansion of extracellular volume, changes that are associated with an increase in blood pressure

and glomerular hyperfiltration, as well as the activation of RAAS and the sympathetic nervous system, exacerbating hypertension and the development of renal damage (Hall et al. 2010).

5.1.2. Insulin resistance

Insulin, a hormone produced in β cells of the pancreas, is involved in the metabolic utilization of nutrients, mostly glucose; its deficiency induces hyperglycemia, which is a characteristic of diabetes mellitus and its excess causes hyperinsulinemia. Insulin resistance is an essential factor of MetSx, and it involves alterations in the carbohydrates, proteins and lipids metabolism, defined as an inability of liver cells, adipose tissue, skeletal muscle, central nervous system and pancreas to capture circulating glucose in response to the insulin. This defect is corrected initially with hyperinsulinemia that favors the entry of glucose into cells and inhibits the production of hepatic glucose. Hyperinsulinemia may be due to two factors: an increase in insulin secretion or β cells hypertrophy; if this mechanism fails there are constant changes: an increase in glucose levels and overstimulation in β cells perpetuating insulin secretion and thus establishing insulin resistance (González and Lavalle, 2009; Lopes et al. 2016).

In MetSx, visceral obesity is an essential component that induces an increase in lipolysis, increasing free fatty acids, decreasing sensitivity to insulin in target organs, favoring hepatic gluconeogenesis and the synthesis of triglycerides leading to an increase in glucose release into the bloodstream creating a vicious circle and perpetuating the insulin resistance. In the nervous system visceral obesity induces hyperphagia and an increase of fat mass, whereas in the β cells of the pancreas it causes hyperglucagonemia that leads to hyperglycemia and reduces the secretion of insulin regulated by glucose (Lopes et al. 2016). When β cells in the pancreas do not compensate for insulin resistance, there is a glucose intolerance, the generation of oxidative stress and apoptosis causing a state of alteration in these cells (González and Lavalle, 2009). Insulin resistance is able to induce vascular endothelium vasoconstriction by antinatriuresis and sodium

retention, but also increase RAAS-activation (Lopes et al. 2016) and renal tubular lipid accumulation that are associated with renal injury in the MetSx. Other factors that have been associated with insulin resistance and renal damage are the increment in sterol regulatory element binding protein-1, the transforming growth factor-β1 (TGF-β1), the lipid droplet deposit in renal tubular cells and the interstitial extracellular matrix accumulation by insulin (Hao et al. 2012). Insulin-like growth factor-1 (IGF-1) in cell migration (Beneit et al. 2016) and dedifferentiation of vascular smooth muscle cells (Xi et al. 2017) induce connective tissue growth factor (CTGF) with profibrotic actions in renal tubular cells (Kinashi et al. 2017). For instance the hyperglycaemia in mesangial cells of rats, inhibits the metalloproteinase-9 which is the enzyme responsible for the degradation of extracellular matrix, thus promoting extracellular matrix expansion and renal fibrosis (Wang et al. 2016).

5.1.3. Inflammation

Inflammation is a local tissue response to damage, characterized by the invasion of immune cells and the release of cytokines and chemokines. However, inflammation is not exclusive to correct tissue damage, but it also causes it. There is evidence that metabolic and inflammatory processes are intimately related to obesity, which is also considered an inflammatory disease. More than a consequence, inflammation is the main cause of insulin resistance, hyperglycemia and hyperlipidemia associated with obesity and MetSx (Park et al. 2017). Visceral obesity has been considered a chronic state of mild inflammation; adipose tissue secretes substances with local and systemic inflammatory and metabolic effects, called adipokines or adipocytokines. These mainly come from brown adipose tissue and participate in homeostasis of physiological processes such as food intake, regulation of energy balance, insulin action, glucose metabolism, vascularization, regulation of blood pressure and coagulation. Among the proinflammatory adipokines involved are reactive C protein, TNF-α, IL–6 (Gui et al. 2017) and anti-inflammatory adiponectin including

resistin and omentin, visfatin, chimaerin (Khan, 2014), angiotensinogen, plasminogen activator inhibitor-1 (PAI-1) and leptin (Gui et al. 2017).

5.1.4. Adipokines

Adipokines play a major role in glucose homeostasis modulating insulin resistance, which is derived from the involvement of these molecules on inflammatory and vascular remodeling processes.

TNF-α: Circulating levels are low in humans and these correlate with the obesity degree and amount of adipose tissue (Gui et al. 2017). TNF-α can induce lipolysis through downregulation of cell death-inducing DFF45-like effector C, which is a lipid droplet-coating protein that promotes triglyceride accumulation and inhibits lipolysis through phosphorylation and nuclear export of peroxisome proliferator-activated receptors ~~(PPARS)~~-γ by Mitogen-activated protein kinase/extracellular signal-regulated kinase cascade (Tan et al. 2016). Along with decreases insulin receptor 1 substrate activity ~~(Kim et al. 2015)~~, an important ligand in insulin response, as well as reducing glucose transport by decreasing expression of its intracellular transporter (GLUT-4) (Kim et al. 2015; Stephens et al. 1997). TNF-α is involved in the oxidation of free fatty acids and in the synthesis of cholesterol (Khan, 2014), thus significantly increases generation of reactive oxygen species (ROS). Additionally, it has been described that TNF-α regulates other adipokines' expression such as adiponectin by adiponectin receptors in the adipose tissues (Geng et al. 2016).

Interleukin-6: Is produced and secreted by visceral adipose tissue exerting a direct effect on insulin resistance through stimulation of interleukin-6α receptor (Xu et al. 2017), hepatic secretion of triglycerides, very LDL-C, activation of gluconeogenesis, insulin receptor 1 substrate and activation of phosphatidylinositol 3-kinase pathway, which is associated with cellular regulation, such as growth, proliferation, mobility and survival. It also regulates adiponectin expression (Senn et al. 2002).

Resistin: This protein is associated with insulin resistance and it is also known as a secretory factor specific to adipose tissue. It belongs to a family of secretory proteins that are rich in cysteine called FIZZ (found in inflammatory zone), expressed in macrophages and adipose tissue. It promotes insulin resistance and decreases glucose transport (Ottobelli Chielle et al. 2016). It also favors the secretion of interleukin-1, -6 y -12, TNF-α, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Ottobelli Chielle et al. 2016; Silswal et al. 2005), and endothelin-1. Endothelin-1 is an important factor in renal vasculature; that promotes promoting pentraxin-3 secretion, implicated on the acute phase of inflammatory responses. It is associated with increased expression of intracellular adhesion molecules and vascular cell adhesion molecule and monocyte chemoattractant protein (González and Lavalle, 2009). The increase in resistin levels in patients with CKD is associated with a reduction in renal function and inflammatory processes in the kidney, which has been associated with endothelial dysfunction (Marouga et al. 2016).

Adiponectin: Hormone synthesized by adipose tissue related to obesity, type 2 diabetes mellitus, atherosclerosis and anti-inflammatory effects, is involved in glucose metabolism and fatty acids oxidation (Guo et al. 2017), increases insulin sensitivity and their circulating levels are inversely proportional to the presence of visceral obesity and insulin resistance, so it is considered a risk factor for the development of MetSx (Cho et al. 2017), cardiovascular (Matsushita et al. 2014) and breast cancer (Gui et al. 2017). The expression of adiponectin is regulated by several mechanisms: through IGF-1, TNF-α, peroxisome proliferator-activated receptors~~PPARs~~, transcriptional factors that control genes for fatty acids synthesis, oxidation and storage. In this regard, it has been found that there is an element of response to peroxisome proliferator-activated receptors~~PPARs~~ in adiponectin promoter (Barnea et al. 2015) favoring an increase in fatty acids oxidation, and reducing the synthesis of glucose by hepatic tissue. Adipokine has been reported to be involved on the development of CKD by reduction in GFR associated with diabetes (Ortega et al. 2015) and appears to be related to the activation of adenosine monophosphate ~~(AMP)~~-activated

protein kinase ~~(AMPK)~~ (Fang et al. 2013; Wang et al. 2017) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Adenosine monophosphate-activated protein kinase ~~AMPK~~ regulates processes such as glycolysis, fatty acid oxidation and gluconeogenesis (Sweiss, 2014), whereas NADPH oxidase is the main cause of superoxide anion ~~($O_2^{\bullet -}$)~~ generation and atherosclerosis. The latter is caused by the accumulation of macrophages containing cholesterol in artery walls which is why this oxidase is considered to be an important source of ROS, a species that in turn causes accumulation of oxidized LDL and cell apoptosis through critical roles of phosphatase receptor type O, toll-like receptor 4 and NF-κB (Liang et al. 2017). At the renal level, an *in vitro* study of renal tubular cells in mice, showed that adiponectin protects against the deleterious effects of angiotensin II on kidney by inhibiting NADPH oxidase activation, ROS production, NF-κB and fibronectin (Fang et al. 2013). Adiponectin deficiency in mice was associated with effacement of foot process and fusion of podocytes, glomerulosclerosis and mesangial expansion, damaging glomerular filtration and generating albuminuria; interestingly, when there is an overexpression of adiponectin in these mice, the renal damage is reduced significantly (Rutkowski et al. 2013).

Omentin: It is negatively correlated with obesity, diabetes mellitus, inflammation, and insulin resistance. More recently it was described in a study on patients with obesity that there is a positive correlation of values of omentin with body weight, insulin resistance, blood pressure and triglycerides levels (Sperling et al. 2016). Changes in omentin circulating levels are considered a risk factor for MetSx, atrial fibrillation (Tao et al. 2016), renal cell carcinoma (Shen et al. 2016) and renal dysfunction in patients with CKD (Tekce et al. 2014).

Visfatin: Is secreted in adipose tissue, correlates with the degree of obesity, mimics insulin actions and is regulated by insulin resistance (Owczarek et al. 2016). It binds to an insulin receptor, however, it does so in different regions and could regulate the synthesis of insulin or intracellular mechanisms of insulin (Chen et al. 2006). Also, an association has been found between visfatin and breast cancer (Gui et al. 2017), renal cell carcinoma (Zhang et al. 2017), renal damage.

Particularly, it was described that increased circulating visfatin levels are associated with subsequent decline in renal function in non-diabetic hypertensive patients by reducing GFR through and endothelial dysfunction (Hsu et al. 2016).

Chemerin: Chemoattractant protein that acts as a ligand for the G protein-coupled receptor, regulates adipocyte-development and metabolic function, and participates in the glucose metabolism in liver and muscle. Serum chemerin levels are elevated in patients with type 2 diabetes mellitus and are positively correlated with adiposity, insulin resistance (Habib et al. 2017), glycated hemoglobin, higher inflammatory cytokines, dyslipidemia and hypertension (Zylla et al. 2017). In kidneys it has been observed that the elevated serum chemerin is associated with renal function deterioration (Blaszak et al. 2015), and is also an independent predictive marker of the presence of atherosclerosis in patients with CKD (Salama et al. 2016).

Angiotensinogen: Substrate that initiates the cascade of RAAS reactions. Angiotensin I is a decapeptide produced from angiotensinogen by renin, a precursor of angiotensin II, an important vasoconstrictor in systemic and renal vasculature. Therefore RAAS is important for regulating blood pressure and hypovolemic shock (Guyton and Hall, 2010; LeMieux et al. 2016). Angiotensinogen is synthetized in the liver and to a lesser extent in adipose tissue; its overexpression is associated with obesity, inflammation, insulin resistance and adipocyte hypertrophy (LeMieux et al. 2016). In knockout mice with angiotensinogen-adipose tissue-specific, it was described a higher expression of genes involved in insulin signaling, glucose transport, fatty acid metabolism, oxidative stress and mitochondrial dysfunction. Furthermore, angiotensinogen inactivation reduced the total macrophage infiltration, the macrophage chemoattractant protein-1, and the interleukin-6 TNF-α gene expressions (LeMieux et al. 2016).

PAI-1: It is an inhibitor of the plasminogen tissue activator and the urokinase, and therefore the main factor for physiological removal of blood thrombi, participating in cell migration, angiogenesis, insulin resistance, hypertension, atherosclerosis and inflammation. It is synthesized

predominantly in vascular endothelium and adipose tissue (Ahirwar et al. 2014). PAI-1 influences the association of fat distribution patterns and the degree of obesity with insulin, triglycerides and body fat percentage in African women (Barnard et al. 2016).

Leptin: Is a hormone that is synthesized in adipocytes that acts in the hypothalamus, regulating hunger and satiety mechanisms; as well as the synthesis of different hormones, the stimulation of gluconeogenesis and glycogenolysis, an increase in lipolysis, stimulating the release of profibrotic cytokines, the proliferation of CD4 lymphocytes and the increment of nitric oxide production. Some of these effects lead to a greater energy supply, and the accumulation of fatty acids and triglycerides in adipose tissue, leading to hypertrophy with insulin resistance (Ekmen et al. 2016). At the immunity level it promotes the secretion of TNF-α, interleukin-6 and -12, induces endothelial dysfunction and increases oxidative stress (González and Lavalle, 2009). Elevated serum leptin is associated with CKD in adults (Lim et al. 2015) and this elevation of serum leptin in CKD patients might contribute to endothelial dysfunction by disarrangement of f-actin cytoskeleton (Ding et al. 2016).

5.1.5. Oxidative stress

Oxidative stress originated from MetSx is an important contributor to renal damage through the generation of ROS derived from hyperglycemia and free fatty acids. Decreased renal function and the redox balance profiles in subjects with MetSx show a possible implication of the myeloperoxidase/hydrogen peroxide axis as a contributor in lipid peroxidation due to the increase of malondialdehyde, myeloperoxidase and hydrogen peroxide plasma levels and a positive correlation between them (Fonseca et al. 2014). Oxidative stress and renal damage has also been reported in overweight and in obese children with insulin resistance, where the GFR decreased and an increase in urinary isoprostanes, hydrogen peroxide and myeloperoxidase levels was reported (Correia-Costa et al. 2016a, 2016b). In pig kidneys, other effects that have been associated with

ROS generation are DNA, protein and lipid oxidation, mitochondrial dysfunction (Eirin et al. 2017) and cell death by apoptosis and/or necrosis. Recently, it has been described that there is participation of a specific pathway in renal tubular damage associated with ROS generation. This pathway involves myo-inositol oxygenase, an exclusively tubular enzyme involved in oxidative stress for having responsive elements to oxidants, antioxidants and the promoter of sterol regulatory element-binding transcription factor 1. And its transcription is heavily influenced by hyperglycemia and oxidant stress, which favors the ROS generation and culminates in a tubulo-interstitial injury in the presence of obesity (Tominaga et al. 2016). However, it is not the only pathway described in relation to oxidative stress, since it is able to activate other pathways such as NF-κB, stimulate angiotensin II synthesis, which in turn increases expression of TGF-β and PAI-1, thus perpetuating glomerular fibrosis (Chalmers et al. 2006). Additionally, the main products of lipoperoxidation including oxidized LDL and isoprostans also contribute to insulin resistance, specifically in the mitochondria, the lipoperoxidation of phospholipids and cardiolipin, induces mitochondrial dysfunction due to the opening of the mitochondrial permeability transition pore, mostly in the heart, the skeletal muscle, and the kidneys (Szeto, 2014).

Another important intrarenal source of ROS is NADPH oxidase, an enzyme involved in the transfer of an electron-NADPH to oxygen, leading to ~~$O_2^{\bullet-}$~~ superoxide anion and nicotinamide adenine dinucleotide phosphate; there are several isoforms that are expressed in the liver, pancreas and kidney (Nita, 2016). In the kidney, NADPH oxidase is present in glomerular endothelial cells, tubulointerstitial cells, and glomerular cells, that is, mesangial cells and glomerular epithelial cells. Numerous stimuli and agonists are capable of upregulating the activity and/or the expression of NADPH oxidases like TGF-β, angiotensin II, hyperglycemia, oxidized LDL, IGF-1, vascular endothelial growth factor and aldosterone. Subsequently leading to the overproduction of ROS with the objective of regulation of renal blood flow, alteration of cell fate, and the regulation of gene

expression (Nita, 2016). In addition, oxidative stress is responsible for reducing the bioavailability of nitric oxide, favoring the formation of ROS (Prabhakar, 2004).

5.1.6. Endothelial dysfunction

The endothelium, a monolayer of cells that lines the luminal wall of blood vessels, regulates cell interaction and the circulation of proteins with cells residing in the vascular wall, vascular homeostasis and control of renal vascular functions. Endothelial dysfunction is considered a manifestation of vascular disease and actively participates in the development of atherosclerosis, an important factor in the pathogenesis of diabetes mellitus, hypertension and diabetic nephropathy along with microalbuminuria (Garg and Bakris, 2002). Insulin causes endothelium-dependent vasodilation through the action of nitric oxide; insulin intervenes at several points in the nitric oxide signaling pathway, favors the transportation of nitric oxide precursor and L-arginine, increases activity of nitric oxide synthases and therefore infers in the production of this vasodilator (Zeng and Quon, 1996). In conditions of insulin resistance, such as MetSx, diabetes mellitus and hypertension, endothelium-dependent vasodilation is very clearly damaged (Steinberg et al. 1996). This dysfunction and the increased nitric oxide contribute to renal hyperfiltration, an initial process characteristic of renal damage. In advanced nephropathy associated with hypertension and proteinuria, there is a progressive loss in bioavailability of nitric oxide, caused by several factors (Prabhakar, 2004). Among those that emphasize greater production of ROS, superoxide anion ~~$O_2^{\bullet -}$~~ inactivates nitric oxide and gives rise to peroxynitrite; ROS promotes oxidative degradation of the cofactor (tetrahydrobiopterin) of endothelial nitric oxide synthase, unleashing the decoupling thereof and giving rise to more generation of superoxide anion~~$O_2^{\bullet -}$~~.

Another important factor in endothelium is endothelin-1, synthesized by vascular endothelium in response to angiotensin II, insulin and hypertension. Endothelin-1 acts on two receptors: ET_A and ET_B, ET_A receptor mediates vasoconstriction, mononuclear cell infiltration and

the production of extracellular matrix proteins, whereas ET_B receptor mediates endothelium-dependent vasorelaxation via prostacyclins and nitric oxide (Xu et al. 1998). Endothelin-1 controls various renal functions, such as increased vascular resistance, contraction of mesangial cells, and the reduction of sodium and potassium reabsorption in different tubular cells of nephron, accumulation of extracellular matrix, decreased renal flow, and glomerular filtration. Endothelin-1 blocking prevents these effects and this is why it has been proposed that endothelin-1 may be a mediator in the progression of renal damage. Insulin stimulates endothelin-1 expression and secretion in glomerular and mesangial endothelial cells, as well as in smooth vascular muscle cells (Ferri et al., 1995). Elevated levels of endothelin-1 have been associated with severe vasoconstriction of renal vasculature, proliferation of mesangial cells and increased retention of sodium and water (Marsen and Schramek, 1994).

5.1.7. Dysbiosis

In a healthy person, it has been estimated that 100 trillion microbes exist in the human intestine (Bäckhed et al. 2005), a 1:1.3 ratio between the number of human cells and microbes (Fändriks, 2017). The microbes that are dominant in adulthood are *Bacteroidetes*, *Firmicutes*, *Proteobacterias* and *Actinobacterias*, which contribute nutrients and energy to the organism through the fermentation of non-digestible nutrients. For example, the polysaccharides that are converted into beneficial metabolites, such as short-chain fatty acids (acetate, propionate and butyrate) in the colon where they are absorbed; acetate and butyrate are used in lipogenesis and gluconeogenesis; butyrate provides energy to colon epithelial cells, these microbes contribute to energy expenditure, satiety and glucose homeostasis (Cani et al. 2013). The intestinal microbiota also participates in supplying vitamins, amino acids and metabolism of bile acids. The environment, diet, sanitation, genetics, and the state of the host's immune system and use of antibiotics modify the microbes (Nieuwdorp et al. 2014).

The microbes also generate harmful metabolites for the organism, there are reports on the association between dysbiosis and different metabolic phenotypes, such as energy consumption, energy expenditure, hyperglycemia (Fändriks, 2017), insulin resistance, dyslipidemia, MetSx, obesity (Fändriks, 2017; Li et al. 2008; Mazidi et al. 2016; Shen et al. 2013), hypertension, diabetes and CKD (Al Khodor and Shatat, 2016; Lau et al. 2015; Nallu et al. 2016; Sabatino et al. 2015; Sampaio-Maia et al. 2016). The dysbiosis are qualitative and quantitative pathological changes in composition, location and function of gut microbes (Wing et al. 2015). These studies describe that the interaction among them is due to an increase in the permeability of the intestinal barrier, changes in the expression of host genes, inflammation, ROS generation and the degree of adiposity.

In particular, the pathological association of intestinal microbiota with CKD begins with changes in the permeability of the intestinal barrier, alterations in the intestinal transit, and a reduction in protein absorption and in fiber consumption. Finally, the frequent use of dietary supplements (oral iron) and drugs (antibiotics) end up favoring systemic inflammation and the accumulation of uremic toxins and dysbiosis (Vaziri, 2012; Vaziri et al. 2013).

The characteristic accumulation of uremic toxins in CKD is enhanced by intestinal microbiota with urease that increases ammonium production, induces changes in the intestinal pH, affecting adherent junctions of enterocyte and thus the permeability of intestinal mucosa, allowing mononuclear leukocytes infiltration and activating innate immunity (Ramezani et al. 2015; Vaziri, 2012). The generation of uremic toxins begins with degradation of a certain amount of amino acids that reaches the colon through the diet by intestinal microbiota and induces the production of phenols, indoles, amines, polyamines and ammonium, a large proportion are excreted via the hepatic way and another proportion is eliminated by the kidneys, which is accumulated during CKD (Evenepoel et al. 2009). If these are not excreted by any of the aforementioned ways, they are metabolized by intestinal microbiota to other uremic toxins: p-Cresyl sulfate ~~(p-CS)~~, indoxyl sulfate,

indoleacetic acid, trimethylamine N-oxide, cortisol, cadaverine, spermine, spermidine, putrescine, phenyl sulfate, cholate, hippurate, dimethylglycine, guanidinobutyrate, glutarate, 2-hydroxypentanoate and phenaceturate (Edamatsu et al. 2014; Mishima et al. 2017). The most studied are:

Phenols

- p-Cresyl sulfate~~*p-CS*~~*:* originates through the degradation of phenylalanine and tyrosine, in mice with nephrectomy it has been associated with the development of renal fibrosis by TGF-β activation and epithelial-mesenchymal transdifferentiation with the loss of tubular cell junctions, increased cellular senescence (Sun et al. 2012) and enhanced ROS production by NADPH oxidase rise (Han et al. 2015; Watanabe et al. 2013)

Indoles

- *Indoxyl sulfate:* is produced by tryptophan degradation, exclusively produced by intestinal microbiota, similar to p-Cresyl sulfate ~~p-CS~~ and have the same mechanisms of renal damage (Sun et al. 2012). Previously, it had been associated with endothelial dysfunction and cardiomyocyte hypertrophy due to a rise on ROS production and a reduction in the generation of nitric oxide and an increase in the angiotensinogen levels (Chu et al. 2017; Lekawanvijit et al. 2010).
- *Indoleacetic acid:* This is generated from tryptophan and microbiota and is related to a loss of cell membrane integrity by ROS induction (De Melo et al. 2004) in renal tubular cells involved in apoptosis (Edamatsu et al. 2014).

Amines and polyamines

- *Trimethylamine N-oxide:* This is an amine produced by the metabolism of choline, phosphatidylcholine, betaine or L-carnitine. Trimethylamine N-oxide is considered a cardiovascular disease predictor, associated with promoting atherosclerosis (Wang et al. 2011) and as a good prognostic marker of mortality in patients with CKD, and has been

associated with tubulointerstitial fibrosis and renal dysfunction (Tang et al. 2015). It is considered a toxin that depends not only on microbiota, but also on diet (Mishima et al. 2017).

- *Cadaverine, spermine, spermidine and putrescine:* Polyamines that depend on diet are due to the decarboxylation of L-arginine, L-ornithine or lysine. Until today, it has been described that serum levels of spermine, spermidine and putrescine are elevated in patients with CKD (Saito et al. 1983), additionally involved in the development of hypertriglyceridemia and inhibit erythropoiesis (Macdougall, 2001; Lutz, 1980).

This association of dysbiosis with CKD becomes relevant in studies such as Vaziri et al (2013) ~~(Vaziri et al. 2013)~~. who published the microbiome concerning intestinal microbiota of humans and rats with CKD through microarrays, concluding the existence of a decrease in *Bacteroidetes* and *Firmicutes* populations in CKD rats compared to healthy animals. In patients the difference was on the distribution of the predominant population, that is, increase of *Firmicutes*, *Actinobacteria* and *Proteobacteria* and reduction in *Bifidobacteria* and *Lactobacilli* (Vaziri et al. 2013). In the same year, the presence of renal damage by kidney stones appearance in 300,000 infants, who consumed milk formula with melamine was reported. Melamine is an additive, which in the presence of Klebsiella, a component of intestinal microbiota, induces generation of cyanuric acid that results in crystal renal deposits and renal dysfunction, which normalizes when melamine is eliminated from diet (Yasui et al. 2014; Zheng et al. 2013).

6. Effects on renal pathophysiology

6.1. Hyperfiltration

Glomerular hyperfiltration is mediated by several pathways: afferent arteriole dilation in glomerulus, mediated by IGF-1, prostacyclin, bradykinin, nitric oxide and atrial natriuretic peptide; efferent arteriole constriction mediated by thromboxane A_2 local (Wardle, 1996). Another important

vasoactive factor is nitric oxide and its pathways production. Glomerular hyperfiltration can also be affected by mitochondrial ROS production associated with activation of cyclooxygenase-2 transcription and the overproduction of prostaglandin E_2 (Nishikawa and Araki, 2007).

6.2. Activation of the RAAS

Participates in the regulation of blood pressure and sodium balance in mammals, encompasses a set of chemical reactions in the form of an enzymatic cascade, it is triggered by renin release (Ondetti and Cushman, 1984). Renin release is regulated by sympathetic stimulation of renal vessels, lower perfusion pressure to the kidney, a baroreceptor mechanism in juxtaglomerular cells and dense macula (Ondetti and Cushman, 1984). Renin acts on angiotensinogen to generate angiotensin I and through the angiotensin I converting enzyme, it is converted to angiotensin II; his binds to its type 1 and 2 membrane receptors (AT_1 and AT_2) located in nervous, renal and cardiovascular system and adrenal glands (van Rodijnen et al. 2002). Angiotensin II is better known for its potent vasoconstrictor effect; however, it has several functions in the body. For example, it affects renal function mediated by acting on blood flow, glomerular filtration and tubular transport per increasing Na^+/H^+ exchanger activity in proximal tubule, stimulates the contraction of glomerular mesangium and the deposition of fibronectin and collagen (Don, 1995). All components of RAAS are present in the kidney (Siragy et al. 1995), AT1 receptor is the most abundant and is located in afferent and efferent arterioles, where the glomerulus and proximal tubule is responsible for regulating vasoconstrictor actions of angiotensin II (Sechi et al. 1992) and the reabsorption of sodium and water, but also promoting hypertrophy cell, proliferation and extracellular matrix deposits in the kidney, and the stimulation of TGF-β and collagen secretion (Kagami et al. 1994). AT2 receptor is located in the renal cortex, particularly in interlobular arterioles but not in glomerulus, and when binding to angiotensin II produces vasodilation (Kagami et al. 1994). Furthermore, aldosterone, a mineralocorticoid hormone that is synthesized in adrenal glands, main function is the extracellular volume maintenance through an

increase in sodium reabsorption and potassium secretion in the nephron and distal tubule, regulating Na^+/Cl^-cotransporter expression, Na^+/K^+ ATPase activity and epithelial sodium channel activity (Guyton and Hall, 2010). It has been reported that aldosterone is associated to hypertension, ventricular hypertrophy, CKD, obesity, and MetSx; therefore, aldosterone may be a biomarker of cardio-renal and metabolic disease (Buglioni et al. 2015). In support of this, recent findings indicate that insulin interferes with RAAS, insulin stimulates production of angiotensinogen hepatic, TGF-β and collagen in mesangial cell cultures (Anderson et al. 1996). It was recently described that changes on dietary fiber content in mice helps intestinal microbiota to produce beneficial metabolites as acetate and, modulation on RAAS and vascular tone (Marques et al. 2017).

6.3. Profibrotic factors and mesangial matrix expansion

There are profibrotic factors altered in MetSx; insulin and IGF-1 have been reported to stimulate the proliferation of vascular smooth muscle cells (Khamaisi et al. 2002), which in turn can induce CTGF and have profibrotic actions on renal tubular cells and interstitial fibroblasts (Wang et al. 2001). At the renal level in the glomerular, mesangial and proximal tubule endothelial cells, the leptin and insulin stimulate cell proliferation, TGF-β synthesis and the production of extracellular matrix proteins as collagen type IV (Wolf et al. 2002). Furthermore, p-Cresyl sulfate ~~p-CS~~ generated by microbiota has been associated to increased profibrotic cytokines (Sun et al. 2012). Endothelin-1 is another profibrotic factor, a vasoactive that induces mesangial matrix expansion and PAI-1; this inhibits the action of plasminogen and prevents the degradation of extracellular matrix. Therefore, proliferative action observed in renal damage plays an essential role in the renal fibrosis development.

6.4. Microalbuminuria

One case-control study and another prospective cohort study demonstrated that there is an association between insulin resistance levels and microalbuminuria (Sarafidis, 2008). So far, the

described possible causes are hyperfiltration, glomerular basement membrane abnormalities, glomerular hypertrophy, hyperlipidemia and an increase in vasoactive and profibrotic factors. MetSx is characterized by the presence of visceral obesity, hyperlipidemias, hypertension, hyperglycemia and diabetes mellitus; together with insulin resistance and hyperinsulinemia, being the two most important causal metabolic factors for MetSx. Also, there is interference with other factors associated with renal damage, such as oxidative stress, proinflammatory, vasoactive and profibrotic factors, endothelial dysfunction and finally dysbiosis, which together lead to the development of CKD (shown in Figure 1). Renal damage involves tubular and glomerular fibrosis and vascular damage associated with several factors of MetSx involved on the regulation of renal disease development.

7. Metabolic Syndrome as a risk factor of Chronic Kidney Disease and their association with social aspects.

Several studies have yielded results connecting the sedentary life style of modern humans with greater incidence of many chronic diseases and low functional capability of an organism (Misigoj-Duraković and Duraković, 2009). Similarly to the studies that investigate the social aspects associated to MetSx, for chronic kidney disease, research shows that a healthy lifestyle and diet are associated with less CKD and may have a substantial impact on the patients' kidney health (Dunkler et al. 2016; Ricardo et al. 2015). The different risk factors considered are physical activity, size of social network, stress, financial worries, education, alcohol intake, tobacco use, diet, and the intake of various food items (Dunkler et al. 2016, 2015; Ricardo et al. 2015). A study showed that while healthy diet had no adverse outcome in CKD patients, physical activity and nonsmoking recommendations were important for the general population but also applicable to persons with CKD (Ricardo et al. 2015). Also a novel study reports an association between a person's number of social contacts (friends and family) and the incidence and progression of CKD and type 2 diabetes;

as well as education, moderate alcohol consumption and regular physical activity as having a significant association with CKD (Dunkler et al. 2015).

Some cross-sectional and cohort studies have suggested a MetSx and CKD association, reporting relationships among CKD and MetSx, microalbuminuria, age, gender and lifestyle factors like alcohol intake, smoking and deficient physical activity (Chen et al. 2007; Cho et al. 2013; Thomas et al. 2011). Chen et al (~~Chen et al.~~ 2007) demonstrate that the risk of CKD increased progressively with a higher number of components of MetSx, independent of age, sex and other potential risk factors for CKD, including non-steroidal anti-inflammatory drug use, education, physical activity, alcohol drinking, cigarette smoking and body mass index. A severance cohort study (Cho et al. 2013) integrated by 20,582 Korean men and women aged 20-84 years old showed through a multivariable analyses controlling for age and lifestyle variables (alcohol intake, smoking status and physical activity) that an increased CKD risk in men and women with MetSx was found compared to those without MetSx. High blood pressure and LDL-C were more likely to be associated with risk of CKD development in apparently healthy Koreans. In addition, the association between MetSx and kidney dysfunction was significantly independent of traditional cardiovascular risk factors (Cho et al. 2013) . Finally, in a cross-sectional study conducted with 260 Chinese adults with MetSx and CKD, results indicate that dietary nutrition is closely correlated with renal damage in patients with MetSx, where high protein intake may be one of the risk factors of renal damage (Bi et al. 2014).

The study of chronic disease from an anthropological perspective has employed chronicity theory to understand poor health in diverse cultural contexts and political and economic settings, and the different textures of inequality that shape the lived experiences of disease (Manderson and Smith-Morris, 2010). At a global scale, industrialization, urbanization, sedentary occupations, changes in food supplies, the increased consumption of processed food and smoking, have all contributed to the rising incidence of chronic conditions. Historically, the economic transition from

an agricultural subsistence to one of industrial wage in urban contexts lead to poor metabolic health as a result of a decline in physical activity and overconsumption of high-fat and nutritionally poor foods, and chronic psychosocial stress (Wiedman, 2010). The economic and political forces of globalization have also been established as responsible for the changed living conditions and behaviors leading to the risk factors for chronic diseases (Manderson and Smith Morris, 2010; Wiedman, 2010). Political, economic, psychological, social and material conditions accumulate during the life experience of the body. Conditions present during gestation, through early childhood, and into adulthood, and are modified by such factors as climate, seasonality, age, gender, ethnicity, technologies, built environments| and socioeconomic status (Wiedman, 2012). Yet we have a limited understanding of how globalization –as a force, a process, and a set of relations- patterns the distribution and trajectories of disease and poor health (Manderson and Smith-Morris L, 2010).

8. Discussion and future perspectives

MetSx is a complex disease that contributes to the deterioration of the various diseases related to this syndrome and the overall health of its patients.

Firstly, the current definition of MetSx depends on the criteria of health organizations or institutions in each country or region, which has led to relative differences between several countries. Despite the different criteria to establish the diagnosis, average MetSx prevalence is around 33.6%. However, the criteria mostly used in clinical practice are the NCEP-ATPIII and IDF, where a higher prevalence with age, gender and socio-cultural context has generally been observed. Whereas the diagnosis of CKD is well established worldwide through the K/DOQI Clinical Practice Guidelines. Despite diagnosis, descriptive, and terminological inaccuracies that make statistical estimates problematic, chronic conditions are increasingly prevalent (Manderson and Smith-Morris, 2010).

Secondly, the CKD has gained attention recently since kidney function deteriorates rapidly in those patients. The mechanisms by which MetSx is associated to a decrease in kidney function have been described, and while some literature attributes it more to metabolic dysfunction, for instance, insulin resistance; there is also literature that has identified adipokine disturbances and lately dysbiosis as important contributors. It is proposed here that the interaction of these factors may be the key to designing or developing strategies for prevention, development and progression of kidney damage associated with MetSx. However, further detailed studies are needed on recently integrated factors such as the role of adipokines and dysbiosis in renal damage. Thus the prevention and treatment of MetSx should be an important priority for reducing the prevalence of CKD.

Dunkler et al. (~~Dunkler et al.~~ 2015) reminds us that the social context of disease causation may be as relevant to today's clinical scientist and practitioner as biomarker-directed risk stratification and therapy. Unhealthy eating habits and a sedentary lifestyle are among the strongest risk factors for obesity, MetSx and type 2 diabetes, thus management programs should tackle these problems. Dietary manipulation should be an integral part of the therapy for patients with progressive CKD (Bi et al. 2014). However, adopting a healthy balanced diet and a physical activity lifestyle requires several behavioral changes, not only at the individual level through multiple social, economic and political transformations. In addition, research is also needed to better promote the patients' adherence and long-term maintenance of implementations (Magkos et al. 2009).

The Chronicities of Modernity Theory is a biocultural paradigm for linking macro sociocultural factors to individual life experiences and biological disabilities. It shifts the emphasis of MetSx interventions from individual education, counseling, regimens and medications to community, national and global institutions. Individuals should engage with planners and policy makers to develop social institutions, ideologies, and built environments that facilitates, rather than hinder

physically active healthy communities (Wiedman, 2012). For controlling and reversing the epidemic of sedentarism, a multidimensional approach with collaboration among pediatric and adult health care providers, city planners, policy makers, employers, the school system, and the media, entertainment and food industries is needed (Ricciardi, 2005). Therefore, ~~As suggested by Cisneros-González and Ceballos (Cisneros-González and Ceballos, 2009) to develop programs or projects for the improvement of the quality of care of patients with chronic disease,~~ collaborative endeavors, where academic, investigators, healthcare professionals and the industry can participate together are essential to develop programs or projects for the improvement of the quality of care of patients with chronic disease~~needed~~ (Cisneros-González and Ceballos, 2009). Community-based participatory research can provide understanding and the elimination of health inequalities (Baker et al. 2001; Gravlee and Sweet, 2008). A success story from the Aboriginal people in north-west Western Australia, demonstrates that community control and ownership that created changes in the social environment enabled the sustainability of a healthy lifestyle program; therefore developmental initiatives facilitating planning, implementation and ownership of interventions by community members and organizations can be a feasible and effective way to achieve sustainable improvements in health behaviors and selected health outcomes for the management and prevention of chronic disease (Rowley et al. 2000). The process by which a community initiates, develops and implements an intervention program can itself contribute to improved health outcomes (Rowley et al. 2000).

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Figure legends

Figure 1. *Association between metabolic syndrome and chronic kidney disease.*

Connective tissue growth factor (CTGF); chronic kidney disease (CKD); ~~Epithelial-mesenchymal transdifferentiation (EMT);~~ Glomerular filtration rate (GFR); Insulin-like growth factor-1 (IGF-1); Intercellular adhesion molecules-1 (ICAM-1); Macrophage chemoattractant protein-1 (MCP-1); Metabolic Syndrome (MetSx); Nicotinamide adenine dinucleotide phosphate oxidase (NADPH); Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); Plasminogen activator inhibitor-1 (PAI-1); ~~p-Cresyl sulfate (p-CS);~~ Reactive oxygen species (ROS); Renin-angiotensin-aldosterone system (RAAS); Transforming growth factor beta (TGF-β); Tumor necrosis factor alpha (TNF-α); Vascular cell adhesion molecule (VCAM-1).

Tables legends

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Table 1. *Criteria for diagnosing metabolic syndrome.*

World Health Organization (WHO, 1998); European Group for the study of Insulin Resistance (EGIR, 1999); National Cholesterol Education/Adult Treatment Panel III (NCEP-ATPIII, 2004); American Heart Association (AHA, 2005) and International Diabetes Federation (IDF, 2005).

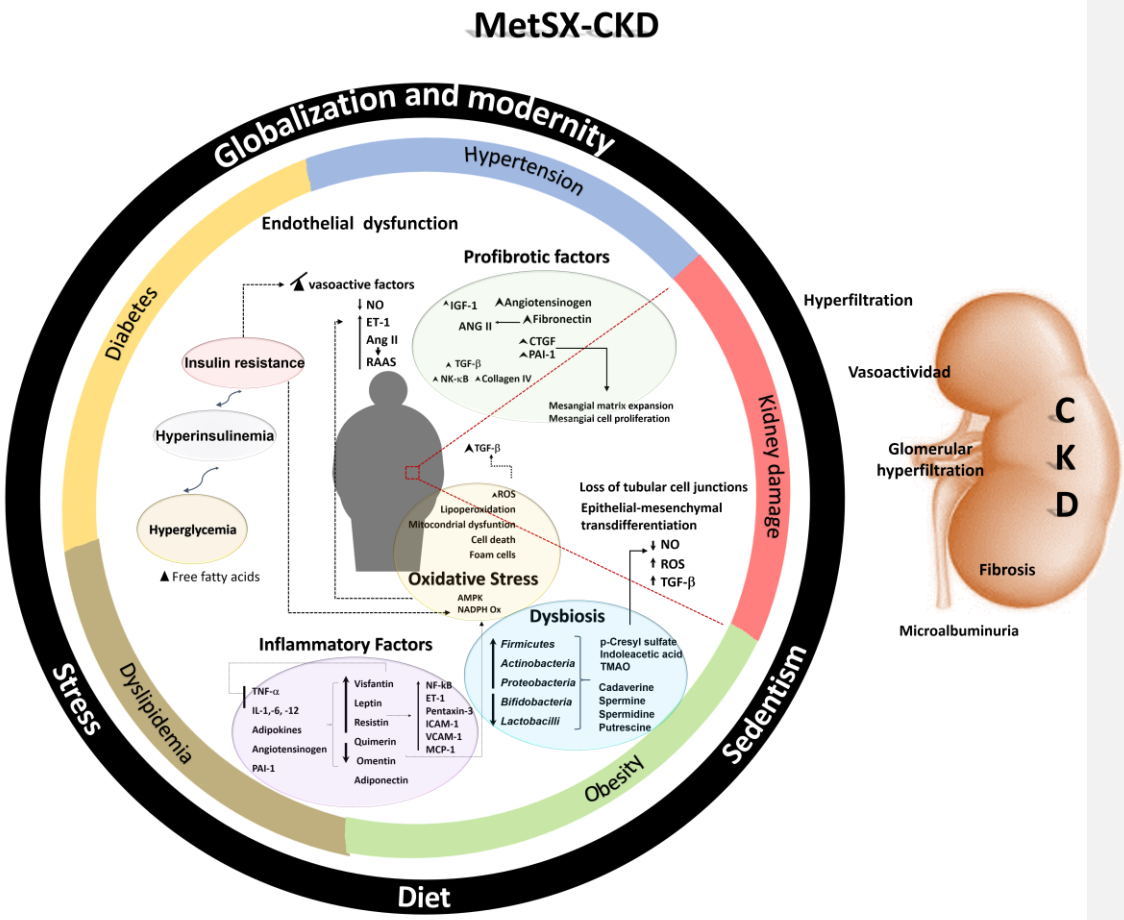
Table 2. *Studies with differs criteria for diagnosing metabolic syndrome*

International Diabetes Federation (IDF); National Cholesterol Education/Adult Treatment Panel III (NCEP-ATPIII); ~~United states (US);~~ World Health Organization (WHO); ♀: woman and ♂: men.

Table 3. *Clinical studies that evaluated the Impact of metabolic syndrome on Chronic Kidney Disease*

Chronic kidney disease (CKD); Glomerular flow rate (GFR); High-density lipoprotein-cholesterol (HDL-C); Homeostatic model assessment of insulin resistance (HOMA-IR); Low-density lipoprotein-Cholesterol (LDL-C); Metabolic syndrome (MetSx)~~; Reasons for Geographic and Racial Differences in Stroke (REGARDS)~~ and Systolic blood pressure (SBP).

1 Figure 1


MetSX-CKD
Globalization and modernity
Hypertension
Kidney damage
Sedentism
Obesity
Diet
Stress
Dyslipidemia
Diabetes
Endothelial dysfunction
vasoactive factors
NO
ET-1
Ang II
RAAS
Insulin resistance
Hyperinsulinemia
Hyperglycemia
Free fatty acids
Profibrotic factors
IGF-1
Angiotensinogen
ANG II
Fibronectin
CTGF
PAI-1
TGF-β
NK-κB
Collagen IV
Mesangial matrix expansion
Mesangial cell proliferation
TGF-β
ROS
Lipoperoxidation
Mitocondrial dysfuntion
Cell death
Foam cells
Oxidative Stress
AMPK
NADPH Ox
Loss of tubular cell junctions
Epithelial-mesenchymal transdifferentiation
NO
ROS
TGF-β
Dysbiosis
Firmicutes
Actinobacteria
Proteobacteria
Bifidobacteria
Lactobacilli
p-Cresyl sulfate
Indoleacetic acid
TMAO
Cadaverine
Spermine
Spermidine
Putrescine
Inflammatory Factors
TNF-α
IL-1,-6, -12
Adipokines
Angiotensinogen
PAI-1
Visfantin
Leptin
Resistin
Quimerin
Omentin
Adiponectin
NF-kB
ET-1
Pentaxin-3
ICAM-1
VCAM-1
MCP-1
Hyperfiltration
Vasoactividad
Glomerular hyperfiltration
C
K
D
Fibrosis
Microalbuminuria

2

Table 1

Criteria	WHO	EGIR	NCEP-ATP III	AHA	IDF
1) Hypertension	≥140/≥90 mmHg	≥140/≥90 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg
2) HDL cholesterol	♀ ≤ 39 mg/dl ♂ ≤ 35 mg/dl	♀ ≤ 39 mg/dl ♂ ≤ 39 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl
3) Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl
4) Serum glucose levels on fasting			> 110 mg/dl	> 100 mg/dl	> 100 mg/dl
5) Visceral obesity	♀ ≥ 88 cm ♂ ≥ 90 cm	♀ ≥ 80 cm ♂ ≥ 94 cm	♀ ≥ 88 cm ♂ ≥ 102 cm	♀ ≥ 88 cm ♂ ≥ 102 cm	♀ ≥ 80 cm ♂ ≥ 94 cm

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Table 2

Country Region	Study type	Criteria used [7]	Year	Duration	N patients	Age	MetSx Prevalence	Ref
United States~~US~~	Cohort	NCEP-ATP III	2015	9 years	9,125	20-60 years old	33% ♀ 35.6% , ♂ 30.3%	Aguilar et al. 2015 ~~23~~
Europe	Cohort	NCEP-ATP III, IDF	2014	12.2 years	69,094	19-78 years old	26.6% ♀ 36.5% , ♂ 16.7%	Vishram~~24~~ et al. 2014
Middle East	cross-sectional	WHO, NCEP-ATP III, IDF	2012	2 years	760	41-43 years old	49.5% ♀ 42.1% , ♂ 59.2%	Hajat et al. 2012~~25~~
China	cross-sectional	NCEP-ATP III, IDF	2016	7 moths	10,100	44-61 years old	24% ♀ 31.8% , ♂ 15.0%	~~26~~Pan et al. 2016
Brazil	cross-sectional	NCEP-ATP III	2013	-	2,130	19-64 years old	32% -	De Carvalho~~27~~ et al. 2013
Mexico	Survey	NCEP-ATP III	2010	8 moths	45,446	>20 years	36.8% ♀ 42.2% , ♂ 30.3%	~~28~~Rojas et al. 2010

Table 3

Patients	Length	Measurement of parameters	Observations	Ref
5, 617 With and without the MetSx	6 years	SBP, plasma glucose level, serum TG, HDL -C, insulin and creatinine levels, GFR, albuminuria, microalbuminuria and proteinuria.	↑ Prevalence of CKD and microalbuminuria by number of the MetSx components.	~~57~~Chen et al. 2004
46,225 Apparently healthy	1 year	SBP, plasma glucose level, TG, HDL-C and creatinine levels, GFR and proteinuria.	A dose-response manner in prevalence of CKD and measurements of MetSx risk factors. SBP and TG/HDL-C ratio were an independent risk factor for CKD.	~~58~~Ho et al. 2015
4,680 Adults without diabetes	6 years	Plasma fasting insulin, insulin sensitivity index, serum glucose, insulin, creatinine and cystatin-C levels and GFR	↓ GFR was associated with insulin resistance. ↓ GFR and β cell function was associated with ↑ impaired glucose tolerance.	~~59~~Pham et al. 2012
98 With and without nondiabetic CKD	-	Insulin sensitivity, clearance, secretion and glucose tolerance	Moderate-severe CKD associated with reductions in insulin sensitivity and clearance	~~60~~de Boer et al. 2016
588 With and without CKD	-	GFR, CRP, HOMA-IR, SBP, plasma glucose level, serum TG and HDL-C levels	↑ Prevalent hypertension and abdominal obesity associated with MetSx	~~62~~Zammit et al. 2016
19,848 Hypertensive	2 years	SBP, blood glucose, TC, TG, HDL-C, LDL-C, serum uric acid and	↑ Serum uric acid and MetSx appear to be associated with an	~~63~~Dai et al. 2016

subjects		creatinine, GFR, proteinuria	increased prevalence of CKD in hypertensive subjects.	
26, 960 **~~REGARDS~~**	6.3 years	Body mass index, waist circumference, spot urine albumin-creatinine ratio and GFR	Obesity is associated with higher ESRD risk	~~65~~Kramer et al. 2016
274, 764 **With ↓GFR**	-	Body mass index and GFR	↑ BMI is associated with rapid loss of kidney function and this association is accentuated in older patients. ↑↑ BMI is associated with high mortality.	~~66~~Lu et al. 2015
6,065 **Without history of CKD and CV**	10 years	SBP, plasma glucose level, serum TG, HDL -C, LDL-C, insulin and creatinine levels, HOMA-IR, HbA1c and GFR.	MetSx have increased risk of not only incident CKD, but also ↓ GFR. ↑ Insulin resistance is also associated with development of CKD and rapid decline in renal function.	~~6~~Huh et al. 2017
106 **Stable renal transplant recipients**	8 moths	SBP, body mass index, waist circumference, plasma glucose level, serum TG, HDL-C.	↑ Prevalence of MetSx in renal transplant recipients, especially during the 1st year after transplantation.	~~71~~Hami et al. 2017

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POINT-BY-POINT RESPONSE.

Reviewer 1

C1. In the present review, the authors compare the criteria for diagnosis of metabolic syndrome among different international health organizations, identify related factors that contribute to the development of chronic kidney disease and explore future perspectives. Overall an interesting, well written and in-depth analysis of the association of metabolic syndrome and chronic kidney disease.

R1. We appreciate your comment.

Reviewer 2

Major concern

C1. As far as I know, a review is written by the author(s) who has(have) his/her (their) own studies (manuscrips etc.) on that related topic. If I am not mistaken, I could not encounter any own labor of the authors in the reference list given, beyond wery well and widely to put together the studies in this field published by other authors. Nevertheless, I think that this review will be helpful for readers interested in the field of MetSx.

R1. In this review, we did not include studies related to the association of MetSx with CKD, because our research lines are focused mainly on renal damage by drugs and their associated mechanisms. However, we conducted this review because our goal is to expand our line of research to kidney damage associated with MetSx and its components.

Minor concerns

C1. The year of the publication should be given in parenthesis where authors are mentioned, thus twice declaration is avoided. For example: Introduction section (page 3), lines 1 and 3: Avogaro et al. lines 15 and 17: Mazidi et al.?

R1. Thank you for your observation. This typographic error has been corrected throughout the document.

(a) Introduction section (page 3) line 6, section 5 (page 8), line 23; page 9, line 19; page 24, line 9; page 28, line 6 and page 30, line 11, we insert only the year in parentheses after the name of the author;
(b) In foots notes (pages 4 and 7) we only leave the references;
(c) In page 3, line 17 we added the phrase “a group of researchers” instead of “Mazidi et al”, and finally
(d) The text was changed on the page 31, lines 4-9.

C2. Page 6, section 4: The point should not be put at the end of the title.

R2. Thank you for your observation. The point was deleted from the title (page 7), line 8.

C3. Page 30, line 11 and 12: The sentence beginning with "As suggested by Cisneros-Gonzales and Ceballos …….". It is enough to write year of the publication in parenthesis, however the names of authors have been written twice. It is similar to the mentioned point before (see above).

Such kind of typographic errors shold be corrected throughout the text.

R3. We appreciate your comment. This typographic error has been corrected throughout the document. The text on the page 31, lines 4-9 was changed.

Q4. Figure 1: It can not be easily read. The words are gray. It should be redrawn in a readable form with larger characters.
R4. We appreciate your comment; we changed the words to black and bold, with a reduction in tones of the background circles and we also made the font size larger.

Additional editor comments

C1. Please considering a section that briefly discusses (2 paragraphs) current and future pharmacological approaches.
R1. In section 3, we have included two paragraphs that briefly discuss the current and future pharmacological approaches:
"At present, the therapeutic pharmacological management of MetSx cannot be treated with a single agent, so several pharmacological agents are indicated that deal with obesity, diabetes, hypertension, and dyslipidemia. These agents can be used alone or in combination: anti-obesity drugs, thiazolidinediones, metformin, statins, fibrates, renin-angiotensin system blockers, aspirin, diuretics, glucagon like peptide-1 agonists, sodium glucose transporter-2 inhibitors, and some antiplatelet (Lim and Eckel. 2014; Sherling et al. 2017).
More recently metabolites and/or natural nutraceuticals compounds are being researched for the treatment of various MetSx components with adequate doses. For example, the soluble fibers from psyllium and other sources; cinnamaldehyde, cinnamic acid and other cinnamon phytochemicals; berberine and corosolic acid from lagerstroemia; charantin from bitter gourd; catechins and flavonols from green tea and cocoa; omega-3 polyunsaturated fatty acids and alliin from garlic; soy peptides; and curcumin from curcuma longa (Cicero et al. 2016; Cicero et al. 2017)."

Furthermore, in regards to the style correction, we eliminate the following abbreviations:
"AMPK: AMP-activated protein kinase; **EMT:** Epithelial-mesenchymal transdifferentiation; **$O_2^{\bullet-}$:** Superoxide anion; **p-CS:** p-Cresyl sulfate; **PPARs:** Peroxisome proliferator-activated receptors; **REGARDS:** Reasons for Geographic and Racial Differences in Stroke **US:** United States**"**.

And also we revised and corrected the references and tables to make them double-spaced. We added, four references:
"Cicero A.F., Coletti A., 2016. Role of phytochemicals in the management of metabolic syndrome. Phytomedicine. 23(11):1134-44. doi: 10.1016/j.phymed.2015.11.009" (Page 34, lines 27-28)
"Cicero A.F., Fogacci F., Morbini M., Colletti A., Bove M., Veronesi M., Giovannini M., Borghi C., 2017. Nutraceutical Effects on Glucose and Lipid Metabolism in Patients with Impaired Fasting Glucose: A Pilot, Double-Blind, Placebo-Controlled, Randomized Clinical Trial on a Combined Product. High Blood Press Cardiovasc Prev. doi: 10.1007/s40292-017-0206-3" (Page 34, lines 29-30)

“Lim S, Eckel RH.,2014. Pharmacological treatment and therapeutic perspectives of metabolic syndrome. Rev Endocr Metab Disord. 15(4):329-41. doi: 10.1007/s11154-014-9298-4” (Page 40, lines 2-3)
“Sherling D.H, Perumareddi P., Hennekens C.H., 2017. Metabolic Syndrome: Clinical and Policy Implications of the New Silent Killer. J Card Pharma and Ther. 22 (4), 365-367. doi.org/10.1177/1074248416686187” (Page 44, lines 15-16)

Lastly, in the acknowledgment section we changed it to:
“We thank Graham Matthew Tippett for copyediting assistance of the manuscript. JT and NMT are supported as researcher fellows by the program “Cátedras CONACYT” (project number 615).
This research did not receive any grant from founding agencies” (Page 31)

Cover Letter

IPICYT
INSTITUTO POTOSINO DE INVESTIGACIÓN CIENTÍFICA Y TECNOLÓGICA, A.C.

07 November 2017

Dr. F.A.M. Redegeld
Editor-in-Chief
European Journal of Pharmacology
Utrecht University, Universiteitsweg 99, Room 2.88. 3584 CG UTRECHT
The Netherlands

Dear Frank:

Enclosed please find the manuscript entitled: “Renal damage in the metabolic syndrome (MetSx): Disorders implicated” by Joyce Trujillo, Yolanda I Chirino, Natalia Martínez-Tagüeña and José Pedraza-Chaverri, which we are submitting respectfully to be considered for publication as a Review, that identifies all factors that contribute to the development of the association between metabolic syndrome and chronic kidney disease. We hope this manuscript may be suitable for publication in European Journal of Pharmacology.

Thank you in advance for taking care of our manuscript.

Yours sincerely,

Joyce Trujillo
Consejo Nacional de Ciencia y Tecnología-Instituto Potosino de Investigación Científica y Tecnológica-Consorcio de Investigación, Innovación y Desarrollo para las Zonas Áridas. San Luis Potosí, 78216. México

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Figure

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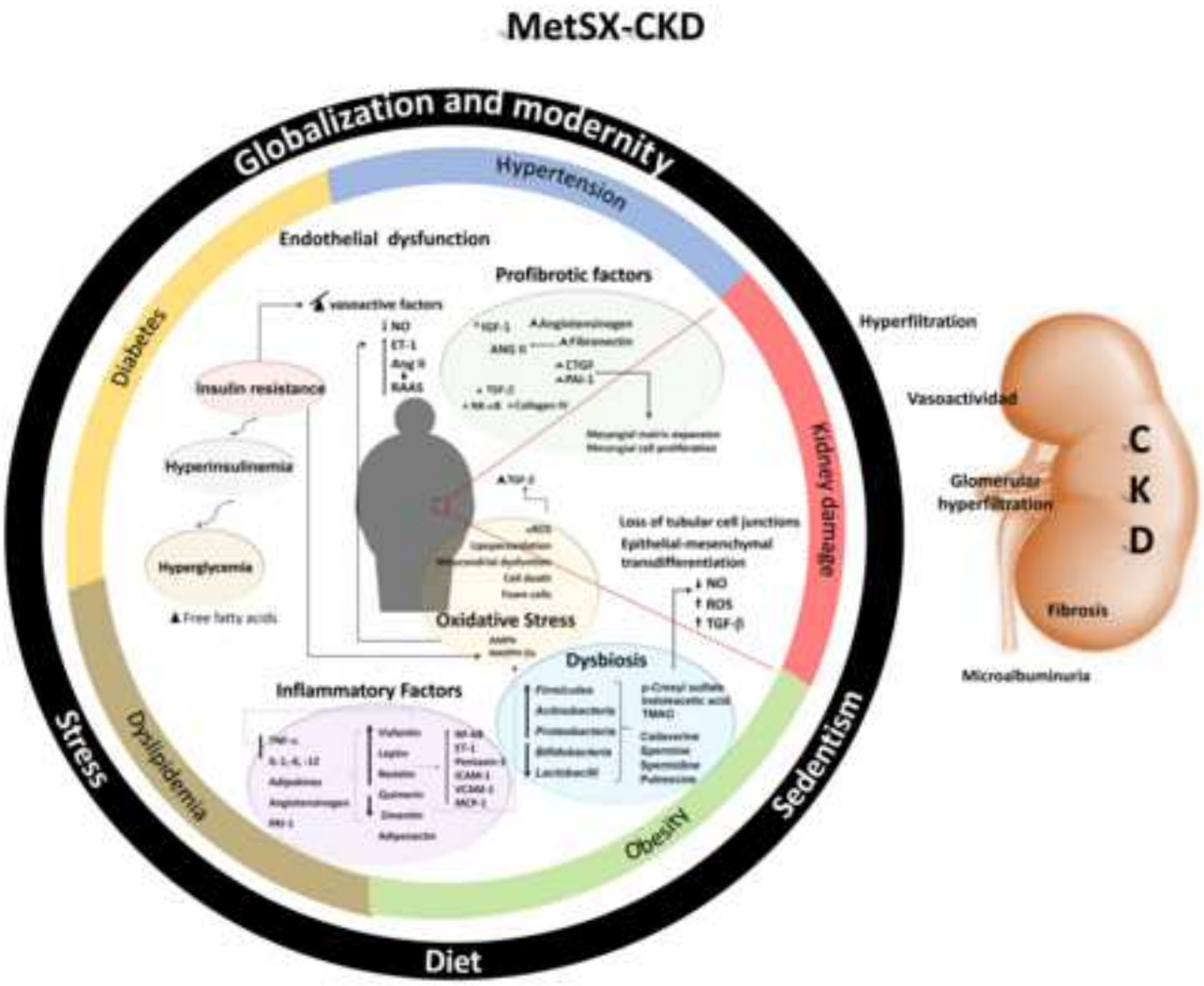

Table

Table 1

Criteria	WHO	EGIR	NCEP-ATP III	AHA	IDF
	Individuals with three or more of the following conditions:				
1) Hypertension	≥140/≥90 mmHg	≥140/≥90 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg
2) HDL cholesterol	♀ ≤ 39 mg/dl ♂ ≤ 35 mg/dl	♀ ≤ 39 mg/dl ♂ ≤ 39 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl	♀ ≤ 50 mg/dl ♂ ≤ 40 mg/dl
3) Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl
4) Serum glucose levels on fasting			> 110 mg/dl	> 100 mg/dl	> 100 mg/dl
5) Visceral obesity	♀ ≥ 88 cm ♂ ≥ 90 cm	♀ ≥ 80 cm ♂ ≥ 94 cm	♀ ≥ 88 cm ♂ ≥ 102 cm	♀ ≥ 88 cm ♂ ≥ 102 cm	♀ ≥ 80 cm ♂ ≥ 94 cm

Table 2

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