The obese child in the Intensive Care Unit. Update

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ABSTRACT

Given that childhood obesity is an epidemic, the frequency of critically-ill patients who are overweight or obese seen at intensive care units has increased rapidly. Adipose tissue is an endocrine organ that secretes a number of protein hormones, including leptin, which stands out because it regulates adipose tissue mass. The presence of arterial hypertension, metabolic syndrome, diabetes mellitus, respiratory disease and chronic kidney disease may become apparent and complicate the course of obese pediatric patients in the Intensive Care Unit. Obesity management is complex and should involve patients, their families and the medical community. It should be coordinated with comprehensive government health policies and implemented in conjunction with a change in cultural context.
Key words: obesity, leptin, metabolic syndrome, hypertension, intensive care.

INTRODUCTION

Discussions regarding obesity or overnutrition and their harmful effect on health have sparked off great interest but relatively small success in terms of the implemented prevention strategies.[1,2]

In developing regions, such as Latin America, which is undergoing an epidemiological transition, the rate of obesity is high. More than 90% of childhood obesity is primary or exogenous, and caused by an excessive calorie intake in a setting of social determinants, such as poverty, lack of education and poor access to food. The remaining 10% includes secondary or "endogenous" obesity, which may be caused by endocrine disorders, obesity-associated genetic defects, or hypothalamic damage conditions.[3]

Child and adolescent obesity is a risk factor for several conditions and is associated with significant chronic morbidity (adult obesity) and early mortality.[4,5] It has been reported that

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life expectancy is reduced between 5 and 20 years.[6]

Obesity is defined as excessive body fat (fat mass) in relation to height. At present, body mass index (BMI), calculated as weight (kg)/square of height (m²), is the recommended and most widely accepted indicator to assess the extent of obesity in the pediatric population,[7] both in the clinical and the epidemiological setting.

The following BMI cut-off values are recommended for children and adolescents aged 2 to 19 years old:[8]
- Z score between 1 and 2 or percentile 85-96: overweight.
- Z score ≥2 or percentile ≥97: obesity.
- Z score ≥3: severe obesity.

An individual weight/age and height/age assessment is recommended for infants.

The objective of this review is to offer, from an intensivist's perspective, an update on the pathophysiology of obesity and the main relevant comorbidities that may be present or develop in obese patients during their stay in the Intensive Care Unit (ICU).

Epidemiology

The prevalence of overweight and obesity among children and adolescents is increasing worldwide and has become an epidemic. For example, in the United States of America, 16.5% of 6-to-19 year-old children are overweight, and 17% are obese.[9]

Such increase in childhood obesity has also taken place in developing countries, and has even tripled in Chile between the 1970s and the 1990s.[10]

A recent systematic review[11] reported that 20-25% of Latin American children and adolescents (aged 0-19 years old) were overweight or obese.

The results of the National Survey on Nutrition and Health (*Encuesta Nacional de Nutrición y Salud*, ENNyS) indicated an obesity prevalence of 10.4% in children aged between 6 and 60 months old. In addition, the rate of overweight and obesity increased with age and reached 20%. This also varies by geographic region and socioeconomic status. This situation is concurrent with deficit conditions.[12]

In Argentina, it has been recently reported that for a population of 13-to-15 year-old adolescents, the prevalence of overweight had increased, over a five-year period, from 24.5% to 28.6%, while that of obesity went from 4.4% to 5.9%.[13] Also in Argentina, overweight or obesity were described as being 45% among 4 year-old children, with a high percentage of alterations in body fat distribution pattern.[14]

Likewise, in Chile, a prospective study in children and adolescents aged 2-18 years old described that 13.9% were overweight and 12%, obese, with no differences by sex or age group.[15]

The origin of obesity involves many factors and is correlated to genes and lifestyle.[16,17] Some factors, such as consuming processed foods and sugar-sweetened beverages, together with a sedentary lifestyle, contribute to said increase.[18]

A recent European population-based study conducted in 3000 children from birth to 5 years old assessed the association between genetic predisposition and obesity. An association between genotype variations and the extent of growth and body composition since the first year of life was identified, but not in the prenatal stage.[19] These findings suggest a greater susceptibility to developing obesity during adulthood.

Finally, childhood obesity complications not only become apparent during adulthood as chronic conditions, but they have early consequences, such as arterial hypertension,[20] hyperlipemia,[21] obstructive sleep apnea (OSA),[22] and asthma worsening.[23]

Given that the frequency of obese children has increased in the general population and due to its associated comorbidities, the prevalence of obese children has also increased in intensive care units and hospital wards. At the same time, an increased prevalence of hospitalized obese children has been described, reaching up to 20%.[24]

Pathophysiology of obesity
Leptin biology
Obesity is a multifactorial disease with several pathophysiological mechanisms involved, either in relation to weight control and energy expenditure and related comorbidities.

Adiposity hormones are called adipokines and include leptin, a hormone made up of 167 amino acids and similar to cytokines, that is mainly synthesized by adipocytes of white fat and coded in the Lep gene, located on chromosome 7q31.3.[25-27] Once leptin is secreted and reaches the systemic circulation (in proportion to the magnitude of body fat depot), it binds to specific cell surface receptors and activates intracellular signaling pathways.[28] The leptin receptor gene (LepR) is a member of the type I cytokine receptor family and codes six leptin receptor isoforms.[28] Only LepRb has structural elements necessary for intracellular signal transduction.[26,29] LepRb is expressed in different neuronal groups of the central nervous system (CNS), mainly the hypothalamus, where it regulates the expression of neuropeptides involved in eating habit adjustment, in addition to thermogenesis and fertility. On a peripheral level, it directly affects the metabolism and functioning of adipocytes, lungs, kidneys, muscles, skeleton, liver, adrenal cortex, and pancreatic β cells, among others.

Childhood obesity is correlated to an increased leptin circulating level.[30,31] Leptin plays an immunomodulatory role[32] and develops, in these patients, a low-grade chronic inflammation,[33] which is associated with macrophage infiltration into adipose tissue. This leads to increased proinflammatory cytokine levels, such as tumor necrosis factor-α, interleukin-1b, interleukin-6, and this situations contributes to insulin resistance[34] and a reduced immune and metabolic reservoir.[35,36] Thus, insulin resistance, hypercoagulability and inflammation characterize obesity as a condition that is similar to a critical disease.[37]

Clinical implications are relevant because the inflammatory response of an obese child is different from that of a non-obese child.

Comorbidities in obese children
As it occurs with adults, several comorbidities are secondary to increased abdominal fat, such as insulin resistance, metabolic syndrome, arterial hypertension, dyslipemia and type 2 diabetes mellitus (T2DM), and are associated with a greater waist circumference and obesity in pediatric patients.[38,39] These conditions may be diagnosed upon admission to the ICU and have an impact on the prognosis of the critically-ill pediatric patient (*Figure 1*).

Another chronic condition associated with childhood obesity is atherosclerotic cardiovascular disease. It has been demonstrated that hyperleptinemia in the adolescent population is associated with a lower arterial distensibility, which is a relevant functional index for atherosclerosis.[40] Hyperleptinemia is an independent factor for cardiovascular risk and, among others, for coronary artery atherosclerosis risk. It is a mediator of endothelial dysfunction and neointimal hyperplasia and causes a paracrine effect of perivascular adipose tissue over the smooth muscle.[41] Among obese children, the intima-media layers are thicker; this is a non-invasive marker of early atherosclerotic changes. It has been demonstrated that this condition may be reversed through BMI normalization during childhood.[42]
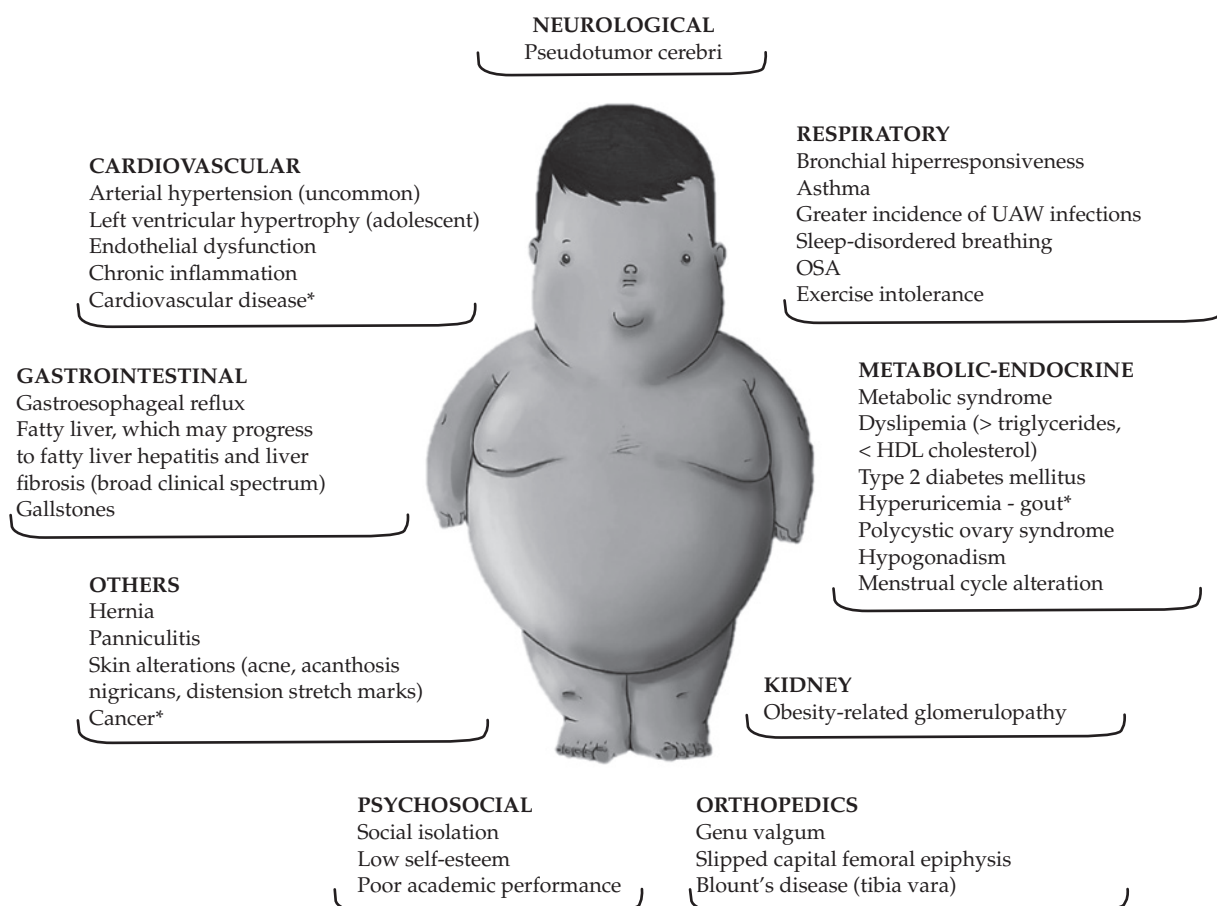
Data evaluating differences in mortality between obese and non-obese cohorts are not conclusive.[43]

During the recent influenza A (H1N1) epidemic, obese children had a worse clinical course.[44]

A recent report indicated that obese children requiring invasive mechanical ventilation did not show a higher mortality nor did they require a longer stay on mechanical ventilation support.[45] On the contrary, it has been reported that obese patients with severe trauma[46] or burns[47] have more complications and a longer stay in the ICU. Many complications in trauma patients are related to existing conditions or premorbidities.[46]

Evidence suggests that childhood obesity is associated with a lower survival rate after in-hospital cardiac arrest.[48] This has led to proposing a review of effectiveness of drugs exclusively based on body weight.[49] Thus, highly water-soluble drugs with a small distribution volume (e.g., epinephrine) may reach high plasma levels in obese children and be potentially unsafe.[50] Conversely, highly lipid-soluble drugs (e.g.,

FIGURE 1. *Medical and psychosocial problems observed in childhood and adolescent obesity*

NEUROLOGICAL
Pseudotumor cerebri

RESPIRATORY
Bronchial hiperresponsiveness
Asthma
Greater incidence of UAW infections
Sleep-disordered breathing
OSA
Exercise intolerance

CARDIOVASCULAR
Arterial hypertension (uncommon)
Left ventricular hypertrophy (adolescent)
Endothelial dysfunction
Chronic inflammation
Cardiovascular disease*

GASTROINTESTINAL
Gastroesophageal reflux
Fatty liver, which may progress
to fatty liver hepatitis and liver
fibrosis (broad clinical spectrum)
Gallstones

METABOLIC-ENDOCRINE
Metabolic syndrome
Dyslipemia (> triglycerides,
< HDL cholesterol)
Type 2 diabetes mellitus
Hyperuricemia - gout*
Polycystic ovary syndrome
Hypogonadism
Menstrual cycle alteration

OTHERS
Hernia
Panniculitis
Skin alterations (acne, acanthosis
nigricans, distension stretch marks)
Cancer*

KIDNEY
Obesity-related glomerulopathy

PSYCHOSOCIAL
Social isolation
Low self-esteem
Poor academic performance

ORTHOPEDICS
Genu valgum
Slipped capital femoral epiphysis
Blount's disease (tibia vara)

UAW: upper airway; OSA: obstructive sleep apnea. * Late complications.

amiodarone) have a large distribution volume in obese patients and higher doses may be required to achieve a comparable effect. [51] It has been recommended that defibrillation doses should be reviewed,[52] as well as standard chest compression techniques.

An increased BMI causes a higher cardiovascular, respiratory and metabolic effort, which results in a significant decline in the physiological reserve. During aerobic performance assessment, it has been demonstrated that such response leads to a reduced cardiorespiratory efficiency in obese children.[53,54]

Among children with acute lymphoblastic leukemia, regardless of existing therapeutic response predictors, obesity has been associated with a poor vital prognosis.[55]

Finally, further studies are required to estimate the actual impact of obesity on the course and prognosis of critically-ill children.

Metabolic syndrome

Overweight and obesity are associated with a greater prevalence of several factors of cardiovascular risk.[56] Metabolic syndrome (MS) is the name for a set of several metabolic anomalies, each an independent risk factor of cardiovascular disease and diabetes, and that together cause a synergistic effect.[8] There are different criteria regarding MS in pediatrics. Criteria applied to adults are extrapolated to children upon adjustment by age and sex. In clinical practice, it is recommended to use Cook's criteria.[57] For the diagnosis of MS, three out of five criteria should be met: waist circumference ≥90th percentile, fasting glucose ≥110 mg/dL, triglycerides ≥110 mg/dL, HDL cholesterol <40 mg/dL, blood pressure ≥90th percentile.

Excess central (intra-abdominal) fat is related to cardiovascular disease and T2DM during adulthood.[58] An assessment of anthropometric indicators, such as waist/height ratio, helps to establish cardiometabolic risk in the pediatric population.[59,60]

An association between overweight, insulin resistance and MS has been established among school children.[61] It has been reported that between 30% and 50% of obese adolescents have MS, compared to 7% of overweight adolescents and 0.6% of those with a normal BMI.[62,63]

Stress-induced hyperglycemia, common in critically-ill patients, may be more marked among obese children and adolescents. Hyperglycemia, which may be initially considered beneficial

(higher substrate to tissues with increased demand), if prolonged over time, it may lead to the formation of free radicals, cellular damage and immune alterations, resulting in an eventual worse prognosis.[64] However, there are no clear data on the relationship between glycemic control and prognosis of critically-ill patients.[65,66] A subgroup of these children may develop T2DM with mild symptoms, therefore delaying diagnosis. In addition, it may appear as hyperglycemic-hyperosmolar state (4%), an uncommon condition that has a significant morbidity and mortality.[67-69]

Arterial hypertension

The worldwide epidemic of childhood obesity has led primary arterial hypertension to become, at present, one of the more common causes of hypertension in children and adolescents.[70]

Obesity is an independent risk factor for arterial hypertension in pediatrics.[71-74] Obese patients have endothelial and vascular smooth muscle dysfunction,[73] as well as a reduced parasympathetic nervous activity.[75,76] Arterial hypertension has been associated with a larger left ventricular mass in obese children.[74] Severe uncontrolled hypertension may lead to early organ damage.[77,78]

Pulmonary physiology

Data on the impact of obesity on pulmonary physiology in the pediatric population are limited. It has been reported that the most prevalent alterations in lung function are a reduced functional residual capacity (FRC) and compromised diffusion.[79] Overweight is also associated with a general reduction in lung volume, which may be reflected in a worse functional capacity.[80]

A recent study in overweight school children and adolescents described that, in the absence of respiratory symptoms, 65% of them had an abnormal pulmonary function. Obstructive ventilatory defect and positive bronchodilator response were the most common abnormalities.[81] Among children, the effects of adiposity on lung function depend on sex and BMI.[82]

Airways

Intensivists should be trained in airway management, be ready to request assistance and have access to the necessary equipment for difficult airway intubation.[83]A recent report assessed the impact of obesity as a risk factor for

respiratory adverse events during procedural sedation and indicated that these patients more commonly required airway interventions.[84]

It is known that classical anatomic airway landmarks are not evident, so management is challenging.[85] The airway is characterized by a small oral cavity with redundant oropharyngeal tissue, hypertrophic tonsils and/or adenoids and a thick, short neck with little mobility; there is also fatty infiltration in the muscles, which causes a direct airway narrowing. All such anatomic factors may complicate visualization during a laryngoscopy.[86,87] This scenario may even become more complicated due to the difficulty to maintain a patent airway before endotracheal intubation, problems to manage ventilation with a face mask and a quick desaturation caused by a lower FRC (presence of atelectasis in dependent regions),[88,89] which is the result of a reduced expiratory reserve volume; all this affects obese patients' capacity to tolerate extended apnea periods[90] and, in the end, the period before oxygen arterial desaturation is brief.[91]

Among adults, neither obesity nor BMI were associated with a predicted difficult intubation.[92] Measuring neck circumference in children is a useful and easy technique during screening and has been associated with respiratory adverse events.[93]

Bronchial asthma

Bronchial asthma has been described in 30% of overweight and obese patients[94] and is more prevalent and severe with an increasing body weight.[23,95,96] Serum leptin levels are positively correlated to BMI and the prevalence of atopic asthma among children.[97]

Obese asthma patients require a longer stay at the ICU because they recover more slowly than non-obese patients with a similar severity status upon admission.[23]

Sepsis in obese patients

Obesity is associated with immune disorders, but its effect on the predisposition and prognosis of sepsis patients has not been clearly established.[98,99] However, there is cumulative evidence that obese patients are more prone to having severe complications from common infections.[100,101]

In an experimental cecal ligation and puncture (CLP) model of sepsis in mice, diet was modified briefly to induce obesity and assess inflammatory response. The model demonstrated that mice had a lower chance of survival and greater organ damage, which was dependent on changes in nuclear factor-κB.[102] However, a recent experimental model of sepsis in obese mice showed that hyperleptinemia improved survival and immune response.[103]

Effects of obesity on the kidneys

Observational studies have shown that obesity is a potential risk factor for renal disease of various origins, predominantly chronic kidney disease, but also kidney stones and renal cell carcinoma.[104] Over the past decades, a significant increase in obesity-associated glomerulopathy has also been described, and this is a condition that is exclusively related to excess weight.[105]

In addition to the known relationship between MS and the development of T2DM and cardiovascular disease,[58] there is evidence of a significant relationship between MS and obesity and albuminuria and end-stage renal disease (ESRD),[106-108] which has been observed to appear early in youth.[109]

It has been proposed that adipocytes are the driving force of glomerular hyperfiltration in obese patients (*Figure 2*). As previously mentioned (see above), adipose tissue is a source of specific proteins (leptin, resistin, adiponectin), inflammatory mediators, oxidative stress generators[110] and components of the renin-angiotensin-aldosterone (RAA) system, all these factors have a direct effect on obesity-associated kidney disease.[111,112] In addition, renal hilum compression by visceral fat and increased intra-abdominal pressure have been attributed a role in the RAA axis activation.[113]

Leptin binds to glomerular and mesangial endothelial receptors and stimulates cell proliferation (mesangial-glomerular expansion), synthesis of transforming growth factor β-1, production of type I and IV collagen, and glucose transport.[114] Then, paracrine communication between endothelial and mesangial cells allows leptin to promote an extracellular matrix depot, which in the end causes glomerulosclerosis and concomitant tubulointerstitial injury. It is also worth remembering that MS causes changes in urine composition, with increased levels of uric acid, oxalate and calcium, and a reduction in citrate level, which leads to stone formation.[115]

CONCLUSIONS

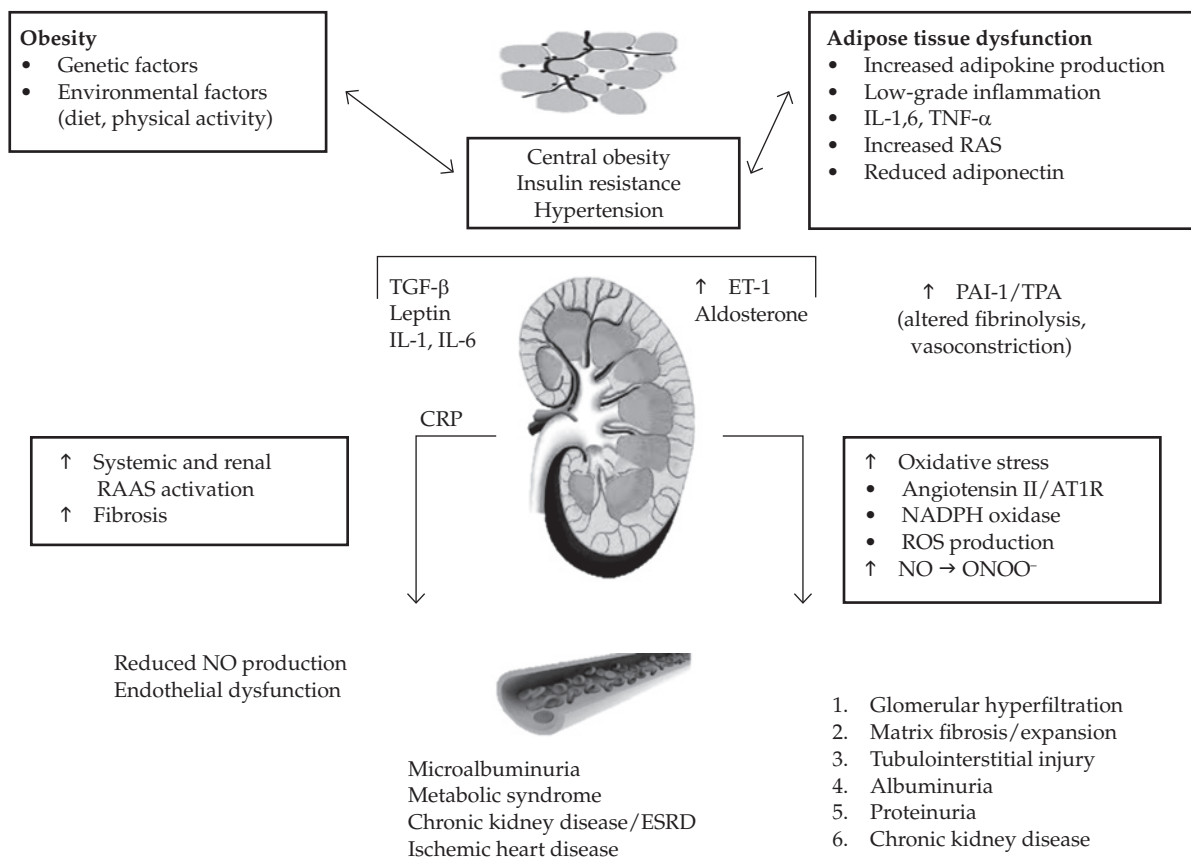Adipose tissue is an endocrine organ that produces several protein hormones. One of

the most common hormones is leptin, whose circulating levels are increased in obese children. Obesity in pediatric patients causes significant pathophysiological effects on different organs and systems and associated conditions, such as chronic inflammation, asthma, arterial hypertension, type 2 diabetes mellitus and chronic kidney disease.

Upon admission to the Intensive Care Unit for varying conditions, obese pediatric patients have a greater number of comorbidities, and this is an additional reason why the medical community and the society should unite to provide effective prevention measures and management to susceptible families. ∎

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Figure 2. *Relationship among obesity, insulin resistance/compensatory hyperinsulinemia, metabolic syndrome components and kidney damage, chronic kidney disease, end-stage renal disease, and cardiovascular disease*

Obesity
• Genetic factors
• Environmental factors (diet, physical activity)

Central obesity
Insulin resistance
Hypertension

Adipose tissue dysfunction
• Increased adipokine production
• Low-grade inflammation
• IL-1,6, TNF-α
• Increased RAS
• Reduced adiponectin

TGF-β
Leptin
IL-1, IL-6

↑ ET-1
Aldosterone

↑ PAI-1/TPA
(altered fibrinolysis, vasoconstriction)

CRP

↑ Systemic and renal RAAS activation
↑ Fibrosis

↑ Oxidative stress
• Angiotensin II/AT1R
• NADPH oxidase
• ROS production
↑ NO → ONOO⁻

Reduced NO production
Endothelial dysfunction

Microalbuminuria
Metabolic syndrome
Chronic kidney disease/ESRD
Ischemic heart disease

1. Glomerular hyperfiltration
2. Matrix fibrosis/expansion
3. Tubulointerstitial injury
4. Albuminuria
5. Proteinuria
6. Chronic kidney disease

Insulin resistance and compensatory hyperinsulinemia cause renin-angiotensin system (RAS) activation, oxidative stress, low-grade chronic systemic inflammation, glomerular hypertension, microalbuminuria, and matrix expansion and fibrosis.
AT1R: angiotensin II type I receptor; CRP: C-reactive protein; ESRD: end-stage renal disease; ET-1: endothelin-1; IL: interleukin; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide; PAI-1: plasminogen activator inhibitor-1; ROS: reactive oxygen species; TGF- : transforming growth factor- ; TNF- : tumor necrosis factor- ; tPA: tissue plasminogen activator; RAAS: renin-angiotensin-aldosterone system; ONOO-: peroxynitrite.

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