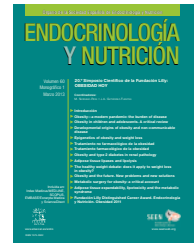




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20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

Obesity and type 2 diabetes in renal pathology

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The western world has recently suffered a worrying increase in the prevalence of obesity, as a result of a sedentary lifestyle and changes in eating habits. Obese people have a higher risk of developing hypertension, coronary disease, insulin resistance, type 2 diabetes and metabolic syndrome. Furthermore, recent studies have also associated chronic kidney disease with obesity. Excess of lipids accumulate in tissues other than adipose tissue contributing to damage through a process called lipotoxicity.

Lipotoxicity is produced by an excess in the intracellular content of nonesterified fatty acids and by the accumulation of toxic products from lipid metabolism, such as diacylglycerols and ceramides. Dysfunction and cell damage caused by the lipotoxicity in different organs are produced by several mechanisms including the generation of reactive oxygen species (ROS), the alteration and/or inhibition of cell signalling pathways and the release of pro-inflammatory and profibrotic factors.¹ This process has been described in multiple tissues including muscle cells, hepatocytes and pancreatic beta cells.²⁻⁵ In 1858, studies suggested for the first time the existence of an association between the presence of lipids and the development of renal pathology. This work described a series of successive stages in metamorphosis of fat, as well as the presence of lipid accumulation in renal epithelium in Bright disease.⁶ Later the work from Kimmelstiel and Wilson⁷ described the pathological signs of nodular sclerosis and also showed the presence of lipid deposits in the kidney from diabetic patients.

Nowadays new evidences suggest that the accumulation of lipids and lipotoxicity might lead to kidney dysfunction. There are several factors involved in renal lipotoxicity and the consequent dysfunction of kidney (Fig. 1). Firstly, the

kidney is affected by dyslipidemia, i.e. an alteration in levels of lipids and lipoproteins in the blood. This alteration could act directly on the kidney and cause deleterious effects due to the accumulation of nonesterified free fatty acids. Indirectly, and due to a systemic inflammation, dyslipidemia may lead to increased oxidative stress and ROS and production/activation of cytokines and hormones associated with renal pathophysiology.

Secondly, renal dysfunction could take place due to the accumulation of lipids at both glomerular and tubular level, basically in the proximal segment. This accumulation of lipids in the kidney is associated with changes in the expression of genes involved in the regulation of lipid metabolism such as SREBP (sterol regulatory element binding protein) and also due to the activation of TGF- β (transforming growth factor- β) pathway by induction of ROS.⁸ These changes in intrarenal lipid metabolism favour kidney damage and show that the kidney is not acting as a passive organ that is only affected by variation that occur at systemic level. It has been observed that, when there is an excess of fatty acids, these are deposited in the kidney in the form of lipid droplets. This process leads to an increase in the intracellular concentration of fatty acids in tubular cells. If this increase exceeds the β -oxidative capacity of mitochondria, the result is an accumulation of triglycerides and the generation of lipid metabolites with potentially toxic effect, such as ceramides. These toxic metabolites could also interfere with mechanisms of cell signaling such as insulin, causing resistance to this hormone.

Finally there are a number of recent studies based on the lipotoxic effect on the podocytes and glomerular filtration barrier. Several studies have shown how segments rich in

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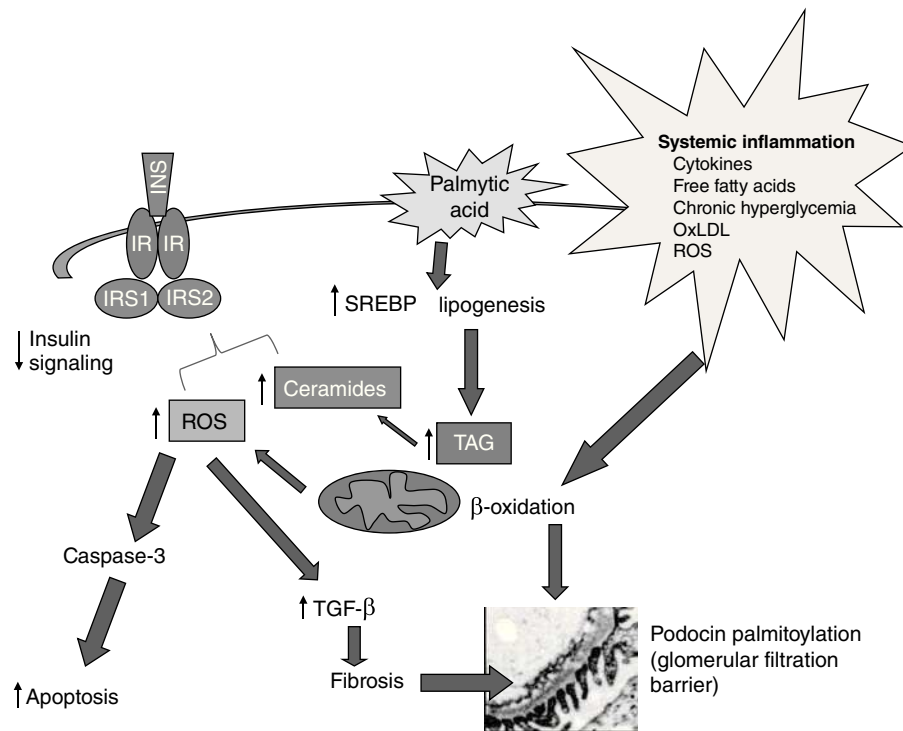


Figure 1 Factors involved in renal lipotoxicity and dysfunction of kidney. INS: insulin; IR: insulin receptor; IRS: insulin receptor substrate; OxLDL: oxidized low-density lipoprotein; ROS: reactive oxygen species; SREBP: sterol regulatory element binding protein; TAG: triacylglycerol; TGF- β : transforming growth factor- β .

cholesterol (lipid rafts) are inserted in the slit diaphragm of podocytes between several proteins such as podocin and nephrin. These lipid rafts help to maintain the union within podocin, nephrin and TRPC-6 (nephrin-transient receptor potential channel 6) in the slit diaphragm. In addition, the podocin suffers a posttranslational modification, a palmitoylation, which maintains its strong interaction with the lipid rafts. The dysregulation of the fatty acid oxidation could affect the process of podocin palmitoylation and therefore, affect the correct insertion into the membrane. An overload of fatty acids could alter the lipid composition of the rafts and interfere with signalling network podocin-nephrin-TRPC-6-actin cytoskeleton to produce a cascade of pathological effects.⁹

Recently it has been shown that the obesity-related glomerulopathy and chronic kidney diseases are complications of obesity. Specifically, the renal effects of obesity in humans and experimental animals include structural and functional adaptations such as the increase in the rate of glomerular filtration ratio (GFR), the increase in the renal blood flow, renal hypertrophy, segmental glomerulosclerosis and glomerulomegalia.

In obese animal models^{10,11} it has been described that there is a lipid accumulation at glomerular and interstitial level, and in the cells of the proximal tubule, accompanied by an increase in the expression of renal SREBP1 and other lipogenic genes. On the other hand it has been shown that a high fat diet induces an elevation of renal triglyceride content in the knockout mouse for SREBP-1c and an increase in the expression of Plasminogen activator inhibitor-1 (PAI-1), Vascular endothelial growth factor (VEGF) and

proteins of the extracellular matrix, in contrast to the control wild type mouse. These data suggest that obesity induced by a high fat diet causes increased renal accumulation of lipids and glomerulosclerosis via a SREBP-1c-dependent pathway.¹²

Treatment with agonists of one of the most important transcription factors in the control of adipogenesis, the Peroxisome proliferator-activated receptor gamma (PPAR γ), attenuates the lipid accumulation and reduces the damage at kidney level. PPAR γ is a member of the nuclear hormone receptors family involved in the regulation of the adipogenic programme. In addition to the adipogenesis control, PPAR γ also has a key role in controlling insulin sensitivity as a therapeutic target for the treatment of type 2 diabetes. This similar effect of attenuation with PPAR agonists is also seen in models of heterozygous mice for PPAR γ , in which a diet with high content of fat induces renal damage.¹⁰

At least there are four transcripts from the mRNAs of PPAR γ which encode two different proteins, PPAR γ 1 and PPAR γ 2. While PPAR γ 1 is expressed in ubiquitous localizations, PPAR γ 2 is expressed exclusively in white and brown adipose tissue in physiological conditions. The lack of both isoforms of PPAR γ produces embryonic lethality due to a lack of placental development.

As described above, various murine models have been generated with partial lack of function of PPAR γ . The PPAR γ 2 knockout (KO) mouse lacks one of the two isoforms of PPAR γ .^{13,14} These mice have not developed an obvious metabolic phenotype in normal conditions, however when crossing them with the genetically leptin deficient obese mouse (ob/ob), the POKO mouse was generated. The

POKO mouse is an example of dissociation between fat and insulin resistance. This mouse has a 10-20% more fat than the wild type mouse, but less than half of the mass of an obese mouse. However, despite being thinner than the obese ob/ob, the POKO mouse presents diabetes and insulin resistance from an early age.¹⁵ The POKO mouse shows: a) hyperphagia; b) insulin resistance; c) hyperglycemia and dyslipidemia at an early age of 4 weeks and complete loss of β -cell at 16 weeks. We investigated the structural and functional changes in the kidneys and blood pressure in POKO mice.¹⁶ At 4 weeks of age, these animals exhibited a significant increase in blood pressure, a higher urinary albumin/creatinine rate similar to ob/ob mice, but a significant increase in the renal hypertrophy ratio compared with their obese littermates. Additionally, POKO mouse showed an incipient glomerular damage associated with a significant increase in the renal expression of the parathyroid hormone related protein (PTHrP), TGF- β and other related factors of inflammation and fibrosis such as monocyte chemo-attractant protein (MCP-1) and collagen IV. These data suggest an accelerated lesion through the glucolipotoxic effects in the renal pathology associated with the metabolic syndrome and insulin resistance in POKO mice.¹⁶

Conflicts of interest

The author declares that she has no conflicts of interest in this article.

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