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Alteraciones metabólicas en tejido adiposo y riñón durante el envejecimiento: papel de la restricción calórica.

Metabolic alterations on adipose tissue and kidney during aging: role of caloric restriction.

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Metabolic alterations on adipose tissue and kidney during aging: role of caloric restriction.

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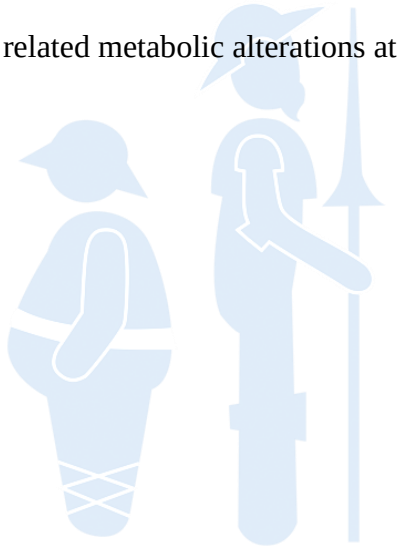
Abstract.

Aging is considered a progressive decline in the physiological functions of the organism, and it is related to the development of insulin resistance, as well as other metabolic complications. Aging progression is associated with an increase, redistribution and functional atrophy of adipose tissue, which may affect the functionality of other organs and tissues, including the kidney. The study of the alterations at early stages of aging may help identify mechanisms and potential biomarkers for a better understanding of the aging process. Caloric restriction, without malnutrition, could be considered a non-pharmacological intervention capable of attenuating insulin resistance and other age-related metabolic alterations at early stages of aging.



Introduction.

Aging is a physiological process of general decay of the organism that finally ends with the death of the individual. During the last years, some cellular and molecular characteristics related to the aging process have been identified. One of these hallmarks is the alteration of the metabolic pathways involved in nutrient uptake, such as the deregulation of insulin signaling [1].

Aging is the result of two phenomena, the organism wear, and the inability to regulate such wear. The control or balance of these two factors will determine, to a greater or lesser extent, the impact of aging on the organism and therefore, the appearance of age-related diseases as well as the lifespan. Specifically, aging is associated with an increased risk of developing Metabolic syndrome-related disorders, such as obesity or insulin resistance (IR), which are further exacerbated with age [2]. Along this line, the kidney experiences a progressive functional deterioration during aging, which is accentuated by systemic comorbities such as obesity, and which predispose to the development of chronic kidney disease (CKD). In this review, we summarize the alterations occurring in adipose tissue and the kidney and their association with the development of IR and CKD during aging (Figure 1).

White adipose tissue as one of the main tissues involved in the aging decline.

Aging is associated with changes in body composition, and characterized by an increased adiposity, a topographic redistribution of adipose tissue, as well as by a decline in the functionality of this tissue [3,4]. Differences in the pattern of adiposity distribution have been described from early stages of aging [5], mainly resulting in a redistribution of fat from subcutaneous to visceral white adipose tissue [5–7]. Therefore, the amount of adipose tissue is not the only factor that contributes to the development of metabolic alterations,

but where it accumulates is also key to determining and preventing these alterations. Thus, adipose tissue plays a very important role in the appearance of IR during aging.

The increase in adiposity and the redistribution of adipose tissue during aging may be aggravated in an overweight or obese state, due to the ectopic accumulation of lipids in other tissues, as a result of an impaired adipose tissue expandability, and the consequent phenomenon known as lipotoxicity. During aging, adipocytes progressively lose their ability to store lipids, i.e., adipose tissue expandability decreases [8]. This failure of adipose tissue expandability with aging is exacerbated by a decrease in adipogenesis, an increase in adipocyte senescence, inhibition of angiogenesis, as well as an altered secretion of adipose tissue-specific adipokines and the development of fibrosis and chronic inflammation in this tissue. The expandability of adipose tissue is the individual-specific capacity of this tissue to expand [8], being decisive in the development of metabolic complications derived from the increase in white adipose tissue. Therefore, the expandability theory proposes that adipose tissue has a lipid expansion and storage limit for each individual that, once exceeded, causes a net flow of these excess lipids to other peripheral tissues such as the liver, the muscle, the pancreas or the kidney -organs not purposely designed to be a main storage compartment-, where they accumulate fat ectopically. These excess of lipids enter alternative non-oxidative pathways when the limited triacylglycerol buffer capacity becomes saturated that results in production of toxic reactive lipid species and which has been related to IR [8].

Overall, the lack of adipose tissue expandability, together with the resulting lipotoxicity in other metabolically relevant organs, favors the development of age-related IR and other organ-specific toxic responses leading to apoptosis [3,6,7]. A positive energy balance increases prevalence of chronic diseases like type 2 diabetes, fatty liver and cardiovascular disease, which also substantially increase in prevalence with age.

Age-related kidney function decline.

During aging, the kidney undergoes physiological changes that result in a decrease in its functionality [9]. These alterations are aggravated by systemic comorbidities such as hypertension, diabetes and obesity, which further predispose to the development of CKD.

Renal function decline during the aging process is characterized by a drop in glomerular filtration rate (GFR). Some studies have described a loss of functional nephrons with age. Thus, the remaining nephrons hypertrophy as a compensatory mechanism to maintain a correct glomerular filtration. Consequently, a proportion of podocytes, which are essential cells for the maintenance of the glomerular filtration barrier (GFB), are lost. Podocytes are differentiated cells, with a minimal turnover rate, so that the remaining podocytes hypertrophy to cover the entire expanded glomerular surface. The stress generated due to this compensatory hypertrophy induces the detachment of podocytes from the glomerular capillaries [10]. The loss and injury of podocytes directly induce damage to the GFB, leading to proteinuria and the development of CKD [11]. Moreover, the production of profibrotic signals during this process induce the deposition of extracellular matrix in the nephron, leading to glomerulosclerosis and tubulointerstitial fibrosis [9,10,12].

Although the consequences of nephron loss with age are well known, the causes and the molecular mechanisms involved in these alterations have not been fully described. Some of the proposals regarding the development of age-associated CKD include alterations in the senescence and/or apoptosis pathways of glomerular and tubular cells, as well as the chronic pro-inflammatory environment associated with aging, which is considered one of the main contributing factors to the progression of kidney disease [9].

In recent years, an important role for adipose tissue in the age-related renal dysfunction has been proposed. Specifically, the accumulation of visceral fat is associated with an increase in the urine albumin-creatinine ratio (ACR) [13]. The deregulation in visceral fat mass accretion is obvious during obesity, and it has been reported to lead to a disease known as obesity-related glomerulopathy (ORG). Nevertheless, the aforementioned ectopic fat accretion that occurs with aging contributes significantly to kidney damage. Thus, already in mild glomerulopathies, the accumulation of lipid droplets is observed both in the glomeruli and in the tubular epithelial cells. Lipid accumulation in podocytes is directly related to the IR of these cells since insulin signaling is essential for their survival [10]. Furthermore, mesangial cells can uptake and store triglycerides. Lipotoxicity favors that these cells transform into "foam" cells, loaded with excess lipids, which alters their function. This results in the deprotection and rarefaction of the glomerular capillaries. In addition to being associated with interstitial fibrosis, the involvement of tubular cells in a pro-obesogenic environment, such as aging, induces an increase in renal gluconeogenesis and contributes greatly to the hyperglycemia observed in this situation [10].

Caloric restriction as a strategy to ameliorate the deleterious effects of aging.

Physiological mechanisms that ensure efficient usage of energy could be targets to prevent the deleterious effects of lipotoxicity during aging. Three therapeutic strategies could be used to minimize the effects of aging- induced lipotoxicity: i) to decrease energy availability through decreased food intake, ii) to increase adipose tissue expandability and/or iii) to increase fat oxidation in peripheral organs.

As first strategy, the benefits of caloric restriction (CR) without malnutrition as a non-pharmacological intervention in the treatment of different pathologies have been largely

described. CR delays the development of age-related disorders such as IR [6,7] and kidney injury [11,14] (Figure 1).

CR decreases body weight, reduces adiposity, improves adipocyte functionality and adipose tissue plasticity, and restores adipokine secretion. It also improves serum glucose and insulin levels and overall insulin sensitivity, and reverses the chronic pro-inflammatory phenotype of aging [7]. Specifically in subcutaneous adipose tissue, CR could reverse IR at early stages of aging. In this context, CR could be an effective strategy to improve metabolic health during aging.

In addition, a benefit in CKD progression associated to body weight loss after bariatric surgery has already been reported [15]. In the kidney, CR prevents glomerular hypertrophy and specifically podocyte hypertrophy, glomerulosclerosis and podocyte stress and loss. At the molecular level, CR ameliorates mitochondrial damage, decreasing free radical production and oxidative stress, and partially increases autophagic activity in aged mice kidneys [9,14], all these contributing to the alleviation of age-related changes in the kidney.

Conclusions

Aging implies a progressive and physiological deterioration of the organism and, consequently, the development of metabolic alterations. The age-associated impairment of adipose tissue functionality and expandability, and the resulting lipotoxicity, leads to complications such as IR, which may be mediated by different mechanisms, which affect adipocyte functionality and adipokine secretion. In the kidney, alterations due to aging, such as loss of podocyte barrier function, may determine the development of CKD. CR could be considered an efficient intervention to prevent or ameliorate the deleterious effects of aging.

Author contributions

PC, MMT, RVB and GMG wrote the manuscript.

Conflict of interest

The authors declare no competing interests.

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Figure legend

Figure 1. Summary of the effects of aging on adipose tissue and kidney and their modulation by caloric restriction. During aging, adipose tissue shows altered adipokine secretion, decreased adipogenesis, increased inflammation and fibrosis, as well as increased adipocyte hypertrophy. This adipocyte hypertrophy corresponds to an increased accumulation of fatty acids, exceeding the expandability limit of the tissue, so that fatty acids (FAs) accumulate ectopically in other tissues (a phenomenon known as lipotoxicity) such as the kidney. In addition to lipotoxicity, there is also increased inflammation and fibrosis in the kidney, along with podocyte hypertrophy. This podocyte hypertrophy results in podocyte detachment, and thus loss of the glomerular filtration barrier, leading to proteinuria. Altogether, the consequences of aging in adipose tissue and kidney lead to insulin resistance and chronic kidney disease. All these effects can be modulated by caloric restriction, which can be considered an effective intervention to ameliorate the detrimental effects of aging.