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The Renal Pathology of Obesity

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Obesity causes various structural, hemodynamic, and metabolic alterations in the kidney. Most of these are likely to be compensatory responses to the systemic increase in metabolic demand that is seen with obesity. In some cases, however, renal injury becomes clinically apparent as a result of compensatory failure. Obesity-related glomerulopathy is the best known of such disease states. Factors that may sensitize obese individuals to renal compensatory failure and associated injury include the severity and number of obesity-associated conditions or complications, including components of metabolic syndrome, and the mismatch of body size to nephron mass, due to nephron reductions of congenital or acquired origin.

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With the worldwide epidemic of obesity, the increase in obesity-related complications is becoming a serious socioeconomic problem.[1–3] The kidney may exhibit health disorders related to obesity. Obesity not only increases the risk of progression of preexisting renal diseases but is itself also an independent risk factor of renal injury.[4,5] Obesity-related glomerulopathy (ORG) is the best-known renal disease secondary to obesity. From observation of this unique disease state, significant knowledge has accumulated regarding the clinicopathological characteristics of renal injury in obesity.[6–9] Importantly, however, there is a large difference between the fraction of the general population that is obese and the fraction that actually develops renal impairment. In addition, the severity of obesity-related renal impairment is not necessarily related to the severity of obesity. Thus, it is conceivable that obesity is not the sole factor causing obesity-related renal injury, and that there may be additional or predisposing factors that explain the considerable differences among individuals in susceptibility to renal injury due to obesity.

In this review, we will outline (i) the renal structural, hemodynamic, and metabolic alterations in obesity and obesity-related renal impairment; (ii) the clinicopathological features of renal injury associated with obesity (primarily in ORG); and (iii) the potential additional or predisposing factors that may sensitize patients to renal structural or functional compensatory failure and subsequent injury.

Renal Alterations in Obesity or Obesity-Related Renal Impairment

Kidney Weight

Studies of adult autopsies have shown that kidney weight increases with increasing body mass index (BMI).[10] The weight of kidneys from autopsies of obese individuals has been found to be significantly greater than those of normal-weight controls.[11] An autopsy study of obese children who died in traumatic accidents found that the weights of all organs except the brain, including the heart, kidneys, pancreas, liver and spleen, were heavier than those of height-, age-, and sex-matched control children.[12] Although the mechanism of increased kidney weight in obesity is unknown, it may be related to compensatory hypertrophy of individual nephrons, as a result of increased tubular and glomerular functions associated with obesity. In addition, intracellular or extracellular accumulation of fluid and lipid components may contribute to the increased weight of the obese kidney.

Glomerular Hypertrophy

Numerous morphometric studies of factors related to glomerular size have been performed, using autopsies or biopsies of nondiseased and diseased kidneys.[13–16] It has been consistently observed in many of these

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studies that body size, especially as defined by obesity or BMI, is 1 of the most important determinants of glomerular size. In obese subjects, glomerular sizes are larger, even in the absence of apparent renal disease or injury.[13–15] Glomerular hypertrophy in obesity may be largely attributable to compensatory changes accompanying glomerular hyperfiltration. Glomerular hyperfiltration can be reduced in obese subjects by weight loss, but it has not been clarified whether glomerular size decreases during such "backtracking" of glomerular function. Although the increases in glomerular size found in obese subjects may be due in part to an increase in the number of glomerular capillaries, no previous study has directly tested this hypothesis in humans.

Tubular Hypertrophy

Compared with those of the glomeruli, there have been very few studies of structural alterations in renal tubules associated with obesity. Morphometric analysis may be hampered by the structural complexity of renal tubules. A study of biopsy samples from proteinuric obese patients found that the cross-sectional area of proximal tubular epithelial cells was 33% larger, and the proximal tubular lumen 54% larger, than in proteinuric nonobese patients.[17]

Hemodynamic Changes

It is known that changes in intrarenal hemodynamics are characteristic of obesity. Previous animal experiments and intervention studies in obese subjects have demonstrated that renal plasma flow (RPF) and glomerular filtration rate (GFR) both increase with obesity.[18–21] Renal tubular overload in obesity is characterized by an increase in the filtration fraction (GFR/RPF), and may stimulate sodium and water reabsorption in the proximal tubules, resulting in decreased pre-glomerular vascular resistance via the tubuloglomerular feedback mechanism.[22] A dilation of the glomerular afferent arterioles leads to a further increase in the GFR (glomerular hyperfiltration). Although the origin of such a vicious circle between increased salt reabsorption in the tubules and glomerular hyperfiltration remains unclear, such alterations in renal hemodynamics may constitute the most important pathophysiological basis for the renal abnormalities of obesity (Figure 1). Consistent with this hypothesis, cetazolamide, a carbonic anhydrase inhibitor that inhibits salt reabsorption in the proximal tubule, has been shown to reduce GFR in obese nondiabetic subjects.[23]

Obesity is often accompanied by systemic hypertension, via several mechanisms.[24] Systemic hypertension caused by obesity additionally increases glomerular blood flow through the dilated AAs, with

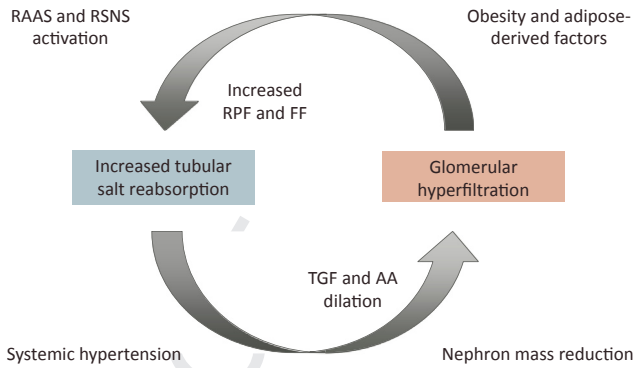

Figure 1. Hemodynamic abnormalities and factors promoting obesity-related renal injury. Renal plasma flow (RPF) and glomerular filtration rate (GFR) increase in obesity. Such renal tubular overload in obesity is characterized by an increase in the filtration fraction (FF: GFR/RPF), and may stimulate sodium and water reabsorption in the proximal tubules, decreasing preglomerular vascular resistance via tubuloglomerular feedback (TGF). A dilation of the glomerular afferent arterioles (AAs) leads to a further increase in GFR, that is, glomerular hyperfiltration. Various factors associated with obesity, including adipose-derived factors, activation of the renin–angiotensin–aldosterone system (RAAS) and renal sympathetic nervous system (RSNS), systemic hypertension, and nephron mass reduction, constitute and promote this vicious circle.

reduced autoregulatory capacity, and promotes irreversible arteriolosclerotic changes that further promote glomerular hypertension and hyperfiltration.

Increased Salt Sensitivity

The changes in renal hemodynamics found in obesity are closely linked to increased salt sensitivity.[25] In fact, compared to lean subjects, obese subjects are more likely to develop salt-sensitive hypertension and proteinuria from excessive salt intake.[26,27] One important mechanism by which salt sensitivity is increased with obesity is an activation of the intrarenal renin–angiotensin–aldosterone system (RAAS).[28,29] Activation of renal sympathetic nerves may also be implicated in the increased salt reabsorption seen in obesity.[30,31]

RAAS Activation

Adipose tissue is known to contain all components of the RAAS system, and activation of this system occurs in obese adipose tissue.[32,33] Production of angiotensinogen, aldosterone, and aldosterone-stimulating factor is increased in obese adipocytes.[34–36] Plasma aldosterone concentrations in obese subjects are high, correlated with visceral fat mass, and decreased by weight loss.[37,38]

In obese individuals, the RAAS is activated in renal tissue, and increases sodium reabsorption by several mechanisms.[39–41] A prospective crossover study conducted in obese patients with proteinuria showed that therapy with an aldosterone antagonist more

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