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The Pathological Mechanisms of Obesity-Related Glomerulopathy: A review article

Ali A. Kasim*[,1] and Ahmed H. Ataimish**

*Department of Clinical Laboratory Sciences, College of Pharmacy, University of Baghdad; Baghdad-Iraq
** Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad; Baghdad-Iraq

Abstract

The rising prevalence of obesity-related glomerulopathy (ORG) occurs in concordance with the rising prevalence of obesity worldwide. Clinically ORG is manifested by slowly progressing microalbuminuria that may develop to clinically evident proteinuria. Pathological characteristics of ORG include; glomerular hypertrophy in the presence or absence of focal segmental glomerulosclerosis (FSGS). ORG can develop into clinically overt chronic renal insufficiency or even end-stage kidney disease. This article reviews the most important mechanisms involved in the development of ORG; that are related to alteration of renal hemodynamics, stimulation of renin-angiotensin-aldosterone system (RAAS), impairment of insulin sensitivity, ectopic lipid deposition, adipose tissue cytokine disorder and local renal micro-inflammation.

Keywords: Obesity-related glomerulopathy, Renin-angiotensin-aldosterone system, Insulin resistance

الاليات المرضية لاعتلال الكبيبات البولية المرتبط بالسمنة : مقال مراجعة

علي عبد الحسين قاسم *،١ و احمد حامد اطيمش**

* فرع العلوم المختبرية السريرية ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق .
**فرع العلوم المختبرية السريرية ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق .

الخلاصة

إن الانتشار المتزايد لاعتلال الكبيبات البولية المرتبط بالسمنة يحدث بالتوافق مع انتشار السمنة في جميع أنحاء العالم .سريريًا يتجلى اعتلال الكبيبات البولية المرتبط بالسمنة بحدوث البيلة الألبومينية الدقيقة بطيئة التقدم والتي قد تتطور إلى بيلة بروتينية ظاهرة سريريًا. تشمل الخصائص المرضية لاعتلال الكبيبات البولية المرتبط بالسمنة تضخم الكبيبات البولية بوجود أو بانعدام وجود تصلب كبيبات مقطعي بؤري. ويمكن أن يتطور هذا الاعتلال إلى قصور كلوي مزمن واضح سريريًا أو حتى المرحلة النهائية لمرض الكلى.

هذه المقالة تستعرض أهم الآليات لتطور اعتلال الكبيبات البولية المرتبط بالسمنة؛ وتشمل ديناميكا الدم الكلوية غير الطبيعية، وتحفيز نظام الرينين - أنجيوتنسين - ألدوستيرون ، وضعف حساسية الأنسولين ، وترسب الدهون خارج النسيج الدهني ، واضطراب سايتوكينات النسيج الدهني واخيرا الالتهاب الدقيق الموضعي الكلوي.

الكلمات المفتاحية: اعتلال الكبيبات البولية المرتبط بالسمنة، نظام رينين- أنجيوتنسين- ألدوستيرون؛ مقاومة الأنسولين ، اضطرابات التمثيل الغذائي للدهون، الالتهاب

Introduction

Obesity represents a global public health problem. According to the World Health Organization (WHO) estimations in 2016, the overweight population worldwide accounted for approximately 1.9 billion adults, of which approximately 650 million are obese (1). Obesity is not just over nutrition, but it is closely related to many diseases.

Pathologically, ORG is usually manifested by glomerular hypertrophy, with focal segmental glomerulosclerosis (FSGS), occurring in obese individuals (2). ORG usually has an insidious onset, manifested by slowly progressing microalbuminuria or clinically evident proteinuria, with or without impairment of renal function, and a small number of patients have microscopic hematuria or nephrotic syndrome (3).

The prevalence of obesity-related glomerulopathy (ORG) increases in parallel with the increasing prevalence of obesity (3). The incidence of ORG is not well documented due to the variation in renal biopsy policy between different countries, and because ORG can occur without overt signs or symptoms (4). Keeping in mind that in obese patients with diabetes mellitus, it cannot be determined whether diabetes or obesity is the principal cause of proteinuria. In a large-scale retrospective study evaluating kidney biopsies, Kambham et al. has recorded a tenfold increase in the prevalence of ORG over 15 years (5).

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[1] Corresponding author E-mail: ali.qasem@copharm.uobaghdad.edu.iq
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Obesity is involved as an independent risk factor in the development of chronic kidney disease (CKD) (6), thus, ORG has attracted increasing attention. This article discusses the pathogenesis of ORG.

Pathogenesis of ORG

Several mechanisms may contribute to the development of ORG; and these mechanisms are mostly interconnected:

Alteration of renal hemodynamics

Obesity alters the renal blood flow; both the glomerular filtration rate (GFR) and the filtration fraction increases in obese individuals regardless of blood pressure (7). The elevated GFR and filtration fraction increases protein concentration in the post-glomerular peritubular capillaries with the subsequent increase in oncotic pressure within these capillaries, and hence, increases sodium reabsorption from the proximal tubules (7). Moreover, increased activity of the renin-angiotensin-aldosterone system (RAAS) is reported in obese individuals (8-10); an effect that is mediated by increased synthesis of renin and renin precursors by adipose tissue (8). Angiotensin II promotes luminal Na^+-H^+ exchange and basolateral Na^+-K^+ ATPase action, activating the epithelial sodium channel (ENaC), with the subsequent increase in sodium reabsorption (11). Sodium reabsorption diminishes solute transfer to macula densa leading to inactivation of the tubuloglomerular feedback and dilation of the glomerular afferent arterioles, i.e. increasing GFR (12). In addition to its effect on proximal tubular sodium reabsorption, angiotensin II has direct vasoconstrictor effect on the glomerular arterioles. The vasoconstrictor effect of angiotensin II on the efferent arteriole is greater than the afferent arteriole, increasing the GFR. In addition, other dietary factors such as high-salt diet and high-protein diet may increase GFR in obese patients (13). Finally, visceral adiposity imposes physical pressure on the visceral organs including the kidneys, with the consequence of elevated intrarenal pressure that compresses the loop of Henle and peritubular capillaries reducing the flow of glomerular filtrate through the renal tubules promoting sodium reabsorption by them(14, 15).

Long-term high perfusion and high filtration increase the pressure within the glomerular capillaries, and thus, endothelial cells, epithelial cells and mesangial cells damage, which further leads to proteinuria, glomerular hypertrophy, segmental sclerosis, and interstitial fibrosis. This can be mediated by a variety of transmitters, including angiotensin II, angiotensin receptor (ATR), transforming growth factor beta (TGF-beta), TGF-β receptor and phospholipase D (16).

Renin-Angiotensin-Aldosterone System activation

As discussed earlier RAAS is overactivated in obese individuals (8-10), and beside the aforementioned effects of this system on renal perfusion, it participates in renal endothelial cell dysfunction and proteinuria, increased inflammation and tissue fibrosis. These detrimental effects are mediated by several mediators such as matrix metalloproteases, cyclooxygenase 2 (COX-2), endothelial nitric oxide synthase (eNOS), reactive oxygen species (ROS), and many cytokines (17-22).

Insulin resistance

Several hypotheses were proposed to explain the link between obesity and insulin resistance, such as inflammation, mitochondrial dysfunction, lipotoxicity and most importantly hyperinsulinemia. These entire hypotheses are centered on interrupting of insulin signaling (23, 24).

In insulin resistance, the body secretes compensatively elevated levels of insulin. Hyperinsulinemia has been reported to promote the synthesis of growth factors including insulin-like growth factor-1 (IGF-1) and IGF-2 and transforming growth factor-β_1 (TGF-β_1), which hasten extracellular matrix deposition aiding in glomerular hypertrophy and fibrosis (25, 26). Moreover, hyperinsulinemia increases renal tubular reabsorption of uric acid via GLUT9 transporter (27). Also, hyperinsulinemia stimulates hepatic lipoprotein synthesis resulting in hyperlipidemia with the subsequent increase in the need for NADPH that is met by the de novo purine nucleotide synthesis, speeding uric acid production (28). Hyperuricemia contributes to renal inflammation (29, 30), vascular endothelial dysfunction (31, 32), fibrosis (33), glomerulosclerosis (34, 35) and proteinuria (36, 37).

Binding of insulin to its receptor on the podocytes is essential to regulate morphological adaptation of podocytes in response to changes in capillary pressure and GFR after meal (38). Accumulation of non-esterified fatty acids (NEFA) in podocytes in obese individuals impairs insulin signaling and induces apoptosis. The remaining podocytes become hypertrophic to compensate for the destroyed ones (39, 40). Renal gluconeogenesis is activated in the context of insulin resistance. In response to the renal hemodynamic and metabolic changes in obesity, the proximal tubules become hypertrophic (41); an effect mediated by the activation of mammalian target of rapamycin complex 1 (mTORC1) in the proximal tubules cells. Insulin activation mTORC1, promote lipid synthesis, angiogenesis, protein synthesis, cellular growth (42). Chen *et al.* has reported that the homeostatic model assessment of insulin resistance (HOMA-IR) index, the most commonly used measure of insulin resistance, to be significantly correlated with the prevalence of ORG and with proteinuria; and suggested the screening for this index as predictive marker for renal damage in obese individuals (43).

Ectopic lipid deposition

Ectopic lipid deposition within mesangial cells results in foam cell formation and glomerular hypertrophy. Mesangial cells are exposed lipoproteins as no basement membrane separates them from the glomerular endothelium (40). Endothelial dysfunction results in lipoprotein outflow to mesangial cells; beside, the phagocytic functions of mesangial cells that make them engulf various lipid particles. Lipoproteins enter mesangial cells via binding to the low-density lipoprotein (LDL) receptors, while, long-chain fatty acids enter via scavenger receptors (44). Lipoprotein lipase hydrolyzes lipoproteins releasing triacylglycerols (45). LDL receptor feedback, which important in preventing cellular cholesterol accumulation, is disrupted by the micro-inflammatory status in obesity, causing unrestricted lipid buildup (46). The deposited lipids in mesangial cells result in the formation of foam cells and loss of contractile function, leading to reduced structural integrity of glomerular arterioles and glomerular hypertrophy (40).

Lipid deposition in podocytes and proximal tubular cells due to the impairment of insulin signaling is discussed above.

Adipose tissue cytokines disorder

The function of adipose tissue is not limited to lipid storage and energy supply; it is considered as an endocrine organ that secretes many cytokines (adipokines) involved in regulation many biological functions and implicated in the pathogenesis of several organ specific diseases, including renal diseases (47). The adipo-renal axis is important for normal renal functions along with the response of the kidney to injury. Obesity is associated with dysregulated synthesis and release of a number of adipokines (48). Many of these adipokines have been reported to disrupt renal cells' functions in vitro, which might mediate ORG (49, 50).

Adipokines whether those produced by the peripheral adipose tissue or those produced by the renal adipose tissue contribute to ORG in obese patients. Leptin and adiponectin have both non-inflammatory and inflammatory roles in this regard. The roles of pro-inflammatory adipokines will be discussed separately with the role of micro-inflammation in ORG.

Leptin is mainly produced by white adipose tissue, and acts to regulate energy-related metabolism. Obese individuals are in a state of hyperleptinemia and leptin resistance that are shown to be independently associated with insulin resistance (51). Both indirect and direct actions of leptin contributes to the development of ORG in obese individuals. Binding of leptin to its functional brain receptor (Ob-Rb) activates the sympathetic nervous system, increasing blood pressure, renal blood flow and GFR (52, 53). While, binding of leptin with glomerular leptin receptor (Ob-Ra), increases expression of glomerular transforming growth factor-β1 (TGF-β1), leading to an increase in the synthesis of type IV collagen in extracellular matrix, promoting fibrosis and glomerulosclerosis (54). Furthermore, leptin has significant pro-inflammatory actions; it regulates cells involved in both innate and adaptive immune responses, including monocytes/macrophages and T-cells (55). Leptin enhances macrophage infiltration to the kidneys (56), and central T-cell production along with peripheral shift toward the pro-inflammatory T helper-1 (Th1) adaptive immune responses (57). Meanwhile, leptin enhances T-cell survival and promotes production of pro-inflammatory cytokines (58). In addition, leptin structurally and functionally resembles pro-inflammatory cytokines, such as interleukin-6 (IL-6) (55). Finally, it binds to C-reactive protein (CRP) and may modulate its activity (59). CRP is an inflammatory mediator involved in the initiation and progression of atherosclerosis and renal disease (60).

Adiponectin is an adipokines with protective properties; it has anti-inflammatory, anti-atherogenic and insulin sensitization effects (61). Adiponectin levels has been reported to be lower in overweight and obese individuals compared to normal weight individuals, and levels are negatively correlated with increased visceral fat (62, 63). Adiponectin helps to maintain structural integrity of podocytes (64). Kim *et al.* showed that binding of adiponectin to its intrarenal receptor (AdipoR1), improves oxidative stress status and inhibits podocytes apoptosis by ameliorating the intracellular pathways associated with lipid deposition and endothelial dysfunction (64).

Moreover, adiponectin is suggested to have significant anti-inflammatory effects by the suppression of tumor necrosis factor-α (TNF-α) production with the subsequent prevention of nuclear factor-*κ*B (NF-*κ*B) activation (65). Adiponectin also inhibits the expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) (66), hence decreasing monocyte adhesion to endothelial cells as well as macrophage-induced cytokine production (67). Moreover, adiponectin is inversely correlated with CRP expression in human adipose tissue (68).

The role of micro-inflammation

Obesity has been considered a state of chronic low-grade inflammation (69). Adiposity induces an inflammatory microenvironment in the kidneys. Adipose tissue of obese individuals is highly infiltrated by macrophages (70), and it has been estimated that macrophages are roughly accounting for 40% of the total cells within *adipose* tissue of obese individuals (71). Adipose tissue macrophages contribute to key regulatory physiological functions such as tissue remodeling

(72), and insulin sensitivity (73). Macrophages secrete both anti- and pro-inflammatory cytokines (74). Anti-inflammatory cytokines secreted by adipose tissue macrophages such as IL-4 and IL-10 conserve insulin sensitivity by neutralizing inflammatory responses (73). Macrophages also secrete pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-12 CRP, monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1) in response to inflammatory stimuli. With progressive obesity and adipocytes hypertrophy, adipose tissue macrophages secrete chemoattractants, such as MCP-1 that recruits more macrophages to renal adipose tissue. Pro-inflammatory cytokines promote a microenvironment of chronic low-grade inflammation and insulin resistance in the kidneys (75).

Macrophages and adipocytes communicate with each other via different mediators. For example, fatty acids released from adipocytes stimulate macrophages for the secretion of TNF-α which increases IL-6 secretion by adipocytes. Both TNF-α and IL-6 are pro-inflammatory cytokines that amplify inflammation in the kidneys as well as in the adipose tissues (76).

Moreover, TNF-α plays an important role in the development of renal fibrosis (77). It was found that the expressions of TNF-α and its receptor is enhanced in renal biopsy samples collected from ORG patients, referring to a potential role of TNF-α in the pathogenesis of ORG (78). Systemically, IL-6 is mainly produced by adipose tissue, while it is produced by macrophages in the kidney (79). IL-6 is also suggested to be a risk factor of renal injury in obese individuals as glomeruli from ORG patients showed increased expression of IL-6 signal transducer (80).

Conclusion

Obesity contributes to hemodynamic and structural changes in the renal system. Pathogenesis of obesity-related glomerulopathy is multifactorial, and the mechanisms involved are mostly interconnected.

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