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

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 may have microscopic hematuria or nephrotic syndrome (3).

The prevalence of obesity-related glomerulopathy (ORG) increases in parallel with the increasing prevalence of obesity (4). 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 (5). 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).

1Corresponding author E-mail: ali.qasem@copharm.uobaghdad.edu.iq
Received: 27/9/2020
Accepted: 14/11/2020

Iraqi Journal of Pharmaceutical Science
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 (9). 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-β1 (TGF-β1), 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 to lipoproteins as no basement membrane separates them from the glomerular endothelium (46). 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 (46).

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, antiatherogenic and insulin sensitization effects (63). Adiponectin levels have 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-κB (NF-κB) 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
Macrophages secrete both anti-inflammatory cytokines (74). Anti-inflammatory cytokines secreted by adipose tissue macrophages such as IL-6 and IL-10 conserve insulin sensitivity by neutralizing inflammatory responses (75). 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 (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.

References
1. World Health Organization. WHO Media Centre. Obesity and overweight: fact sheet (No. 311). [Internet]. 2015 [cited September 2020]. Available from: www.who.int/mediacentre/factsheets/fs311/en/.
2. Xu T, Sheng Z, Yao L. Obesity-related glomerulopathy: pathogenesis, pathologic, clinical characteristics and treatment. Frontiers of medicine. 2017;11(3):340-8.
3. Yang S, Cao C, Deng T, Zhou Z. Obesity-Related Glomerulopathy: A Latent Change in Obesity Requiring More Attention. Kidney and Blood Pressure Research. 2020;45(4):510-22.
4. Serra A, Romero R, Lopez D, Navarro M, Esteve A, Perez N, et al. Renal injury in the extremely obese patients with normal renal function. Kidney international. 2008;73(8):947-55.
5. Kambham N, Markowitz GS, Valeri AM, Lin J, D’Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney international. 2001;59(4):1498-509.
6. Rhee CM, Ahmadi S-F, Kalantar-Zadeh K. The dual roles of obesity in chronic kidney disease: a review of the current literature. Curr Opin Nephrol Hypertens. 2016;25(3):208-16.
7. Chagnac A, Herman M, Zingerman B, Erman A, Rozen-Zvi B, Hirsh J, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2008;23(12):3946-52.
8. Schütten MTJ, Houben AJHM, Leeuw PWd, Stehouwer CDA. The Link Between Adipose Tissue Renin-Angiotensin-Aldosterone System Signaling and Obesity-Associated Hypertension. Physiology. 2017;32(3):197-209.
9. Cabandugama PK, Gardner MJ, Sowers JR. The Renin Angiotensin Aldosterone System in Obesity and Hypertension: Roles in the Cardiorespiratory and Metabolic Syndrome. Med Clin North Am. 2017;101(1):129-37.
10. Kawarazaki W, Fujita T. The Role of Aldosterone in Obesity-Related Hypertension. American Journal of Hypertension. 2016;29(4):415-23.
11. Cogan MG. Angiotensin II: a powerful controller of sodium transport in the early proximal tubule. Hypertension (Dallas, Tex : 1979). 1990;15(5):451-8.
12. Lorenz JN, Greenberg SG, Briggs JP. The macula densa mechanism for control of renin secretion. Seminars in nephrology. 1993;13(6):531-42.
13. Ogna A, Forni Ongi V, Bochud M, Guesossi I, Paccaud F, Burnier M, et al. Association between obesity and glomerular hyperfiltration: the confounding effect of smoking and sodium and protein intakes. European journal of nutrition. 2016;55(3):1089-97.
14. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE. Obesity, hypertension, and chronic kidney disease. International journal of nephrology and renovascular disease. 2014;7:75-88.
15. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal
mechanisms. Circulation research. 2015;116(6):991-1006.
16. Kriz W, Lemley KV. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. Journal of the American Society of Nephrology : JASN. 2015;26(2):258-69.
17. Butler MJ, Ramnath R, Kadoya H, Desposito D, Riquier-Brison A, Ferguson JK, et al. Aldosterone induces albuminuria via matrix metalloproteinase-dependent damage of the endothelial glyocalyx. Kidney international. 2019;95(1):94-107.
18. Gawrys J, Gawrys K, Szahidewicz-Krupska E, Derkacz A, Mochoł J, Doroszko A. Interactions between the Cyclooxygenase Metabolic Pathway and the Renin-Angiotensin-Aldosterone Systems: Their Effect on Cardiovascular Risk, from Theory to the Clinical Practice. BioMed research international. 2018:2018:7902081.
19. Bauersachs J, Fraccarollo D. Endothelial NO Synthase Target of Aldosterone. Hypertension (Dallas, Tex : 1979). 2006;48(1):27-8.
20. Griendling KK, Touyz RM, Zweier JL, Dikalov S, Chilian W, Chen YR, et al. Measurement of Reactive Oxygen Species, Reactive Nitrogen Species, and Redox-Dependent Signaling in the Cardiovascular System: A Scientific Statement From the American Heart Association. Circulation research. 2016;119(5):e39-75.
21. Shao Y, Cheng Z, Li X, Chernenya V, Wang H, Yang X-f. Immunosuppressive/anti-inflammatory cytokines directly and indirectly inhibit endothelial dysfunction- a novel mechanism for maintaining vascular function. Journal of Hematology & Oncology. 2014;7(1):80.
22. Gilbert KC, Brown NJ. Aldosterone and inflammation. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):199-204.
23. Ye J. Mechanisms of insulin resistance in obesity. Frontiers of medicine. 2013;7(1):14-24.
24. Nicholas LM, Morrison JL, Rattanatray L, Zhang S, Ozanne SE, McMillen IC. The early origins of obesity and insulin resistance: timing, programming and mechanisms. International journal of obesity. 2016;40(2):229-38.
25. Frystyk J, Skjaerbaek C, Vestbo E, Fisker S, Orskov H. Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes. Diabetes/metabolism research and reviews. 1999;15(5):314-22.
26. Aihara K-i, Ikeda Y, Yagi S, Akaie M, Matsumoto T. Transforming Growth Factor-b1 as a Common Target Molecule for Development of Cardiovascular Diseases, Renal Insufficiency and Metabolic Syndrome.
kidney function. Cell metabolism. 2010;12(4):329-40.

39. Lennon R, Pons D, Sahin MA, Wei C, Shield JP, Coward RJ, et al. Saturated fatty acids induce insulin resistance in human podocytes: implications for diabetic nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2009;24(11):3288-96.

40. de Vries AF, Ruggenenti P, Ruan XZ, Praga M, Cruzado JM, Bajema IM, et al. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. The lancet Diabetes & endocrinology. 2014;2(5):417-26.

41. Tobar A, Ori Y, Benchetrit S, Milo G, Herman-Edelstein M, Zingerman B, et al. Proximal tubular hypertrophy and enlarged glomerular and proximal tubular urinary space in obese subjects with proteinuria. PloS one. 2013;8(9):e75547.

42. Yamahara K, Kume S, Koya D, Tanaka Y, Morita Y, Chin-Kanasaki M, et al. Obesity-Mediated Autophagy Insufficiency Exacerbates Proteinuria-induced Tubulointerstitial Lesions. Journal of the American Society of Nephrology. 2013;24(11):1769-81.

43. Chen H-M, Chen Y, Zhang Y-D, Zhang P-P, Chen H-P, Wang Q-W, et al. Evaluation of Metabolic Risk Marker in Obesity-related Glomerulopathy. Journal of Renal Nutrition. 2011;21(4):309-15.

44. Ruan XZ, Varghese Z, Powis SH, Moorhead JF. Human mesangial cells express inducible macrophage scavenger receptor. Kidney international. 1999;56(2):440-51.

45. Li J, Li H, Wen YB, Li XW. Very-low-density lipoprotein-induced triglyceride accumulation in human mesangial cells is mainly mediated by lipoprotein lipase. Nephron Physiology. 2008;110(1):p1-10.

46. Chen Y, Ruan XZ, Li Q, Huang A, Moorhead JF, Powis SH, et al. Inflammatory cytokines disrupt LDL-receptor feedback regulation and cause statin resistance: a comparative study in human hepatic cells and mesangial cells. American journal of physiology Renal physiology. 2007;293(3):F680-7.

47. Zhu Q, Scherer PE. Immunologic and endocrine functions of adipose tissue: implications for kidney disease. Nature reviews Nephrology. 2018;14(2):105-20.

48. Gruzdeva OV, Borodkina AD, Akbasheva OE, Dileva YA, Antonova LV, Matveeva VG, et al. Influence of visceral obesity on the secretion of adipokines with epicardial adipocytes in patients with coronary heart disease. Terapevticheskii arkhiv. 2018;90(10):71-8.

49. Lee MPS, Orlov D, Sweeney G. Leptin induces rat glomerular mesangial cell hypertrophy, but does not regulate hyperplasia or apoptosis. International journal of obesity. 2005;29(12):1395-401.

50. Sharma K, Ramachandrarao S, Qiu G, Usui HK, Zhu Y, Dunn SR, et al. Adiponectin regulates albuminuria and podocyte function in mice. The Journal of clinical investigation. 2008;118(5):1645-56.

51. Mantzoros CS, Liolios AD, Tritos NA, Kaklamani VG, Doulgerakis DE, Griveas I, et al. Circulating insulin concentrations, smoking, and alcohol intake are important independent predictors of leptin in young healthy men. Obesity research. 1998;6(3):179-86.

52. Rahmouni K. Leptin-Induced Sympathetic Nerve Activation: Signaling Mechanisms and Cardiovascular Consequences in Obesity. Curr Hypertens Rev. 2010;6(2):104-209.

53. Wofford MR, Hall JE. Pathophysiology and Treatment of Obesity Hypertension. Current pharmaceutical design. 2004;10(29):3621-37.

54. Sikorska D, Grzyniawska M, Koszak M, Gulbicka P, Korybalska K, Witowski J. Simple obesity and renal function. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2017;68(2):175-80.

55. Lam QL, Lu L. Role of leptin in immunity. Cellular & molecular immunology. 2007;4(1):1-13.

56. Tanaka M, Sugarani T, Sugita S, Shimoda Y, Kasahara M, Aoe S, et al. Role of central leptin signaling in renal macrophage infiltration. Endocrine journal. 2010;57(1):61-72.

57. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. Journal of the American College of Cardiology. 2008;52(15):1201-10.

58. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 1998;12(1):57-65.

59. Chen K, Li F, Li J, Cai H, Strom S, Bisello A, et al. Induction of leptin resistance through direct interaction of C-reactive protein with leptin. Nature medicine. 2006;12(4):425-32.

60. Heidari B. C-reactive protein and other markers of inflammation in hemodialysis patients. Caspian J Intern Med. 2013;4(1):611-6.

61. Esfahani M, Movahedian A, Baranchi M, Goodarzi MT. Adiponectin: an adipokine with protective features against metabolic syndrome. Iran J Basic Med Sci. 2015;18(5):430-42.

62. Gariballa S, Alkaabi J, Yasir J, Al Essa A. Total adiponectin in overweight and obese subjects and its response to visceral fat loss. BMC Endocrine Disorders. 2019;19(1):55.
63. Meilleur KG, Doumatey A, Huang H, Charles B, Chen G, Zhou J, et al. Circulating Adiponectin Is Associated with Obesity and Serum Lipids in West Africans. The Journal of Clinical Endocrinology & Metabolism. 2010;95(7):3517-21.

64. Kim Y, Lim JH, Kim MY, Kim EN, Yoon HE, Shin SJ, et al. The Adiponectin Receptor Agonist AdipoRon Ameliorates Diabetic Nephropathy in a Model of Type 2 Diabetes. Journal of the American Society of Nephrology: JASN. 2018;29(4):1108-27.

65. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation. 2000;102(11):1296-301.

66. Rosenson RS. Effect of fenofibrate on adiponectin and inflammatory biomarkers in metabolic syndrome patients. Obesity. 2009;17(3):504-9.

67. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyma A, Ouchi N, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000;96(5):1723-32.

68. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation. 2003;107(5):671-4.

69. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860-7.

70. Lee CH, Lam KS. Obesity-induced insulin resistance and macrophage infiltration of the adipose tissue: A vicious cycle. 2019;10(1):29-31.

71. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of clinical investigation. 2003;112(12):1796-808.

72. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. The Journal of clinical investigation. 2011;121(6):2094-101.

73. Ricardo-Gonzalez RR, Red Eagle A, Odegaard JJ, Jouihan H, Morel CR, Heredia JE, et al. IL-4/STAT6 immune axis regulates peripheral nutrient metabolism and insulin sensitivity. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(52):22617-22.

74. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN inflammation. 2013;2013:139239.

75. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. Immunology. 2018;155(4):407-17.

76. Tang J, Yan H, Zhuang S. Inflammation and oxidative stress in obesity-related glomerulopathy. Int J Nephrol. 2012;2012:608397-.

77. Wang H, Li J, Gai Z, Kullak-Ublick GA, Liu Z. TNF-α Deficiency Prevents Renal Inflammation and Oxidative Stress in Obese Mice. Kidney & blood pressure research. 2017;42(3):416-27.

78. Wu Y, Liu Z, Xiang Z, Zeng C, Chen Z, Ma X, et al. Obesity-related glomerulopathy: insights from gene expression profiles of the glomeruli derived from renal biopsy samples. Endocrinology. 2006;147(1):44-50.

79. Su H, Lei CT, Zhang C. Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Frontiers in immunology. 2017;8:405.

80. Hunley TE, Ma LJ, Kon V. Scope and mechanisms of obesity-related renal disease. Curr Opin Nephrol Hypertens. 2010;19(3):227-34.