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The role of Apelin, Adipsin and C-reactive protein in patients with chronic kidney disease

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***Abstract*---**Chronic kidney disease (CKD) is a growing global health problem. The adipose tissue may directly affect the kidney through its activity as an endocrine gland through the secretion of adipokines. This study was a cross sectional which conducted in Kirkuk city for the period from June 2020 to September 2021.study population age ranged from (30 – 90) years old. The total of 80 subjects was separated to two groups as following: Kidney failure group: 65 patients and control group: 15 patients. The results referred to the increased levels of Apelin, Adipsin and C reactive protein (CRP) in CKD with highly significant differences (P≤0.01) when compared with control group, also a positive correlation was found between Adipsin and Apelin in the second stage (r = 0.742) , the third stage (r = 0.573) and in the fifth stage (r = 0.552).

***Keywords*---**Apelin, Chronic kidney disease (CKD), Adipsin.

Introduction

Chronic kidney disease (CKD) is a growing global health problem. It is estimated that this disease will become the fifth leading cause of death worldwide by 2040 (Vanholder, R. et al. 2021). CKD refers to the gradual and irreversible deterioration in kidney function and is defined as 3-month renal damage based on the presence of abnormal structure or function or abnormal glomerular filtration rate with or without evidence of kidney damage (Denker et al., 2015). CKD is divided into five stages based on kidney function, early stage CDK is the least mild, stages 2 and 3 manifest in kidney damage and are generally asymptomatic, while more advanced stages of CKD stages 4 and 5 require treatment Uremia and its complications and eventual renal replacement therapy

in end-stage renal disease (Rangel-López et al., 2013). End-stage renal disease or ESRF is a condition of progressive loss of kidney function that leads to the necessity of renal replacement therapy (dialysis/organ transplantation) (Aeddula, 2020).

Adipocytokines, which are regulatory peptides, are secreted primarily by adipose tissue (Scheja and Heeren., 2019), collectively defined as molecules such as cytokines and hormones and function with endocrine activity, more than 600 have been identified (Raimo, 2015). These molecules are involved in the regulation of various pathophysiological processes, including secretion of adipokines, oxidative stress, inflammation, and metabolic changes that lead to hyperglycemia, insulin resistance, and hypertension. Abnormal leakage of fatty acids within or between tissues contributes, for example, to the development of obesity and related metabolic disorders (Stern,J.et al,2016). The adipose tissue may directly affect the kidney through its activity as an endocrine gland through the secretion of adipokines. (Kovesdy CP, et al. 2017).

Apelin is a biologically active peptide produced from white adipose tissue (Kleinz MJ et al., 2005). Apelin is an APJ receptor (a G-protein coupled receptor bound to angiotensin II receptors). Studies have shown that the apelin/APJ system is widespread in the body and is involved in important physiological functions, including cardiovascular homeostasis, renal homeostasis, energy metabolism, and fluid homeostasis (Knauf et al., 2013). The Apelin/APJ system is expressed in the kidney. Serum apelin levels have been reported to be closely associated with the development of a variety of kidney diseases (Day RT et al., 2013). The apelin/APJ system may have potential therapeutic value for the treatment of vascular calcification in chronic kidney disease (Han et al., 2016). Apelin also has complex effects on renal hemodynamics and tubular function (Hus-Citharel et al., 2014).

Adipsin (Complement factor D) was first described in 1987 (Cook KS et al., 1987). It is required for alternative complement pathway activation and is primarily synthesized by adipocytes and macrophages (Ouchi et al., 2011). Adipsin has been identified as a complement factor (complement) , which plays an important role in the immune system (Ricklin D et al., 2010) The main function of Adipsin is to catalyze the breakdown of complement factor C3 to C3a, in which it acts Factor D dissociates factor B bound to C3b, resulting in the formation of the C3bBb complex, which is the alternative pathway of C3 convertase (Zhou et al.,2018). Adipsin is synthesized during lipolysis and stimulates the hunger center (Lo, J.C. et al., 2014).

C-reactive protein (CRP) is a classic acute phase protein that is produced in the liver under the stimulation of cytokines such as TNF, IL-1 and IL-6 (Gohel et al., 2013). It is the most commonly used inflammatory marker. It is associated with a higher risk of cardiovascular events and mortality (Tsai Y et al., 2016). CRP is an established marker of systemic inflammation in the general population as well as patients with CKD. Inflammation plays an essential role in the pathophysiology of CKD and is associated with cardiovascular disease and mortality in CKD. A consistently elevated CRP level is associated with all-cause mortality in ESRD. It is also an indicator of malnutrition and cardiovascular disease in dialysis patients

(Abraham et al., 2009). Patients with CKD had higher levels of CRP than those without CKD (Fox et al., 2010). The study aimed to assess the role of Apelin, adipcin and Crp in Chronic kidney disease patient.

Materials and Method

A cross section study done in Kirkuke city for the period from June 2020 to September 2021.study population age ranged from (30 – 90) years old. The total of 80 subjects was separated to groups as following:

- Kidney failure group: 65 patients include (the first stage: 13 patients, the second stage: 13 patients, the third stage: 13 patients, fourth stage: 13 patients, the fifth stage or the stage of hemodialysis: 13 patients)
- control group: 15 patients

Serum adipsin was measured using Human CFD(Complement Factor D) ELISA Kit with Sensitivity: 0.94ng/mL by Elabscience, Inc. serum Apelin was measured using Human APLN(Apelin) ELISA Kit with sensitivity: 37.50 pg/mL by Elabscience, Inc. The CRP concentration is determined by comparing the turbidity of the samples with the standard concentration. Using the HP-AFS/1 Immunoassay Analyzers.

The Result and Discussion

Table 1 shows the concentration of Apelin, Adipsin and CRP in CKD stages compared to the control (P≤0.01).

Group	Mean ± SD CRP	Mean ± SD Adipsin	Mean ± SD Apelin
Control Group	2.33 ± 0.814 F	1.5166 ± 0.1191 b	0.4116 ± 0.1280 cd
Stages1	16.96 ± 6.06 E	1.3315 ± 0.1476 c	0.3510 ± 0.0770 d
Stages 2	25.18 ± 8.78 D	1.3517± 0.0764 c	0.4414 ± 0.1004 c
Stages 3	62.12 ± 4.58 C	1.5079 ± 0.0631 b	0.4914 ± 0.0956 bc
Stages 4	109.26 ± 14.25 B	1.5770 ± 0.1248 b	0.5305 ± 0.0847 b
Stages 5	128.67 ± 25.12 A	1.8875± 0.1668 a	0.6363 ± 0.1978 a

Apelin concentration were high significantly increased in CKD patients stages 1,2,3,4,5 (0.3510 ± 0.0770, 0.4414 ± 0.1004, 0.4914 ± 0.0956, 0.5305 ± 0.0847, 0.6363 ± 0.1978 pg/ml) respectively compared with the healthy controls(0.4116 ± 0.1280 pg/ml) (P ≤0.01) as shown in table (1) and figure (1) .

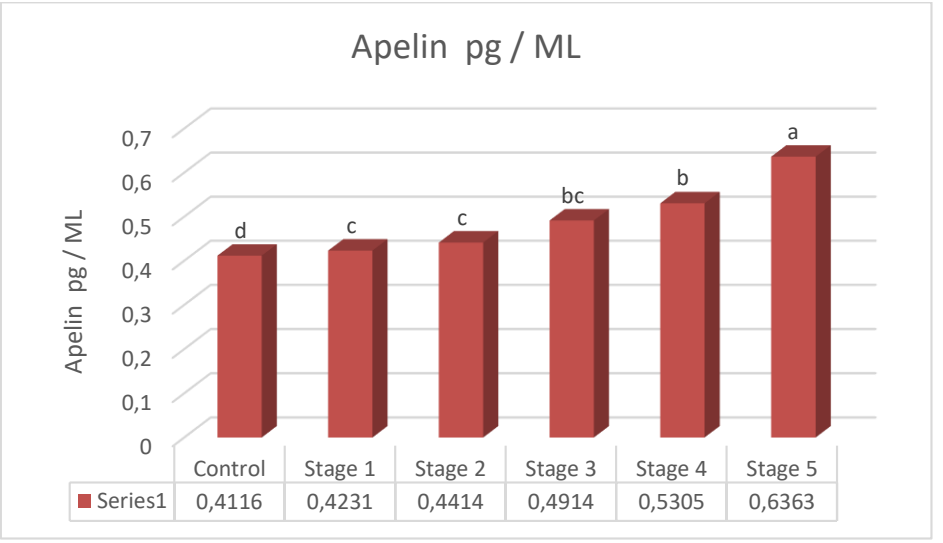

Figure 1: Levels of Apelin (pg/ml) in CKD Stages 1, 2, 3, 4, 5 patients and control

A positive correlation was found between Apelin and Adipsin in the second stage (r = 0.742), the third stage (r = 0.573). and in the fifth stage (r = 0.552).

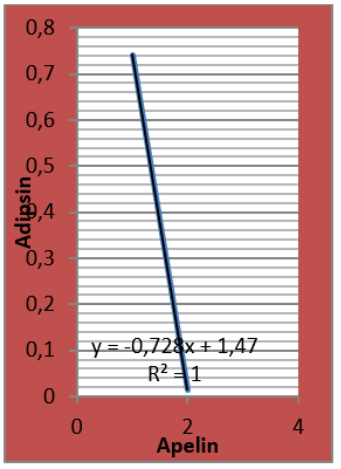

Figure 2: correlation between Apelin and Adipsin stage2

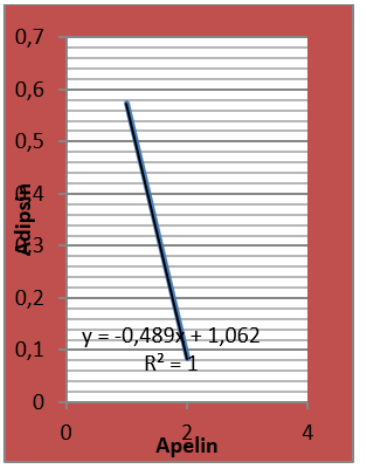

Figure 3: correlation between Apelin and Adipsin stage3

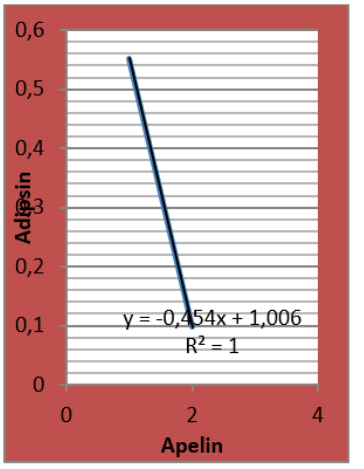

Figure 4: correlation between Apelin and Adipsin stage5

Apelin, according to Mafra et al. (2012), is an osteoblastic factor, which protects bone in adult patients undergoing dialysis. It may promote growth and increase its focus with age. In addition, apelin concentration can be increased as a result of the development of endothelial dysfunction/inflammation in CKD patients (Malyszko et al., 2008). It acts as a vasoactive peptide. It is also expressed in glomeruli and causes inflammation and endothelial dysfunction in CKD (Briffa et al., 2013).

In a study by Szczepańska et al. (2015) the concentration of apelin was significantly higher in children with CKD than in the control group. Several studies have shown the importance of the apelin/APJ system in kidney disease (Huang et al., 2018) as it was found to be increased in patients with stage 5 CKD, even after treatment and dialysis (Szczepanska et al., 2015).

The results of the current study are in agreement with the results of Zhang et al (2009), Büyükbakkal et al (2015). They found that apelin levels were higher in dialysis patients than in healthy individuals. However, Khaled et al (2017) found that serum apelin was significantly lower in ESRD patients on dialysis compared to the control group, and Leal et al (2012) observed no difference between apelin levels in dialysis patients and those in healthy individuals.

The results of the current study did not agree with Xuehong et al (2020) where it was found that serum apelin levels were not significantly associated with the development of chronic kidney disease, and there were also no significant differences in apelin levels between CKD groups in the study of Yavuz et al. (2015).
Fig. 5 shows that there was a high significant increase in Adipsin concentration in CKD patients stages 1,2,3,4,5 (1.3315 ± 0.1476, 1.3517± 0.0764, 1.5079 ± 0.0631, 1.5770 ± 0.1248, 1.8875± 0.1668, 1.1163 ± 0.1008 ng/ml) respectively compared with the healthy controls (1.5166 ± 0.1191 ng/ml) (P ≤0.01) as shown in table (1) and figure (5).

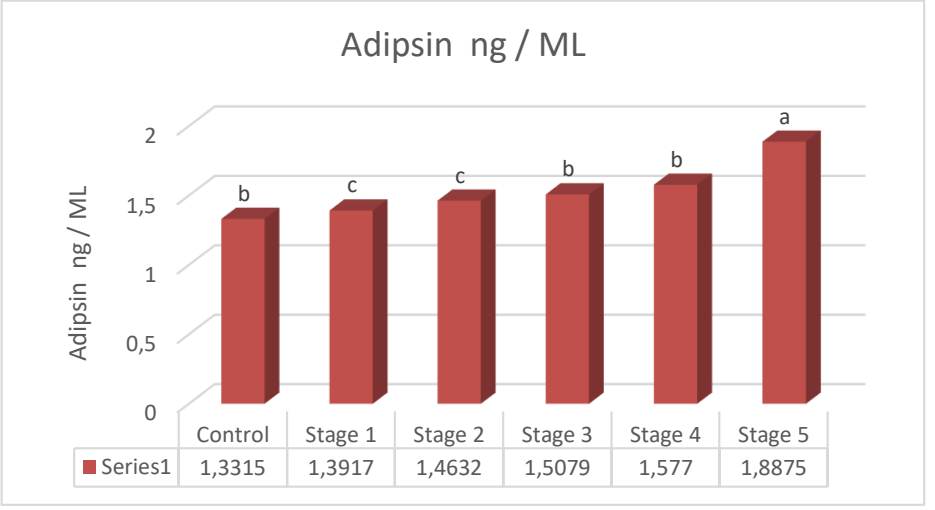

Figure 5: Levels of Adipsin (ng/ml) in CKD Stages 1,2,3,4,5 patients and control

Pascual et al. (1988) studied the metabolism of adipsin in humans by injecting radioactive Adipsin in 5 healthy individuals and 12 patients with various renal diseases or renal failure, and urinary elimination of Adipsin was increased in patients with tubular defect, indicating It was found that, under normal conditions, adipsin is filtered through the glomeruli and reabsorbed by the tubular cells, circulating adipsin is eliminated through the kidneys and the concentration of adipsin in the blood is significantly higher in patients with chronic renal failure compared to healthy controls (Volanakis JE et al. .,1985).

Factor D synthesis was not significantly altered by renal function, nor was it bound to C-reactive protein, indicating that Factor D is not an acute phase protein (Pascual et al.,1988). Inagi et al. (1994) found that plasma levels of adipsin increase 10-fold in end-stage renal failure, indicating that its metabolic processes are closely related to renal function.

In a study by Clark et al. (2002), serum concentrations of Factor D in patients with end-stage renal disease (ESRD) were higher than in those with normal kidney function. There was also a significant correlation between the concentration of factor D in the blood and serum creatinine. In this study, there is a high significant increase in the concentration of CRP in all stages of CKD (16.96 ± 6.06, 25.18 ± 8.78, 62.12 ± 4.58, 109.26 ± 14.25, 128.67 ± 25.12 mg/l) respectively compared with the healthy controls (2.33 ± 0.814 mg/l) (P ≤0.01) as shown in table (1) and figure (6).

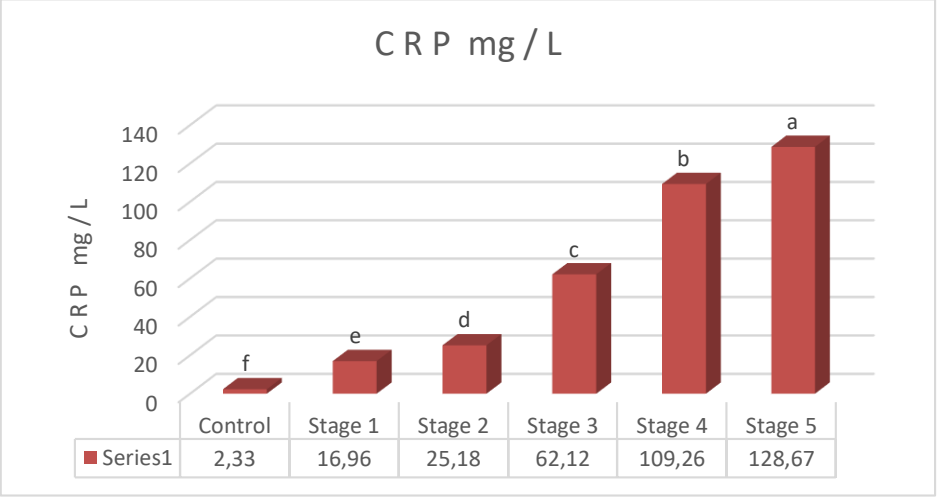

Figure 6: Levels of CRP (mg/l) in CKD Stages 1,2,3,4,5 patients and control

In this study, high concentration of CRP appeared in CKD, and this finding is consistent with other studies, where the mean serum levels of CRP were significantly higher in patients with CKD compared to controls in the study of (Lee et al .,2015) and in the study of Ambarkar et al (2016.) Some studies did not agree with these findings as the level of C-reactive protein in the blood was not independently associated with CKD. (Ridker et al., 2001: Lee et al., 2015).

CRP is an established marker of systemic inflammation in the general population as well as patients with CKD. Inflammation plays an essential role in the pathophysiology of CKD and has been associated with cardiovascular disease, protein energy wasting, and mortality in CKD (Akchurin and Kaskel.,2015). patients with CRP levels ≥2 mg/L had a higher risk of developing CKD. (Fu, et al., 2019;Ocak, N al., 2016). A consistently elevated CRP level is associated with all-cause mortality in ESRD. It is also considered an indicator of malnutrition and cardiovascular disease in dialysis patients (Abraham et al.,2009) .elevated CRP levels in CKD patients may be due to deteriorating renal function as well as increased IL-6 which stimulates CRP production in the liver (Chudek et al., 2006).

Conclusion

The findings of the current study that the Adipsin, Apelin and CRP are plays an important role in the chronic kidney disease.

References

Abraham, G.; Sundaram, V.; Sundaram, V.; Mathew, M.; Leslie, N.; Sathiah, V. C-Reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis Transpl. 2009; 20: 811-5.

Aeddula, S.; (2020). Chronic renal failure. Urologiia, 1, 11–18. https://doi .org/10.18565/urol.2017.1-supplement.11-18.

Ambarkar, M.; Pemmaraju, S. V.; Gouroju, S.; Manohar, S. M.; Bitla, A. R.; Yajamanam, N. & Vishnubhotla, S. (2016). Adipokines and their relation to endothelial dysfunction in patients with chronic kidney disease. *Journal of clinical and diagnostic research: JCDR*, *10*(1), BC04.

Briffa, J. F.; McAinch, A. J.; Poronnik, P; & Hryciw, D. H. (2013). Adipokines as a link between obesity and chronic kidney disease. *American Journal of Physiology-Renal Physiology*, *305*(12), F1629-F1636.

Büyükbakkal, M.; Canbakan, B.; Eser, B.; Yayar, Ö.; Ercan, Z.; Merhametsiz, Ö, et al. The relation between apelin levels, echocardiographic findings and carotid intima media thickness inperitoneal dialysis patients. Ren Fail 2015; 37:433–438.

Chudek ,J.; Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. Pharmacol Rep. 2006;58:S81-88.

Clark, W. R.; & Gao, D. (2002). Low-molecular weight proteins in end-stage renal disease: potential toxicity and dialytic removal mechanisms. *Journal of the American Society of Nephrology*, *13*(suppl 1), S41-S47.

Denker ,M.; Boyle S.; Anderson, AH.; Appel, LJ.; Chen, J.; Fink, JC.; Flack ,J. ; Go AS.; Horwitz, E.; Hsu , CY.; Kusek, JW. Chronic Renal Insufficiency Cohort Study (CRIC): overview and summary of selected findings. Clinical Journal of the American Society of Nephrology. 2015 Nov 6;10(11):2073-83.

Fox ,ER.; Benjamin, EJ.; Sarpong, DF.; Nagarajarao, H.; Taylor, JK.; Steffes, MW.; Salahudeen, AK.; Flessner, MF.; Akylbekova, EL.; Fox, CS.; Garrison, RJ.; Taylor, HA. The relation of C-reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study. BMC Nephrol 2010;11:1.

Fu, E. L.; Franko, M. A.; Obergfell, A.; Dekker, F. W.; Gabrielsen, A.; Jernberg, T; & Carrero, J. J. (2019). High-sensitivity C-reactive protein and the risk of chronic kidney disease progression or acute kidney injury in post–myocardial infarction patients. *American heart journal*, *216*, 20-29.

Gohel, MG.; Chacko, AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: An evidence linking oxidative stress, inflammation and glycemic control. J Diabetes Metab Disord 2013;12(56):1–8.

Han ,X.; Wang ,LY.; Diao, ZL.; Liu ,WH. 2016. Apelin: A novel inhibitor of vascular calcification in chronic kidney disease. Atherosclerosis 244:1-8.

Huang ,Z.; Wu, L.; Chen, L. Apelin/APJ system: a novel potential therapy target for kidney disease. J Cell Physiol. 2018;233(5):3892–3900.

Hus-Citharel, A.; Bodineau, L.; Frugiere A.; et al. Apelin counteracts vasopressin-induced water reabsorption via cross talk between apelin and vasopressin

receptor signaling pathways in the rat collecting duct. Endocrinology. 2014;155(11):4483–4493.
Inagi, R.; Miyata ,T.; OdaO.; Maeda, K.; Inoue K. Evaluation of the proteolytic activity of factor D accumulated as an active serine protease in patients with chronic renal failure. Nephron. 1994;66:285–290.
Kleinz, MJ.; Davenport, AP. Emerging roles of apelin in biology and medicine. Pharmacol Ther 2005;107:198–211.
Knauf, C.; Drougard ,A.; Fournel, A; et al. Hypothalamic actions of apelin on energy metabolism: new insight on glucose homeostasis and metabolic disorders. Horm Metab Res. 2013;45(13):928–934.
Kovesdy, CP.; Furth, S and Zoccali C.; World Kidney Day Steering Committee: Obesity and kidney disease: Hidden consequences of the epidemic. Indian J Nephrol 27: 85-92, 2017.
Leal, VO.; Lobo, JC.; Stockler-Pinto MB et al. Apelin: a peptide involved in cardiovascular risk in hemodialysis patients? Ren Fail 2012; 34: 577–581.
Lee, JO.; Kim, N.; Lee, HJ.; Lee, YW.; Kim, JK.; Kim, HI et al. Visfatin, a novel adipokine, stimulates glucose uptake through the Ca2 +-dependent AMPK-p38 MAPK pathway in C2C12 skeletal muscle cells. J Mol Endocrinol. 2015;54(3):251-62.
Lo, J.C.; Ljubicic, S.; Leibiger, B.; Moede, T.; Kelly, M.E; Chatterjee Bhowmick, D.; Murano, I.; Cohen, P.; Banks, A.S.; Khandekar, M.J.; Dietrich, A.; Flier, J.S.; Cinti, S.; Blüher, M. ; Danial, N.N; Berggren, P.O; and Spiegelman, B.M; Cell, 2014, vol. 158, no. 1, pp. 41– 53.
Mafra, D.; Lobo ,JC.; Farage, NE et al. The relationship between apelin and parathyroid hormone in hemodialysis patients. Ren Fail 2012; 34: 970–973.
Malyszko, J.; Malyszko, JS.; Mysliwiec, M. Visfatin a new adipocytokine is predominantly related to inflammation/Endothelial damage in Kidney Allograft Recipients. Transplant proceedings 2009; 41(1): 150- 3.
Malyszko, J.; Malyszko, JS.; Mysliwiec, M. Visfatin a new adipocytokine is predominantly related to inflammation/Endothelial damage in Kidney Allograft Recipients. Transplant proceedings 2009; 41(1): 150- 3.
Ocak, N.; Dirican, M.; Ersoy, A.; Sarandol, E. Adiponectin, leptin, nitric oxide, and C-reactive protein levels in kidney transplant recipients: Comparison with the hemodialysis and chronic renal failure. Ren. Fail. 2016, 38, 1639–1646.
Ouchi, N.; Parker, JL.; Lugus ,JJ.; Walsh, K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85–97.
Pascual, M.; Steiger, G.; Estreicher, J.; Macon, K.; Volanakis, JE.; Schifferli, JA. Metabolism of complement factor D in renal failure. Kidney Int. 1988;34:529–536.
Rangel-López, A.; Paniagua-Medina, M. ; Urbán-Reyes, M.; Cortes-Arredondo, M.; Álvarez-Aguilar, C.; López-Meza, J.; Ochoa-Zarzosa, A.; Lindholm, B.; García-López, E. ;and Paniagua, J. R. (2013). Genetic damage in patients with chronic kidney disease, peritoneal dialysis and haemodialysis: A comparative study. Mutagenesis, 28(2), 219–225. https://doi.org/10.1093/ mutage /ges075.
Ricklin, D.; Hajishengallis ,G.; Yang, K.; Lambris, JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol. 2010;11(9):785–797.
Scheja, L.; Heeren, J. The endocrine function of adipose tissues in health and cardiometabolic disease. Nat Rev Endocrinol. 2019;15(9):507–24.

Stern, J. H.; Rutkowski, J. M.; & Scherer, P. E. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metab. 23, 770–784 (2016).

Szczepańska, M.; Machura, E.; Adamczyk, P.; Świętochowska, E.; Trembecka-Dubel, E.; Lipiec, K., & Ziora, K. (2015). Evaluation of adipocytokines in children with chronic kidney disease. *Endokrynologia Polska*, *66*(2), 100-107.

Tsai, YW.; Lu, MC.; Lin, YH.; Lee, YC.; Li ,WC.; Chen, JY. et al. Combined body mass index with high-sensitivity C-reactive protein as independent predictors for chronic kidney disease in a relatively healthy population in Taiwan. Eur J Clin Nutr. 2016; 70: 766-72.

Vanholder, R. et al. Fighting the unbearable lightness of neglecting kidney health: the decade of the kidney. Clin. Kidney J. 14, 1719–1730 (2021).

Volanakis, JE.; Barnum ,SR.; Giddens, M.; Galla, JH. Renal filtration and catabolism of complement protein D. N Engl J Med. 1985;312: 395–399.

Xuehong, Lu.; Shengmao, Liu.; Rumei Luan, Wenpeng Cui, Yu Chen, Yixian Zhang, Yue Lu, Hong Zhang, Lin Shi, Lining Miao & Feng Xu (2020) Serum elabela and apelin levels during different stages of chronic kidney disease, Renal Failure, 42:1, 667-672.

Yavuz, Y. C.; Sevinc, C.; Deniz, M. S.; Yavuz, S.; Altunoren, O.; Sayarlioglu, H.; & Dogan, E. (2015). The role of Apelin 13 in progression of chronic kidney disease. *Iranian journal of kidney diseases*, *9*(5), 369.

Yavuz, Y. C.; Sevinc, C.; Deniz, M. S.; Yavuz, S.; Altunoren, O.; Sayarlioglu, H.; & Dogan, E. (2015). The role of Apelin 13 in progression of chronic kidney disease. *Iranian journal of kidney diseases*, *9*(5), 369.

Zhang, Y.; Shen, C.; Li, X.; Ren, G.; Fan ,X.; Ren ,F. et al. Low plasma apelin in newly diagnosed type 2 diabetes in Chinese people. Diabetes Care 2009;32:e150.

Zhou ,Q.; Ge ,Q.; Ding ,Y.; Qu, H.; Wei, H.; Wu, R.; Yao, L.; Wei, Q.; Feng, Z.; Long, J.; Deng H. Relationship between serum adipsin and the first phase of glucose-stimulated insulin secretion in individuals with different glucose tolerance. J Diabetes Investig. 2018;9(5):1128–1134.

Abraham, G.; Sundaram, V.; Sundaram, V.; Mathew, M.; Leslie, N.; Sathiah, V. C-Reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis Transpl. 2009; 20: 811-5.

Akchurin, OM.; Kaskel ,F. Update on inflammation in chronic kidney disease. Blood Purif. 2015; 39: 84-92.