IASJ المجلات الاكاديمية العراقية

Tikrit Journal of Pure Science

ISSN: 1813 – 1662 (Print) --- E-ISSN: 2415 – 1726 (Online)

Journal Homepage: http://tjps.tu.edu.iq/index.php/j

Using Serum Interleukin-18 (IL-18) as a Biomarker of Chronic Kidney Failure and its relationship with Prolactin Level

Wasan Abdul Malik Izz al-Din[1] , Nadia Ibrahim Salih[2]

[1] *College of Pharmacy , Tikrit University , Tikrit , Iraq*

[2] *College of Medicine , Tikrit University , Tikrit , Iraq*

https://doi.org/10.25130/tjps.v25i3.246

ARTICLE INFO.

Article history:

-Received: 4 / 12 / 2019

-Accepted: 25 / 2 / 2020

-Available online: / / 2020

Keywords: Chronic Kidney Failure, IL-18, Prolactin hormone.

Corresponding Author:

Name: Nadia Ibrahim Salih

E-mail:

Nadiaibraheem488@gmail.com

Tel:

ABSTRACT

Kidney failure usually occurs as a result of lacking the normal functions of kidney as either partly or completely. In the last years, it was announced that the Interleukin-18 has received significant interest as inflame marker. IL-18 also strongly associated with renal function, and was a powerful predictive marker of renal function turbulence.

Aims: The main aim of this research is to study the relation of prolactin levels with chronic kidney failure, and to assess the relationship between serum Interleukin-18 and chronic kidney failure. **Methods:** The study was carried out in Tikrit Teaching Hospital from 1st of March Until the 15th of July 2019, and included 150 blood samples from patients suffering from chronic kidney failure, and 50 samples from healthy individuals as control group. **Results:** The study revealed the highest rate of prolactin level 58% was found in female and 23% was found in male. While in control group, the lowest level of prolactin 7% was found in male and 11% was found in female. The present study showed the highly significant relation ($P<0.01$) between IL-18 level and CKF. IL-18 was increased in patients with renal failure comparing with the control group (66.5±49.6 vs. 49.5±27).

Introduction

CKF is a global health problem, defined as persistent damage in bilateral kidney for more than 3 months, this can be functional or structural, and with or without reduce in glomerular filtration rate [1]. CKF is considered as a major health problem. However, the proportion of CKF varies from one geographical area to others due to environmental and genetic factors [2]. Most prevalent renowned causes of CKF are Hypertension, diabetes mellitus [3]. Prolactin is a hormone secreted mostly from anterior pituitary gland, as well as, is secreted by various body tissues. Major action of prolactin is stimulation of lactation after delivery and to control the development of the breast and lactation in women. In men, the function of prolactin stayed to be studied. Prolactin clearance is decreased in CKF, and its production is changed. Prolactin's biological activity is also increased [4]. Biological activity of prolactin is increased [5]. In male patients of CKF, hyperprolactinemia is linked with sexual dysfunction and gynecomastia and also common among women CKF patients [6]. Hyperprolactinaemia can be caused by physiological processes, pharmacological effects, and pathological effects [7].

IL-18 possess pivotal role in it's used as a marker in diagnosis of kidney disease. IL-18 produce when damage occurs in renal tubular, therefore, it's can provide the ability to define diagnosis of loss of renal tubular functions [8, 9], IL-18is pro-inflammatory cytokine of the IL-1 super family is included in both innate and acquired immunity reactions [10]. IL-18 precursor is found fundamentally in approximately in all cells involving hematopoietic cells, mesenchymal cells, and epithelial cells of the gastrointestinal tract in healthy human and animals. IL-18 produce from active immune cells as monocyte, macrophages, neutrophils and natural killer cell, as inactive molecules in molecular weight 24KD. The role of IL-18 as an important mediator of inflammation is produced by renal tubular epithelia and interstitial macrophage. It plays an effective role in a different of kidney diseases, like urinary tract infection, ischemia-reperfusion and transplant rejection [11]. The levels of plasma IL-18 are showed increased in variety

pathophysiologic cases, such as inflammatory bowel disease, systemic lupus erythematosus and inflammatory arthritis [12]. Interleukin-18 is linked with chronic inflammation; IL-18 and IL-1β are contributed in host defense versus pathogen injuries [13]. IL-18 is more useful for the evaluation of chronic inflammation and renal function disorder.

The aims of the current study was conducted to valuation of levels of prolactin in patients with chronic kidney disease, and to estimate the IL-18 concentration in serum of patients with chronic kidney failure.

Patients & Methods

Study Design: Across sectional study which was conducted in Dialysis Unit in Tikrit Teaching Hospital in Tikrit city. The period of study started from the first of March until the 15th of July 2019on study population age ranged from (18 –83) years old .A personal interview with patients was conducted to take patients information such as age, sex, data of chronic kidney disease, and diseases associated with chronic kidney disease. The totals of subjects were 200 individuals, 50 (28 male and 22females) individuals control group and 150 patients' group had hormonal assay (Prolactin hormone), who agreed to participate in the study were recruited and separated to two main groups as following:

1-Group one: -Control group. This group consists of 50 healthy individuals (22 females and 28males) who aged range from (18-83) years.

2-Group two:-Chronic kidney failure patients, the group consists of 150 CKF patients (64 females & 86 males) which aged range from (18-83) years.

All samples were distributed to several groups to study objectives.

Inclusion Criteria: Patients clinically presented with chronic kidney disease (with and without dialysis) were included in this study, which the specialist doctors and biochemical investigations were diagnosed these diseases.

Sample Collection: About of 5 ml of blood samples were pulled by using sterile syringes, 2 ml from each blood sample was put in plain tubes which containing gel to separate red blood cells from serum, these tubes were left about (10-15) minutes in room temperature to agglutination of blood, after agglutination, the samples were centrifuge at4000 rpm for 10 min. Fresh non hemolysis serum collected and kept in deep freeze(-20º C).Serum collected was divided in 6 eppendorf tubes to from hormonal, serological, and biochemical tests.

Determination of Serum Prolactin Concentration: Serum Prolactin concentration was limited by kits of American Monobind Company, by using Enzyme Linked Immunosorbant Assay (ELISA) technique. The main reagent needed for the enzyme immunoassay of the solid phase include immobilized antibody, of conjugate enzyme-antigen and native antigen. Upon mixing up immobilized antibody, enzyme-antigen conjugate and a the native antigen containing serum, the results of the competition reaction between the enzyme antigen and the native antigen conjugate for fixed number of insolubilized binding sites. After balance is achieved, the antibody-bound portion is separated from unrestricted antigen by aspiration or selection. The enzyme activity in the part of antibody-bound is in reversely commensurate to the native antigen concentration. By using several various serum references of recognized antigen concentration, a dosage response curve can be configured from which the antigen concentration of unknown can be achieved.

Principle of Human Interleukin 18 (IL-18): Sandwich-ELISA was used in this ELISA kit as the method. The Micro Elisa strip plate provided in this kit has been pre-coated with an antibody specific to IL-18Standards or samples are added to the suitable Micro Elisa strip plate wells and joined to the specific antibody. Then a Horseradish Peroxidase (HRP) - conjugated antibody specific for IL-18 is added to all Micro Elisa strip plate well and incubated. Next free components are washed, and then added TMB substrate solution to each well. Just those wells that containsIL-18and HRP conjugated IL-18antibodywill show blue color and then change yellow after the stop solution was added. The optical density (OD) is applied spectrophotometrically at a wavelength of 450 nm. The OD evaluate is proportional to the concentration of IL-18. The account concentration of IL-18 in the samples by comparing the OD of the samples to the standard curve.

Results & Discussion

The Relationship between Prolactin level and Chronic Kidney Failure: As shown in Table (1), the highest rate of prolactin level (58%) was found in patients female and (23%) was found in patients male, while in control group the lowest level of prolactin (7%) was found in male and (11%) was found in female.

Table 1: The relationship between Prolactin level and kidney failure.

Study group	CKF with Prolactin (+)		CKF with Prolactin (-)		Total
	Female NO. (%)	Male NO. (%)	Female NO. (%)	Male NO. (%)	
Patients	87 (58%)	35 (23%)	17 (11%)	11 (7%)	150 (75)
Control	8 (16%)	3 (6%)	23 (46%)	16 (32%)	50 (25)
Total	95 (48%)	38 (19%)	40 (20%)	27 (14%)	200 (100)
T-Value= 6.43 P-Value= 0.0002 Highly Significant					
The age of all Patient and healthy individuals were ranged between (18-83) years.					

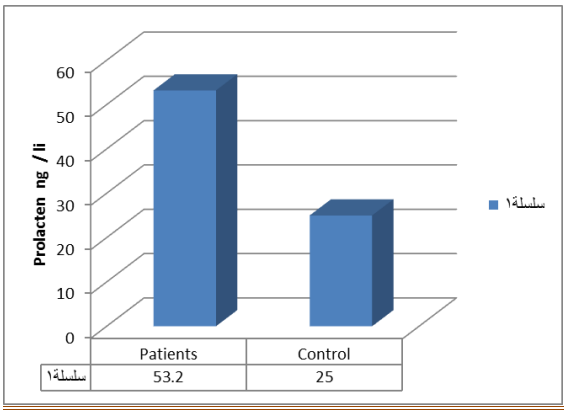


Fig. 1: The relationship between Prolactin level and kidney failure.

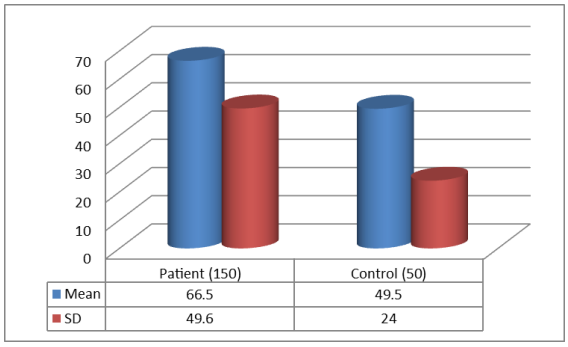
The previous study in 2016 showed a significant relationship between increased serum prolactin levels and presence of CKF [14].

In CKF patients there were alternation in signal feedback mechanism of various hormones in the body. In addition alternation hormonal production and elimination occurred [15]. Several studies have shown that serum prolactin levels remain elevated in patients with CKF. This increase occurred in both male and female patients with CKF. This in thought to be mainly due to reduced clearance by the kidneys. There was an alternation in the dopaminergic activity in patients with CKF. This leads to increased production of prolactin hormone. This also contributes to increased prolactin levels seen in these group patients.

A similar study of elevating serum prolactin level in chronic renal failure patients, CKF patients was conducted by peces *et al*., in this study, who conducted serum prolactin estimation in twelve patients with CKF who were on hemodialysis, and nineteenth patients with CKF who were post-transplant recipients with a function kidney [16]. At the end of their study, authors have shown that basal levels of serum prolactin remain elevated in patients with CKF. This increased serum levels of hormone prolactin was demonstrated in both CKF patients who were on concentrative line of treatment and in CKF patients who were on hemodialysis. In their study the authors also demonstrated that the elevated serum prolactin hormone level showed a blunted and delayed response to stimulation with TRH. In this study Peces *et al*., also have shown that serum prolactin levels remain normal in those CKF patients who have received a transplant with functioning kidney. In this study, authors have attributed the increased serum prolactin hormone levels to decreased renal catabolism and impaired hypothalamo pituitary regulation, this result was non-agreed with Peces *et al* results.

Other study by Lim *et al*., in 2007 demonstrated increased serum prolactin level in patients with CKF [15].

Relation of IL-18 level in renal failure patients and the control group: The study showed that IL-18 was increased in renal failure patients comparing with the control group (66.5 ± 49.6 vs 49.5 ± 27).



T. value= 3.21 P= <0002 P<0.01 highly significant

Fig. 2: Relation of IL-18 level in renal failure patients and the control group

Study in 2017 showed elevated (IL-18) levels in urine and serum of patients with chronic kidney damage [17]. Other study in 2015, showed that an increase in serum IL-18 concentrations above the cutoff point (1584.5 pg/mL) [18].

The most important and the closest detected function of IL-18 is its activation as a part of a Th1. Type of immunity responses or the ability of IFN gamma stimulus by T-helper 1 and Natural Killer cells [19].

So IL-18 is included in the immune responses to the induces of Th2 type to produce IL-4, IL-13 in Th2 cells, NK cells, and in most cells as well as basophile [20].

IL-18 may induce the Th17 cells population to produce IL-17, therefore establishing the auto immune responses [21].

The reasons for the high levels of serum IL-18 as compared with the control group may be due to the kidneys are the main sites of cytokines elimination, the essential factor which might affected these results, was CKD diagnosis, responsible for observed of the lowered renal clearances of IL-18, IL-18 is a middle molecule and protein-bound uremic toxin, which is difficult to remove by any of the currently available dialysis strategies thus the observed accumulation of IL-18 in dialyzed patients. Also the monocyte macrophage network activation was found during dialysis seance producing multiple inflammatory cytokines, what may also illustrate the serum [17].

References

[1]. Alenezi, A. M. (2016). Chronic Kidney Disease in Children in Arar, Kingdom of Saudi Arabia. *Int. J. Adv. Res. 4(8), 1313-1321. ISSN: 2320-5407.*

[2]. Safouth, H.; Fadel, F.; Essam, R.; Salah, A.; and Bekhet, A. (2015). Causes of Chronic Kidney Disease I Egyptian Children. Saudi J Kidney Dis Transpl; 26(4): 806-809. Changes and Prolactin Level Evaluation in Patients with Chronic Kidney Disease.

[3]. Treacy, O.; Brown, N. N.; and Dimeski G. (2018). Biochemical evaluation of kidney disease. PMCID: PMC6559936. PMID: 31236339.

[4]. Osman, N.M.; and Ismail, A. M. (2016). The Impact of Hemodialysis on Serum Prolactin and Testosterone Level in CKD Male Patients. *IOSR Journal of Dental and Medical Science. Volume 15, ISSue 1 Ver. PP 61-65.*

[5]. Mahto, a. k. (2017). Estimation of levels of serum prolactin in chronic kidney disease. International Journal of Medical and Health Research. ISS: 2454-9142. Volume 3; Issue 12.

[6]. Nehru, D.; Kandasamy, S.; Chndramouli, R.K.; and Muthumani L (2016). Evaluation of Serum Prolactin Level in Chronic Kidney Disease. Asian Journal of Pharmaceutical and Clinical Research. Vol. 9, Issue 4.

[7]. Kars, M.; Dekkers, O. M.; Pereira, A. M.; and Romijn, J. A. (2016). Update in Prolactinomas. The Nethelands Journal of MedicineVol. 68. No. 3.

[8]. Beili, S.; Ni, Z.; Cao, L.; Zhou, M. *et al* (2012). Serum IL-18 is Closely Associated with Renal Tubulointerstitial Injury and Predict Renal Prognosis in IgA Nephropathy, *Mediators of Inflam.*, 1-9.

[9]. Orluwene, C. G.; Deebii, N. and Odum, E. P. (2015). Urinary Interleukin (IL-18)as an Early Predictive Biomarker of Subclinical Proximal Tubular Dysfunction in HIV-Infected Patients Exposed to Tenofovir. J. AIDS Clin. Res. 6(9):1-4.

[10]. Oleg, K.; Alexander, B.; Mariya, D.; and S. A. (2016). Serum Interleukin-18 as a Biomarker of Tubular Kidney Damage in Patients with Chronic Glomerulonephritis. Biological Markers and Guided Therapy, Vol. 3, no. 1, 185-191.

[11]. Yawei Liu, M.D.; Wenyuan Guo, M.D.; Jiayou Zhang, M.D.; Chenggang Xu, M.D.; et al. (2013). Urinary Interleukin 18 for Detection of Acute Kidney Injury: A Meta-analysis. National Kidney Foundation, Inc. AmJ Kidney Dis. 62(6): 1058-1067.

[12]. Dr. Devarajan (2011). Biomarkers for the Early Detection of Acute Kidney Injury. Center of Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA. Curr Opin Pediatr 23(2): 194-200.

[13]. Masafumi, T (2012). Role of the inflamosome in vascular injury and atherosclerosis. Inflamm Regen. 32(3): 112-118.

[14]. Nehru, D.; Kandasamy, S.; Chandramouli, R.K.; and Muthumani, L. (2016). Evaluation of Serum Prolactin Level in Chronic Kidney Disease. Vol 9, Issue 4. Online-2455-3891.

15]. Lim, V.S.; Kathpalia, S.C.; Frohman, L.A. (2007). Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: Reversal aftertransplantation. J Clin Endocrinol Metab, 48(1): 101-7.

[16]. Peces, R.; Casado, S.; Frutos, M.; *et al.* (2010). Prolactin in Chronic Renal Failure, haemodialysis, and transplantation Patients. Proc Eur Dial Transplant Assoc. 16: 700-2.

[17]. Lipiec, L.; Adam czyk, P.; Swietochowska, E.; *et al.* (2017). Angiotensin gene and Interleukin-18 as Markers of Chronic Kidney Damage in Children with a history of Hemolytic uremic syndrome. Physiol. Res. 66: 251-261).

[18]. Formanowi, Z. D.; Kossowska, M.; Pawlic Zak, E.; *et al.* (2015). Usefulness of Serum interleukin-18 in predicting cardiovascular mortality in patients with chronic kidney disease. System and Clinical approach.

[19] Gil, M; Kim, K. E. (2019). Interleukin-18 Is a Prognostic Biomarker Correlated with CD8+ T Cell and Natural Killer Cell Infiltration in Skin Cutaneous Melanoma. Journal of Clinical Medicine, 8(11), 1993

[20]. Golab, J.; Jakobisiak, M.; Firczuk, M. (2012). Cytokines (in polish). In: Immunology. GOLAB J-Jakobisiak M. Lasek W. StokLosa T(eds), wydawnictwo nankowe PWN, Warszawa, pp 157-197.

[21]. Lalor, S. J.; Dungan, L. S.; Suttan, C.E., *et al* (2011). caspase 1-processed cytokines IL-1 beta and IL-18 promote IL-17 production by gamma delta and CD4 T cells that mediate autoimmunity. J Immunol 186: 5738-5748.

استخدام مصل انترليوكين 18 كمؤشر حيوي للفشل الكلوي المزمن وعلاقته بمستوى البرولاكتين

سوسن عبد الملك عز الدين[1] ، نادية ابراهيم صالح[2]

[1]كلية الصيدلة ، جامعة تكريت ، تكريت ، العراق

[2]كلية الطب ، جامعة تكريت ، تكريت ، العراق

الملخص

الفشل الكلوي تحدث عادة كنتيجة لفقدان الكلى الطبيعية لوظائفها اما بشكل كلي او جزئي. في السنوات الأخيرة, هناك تقاريرتشير الى ان الانترليوكين-18 تلقت انتباه هام كمؤشر التهابي. وترتيط الانترليوكين- 18 ارتباطا وثيقا بوظائف الكلى وتعتبرمؤشرتنبؤي قوي لأضطرابات وظائف الكلى.

الهدف الأساسي لهذا البحث هو دراسة علاقة مستوى البرولاكتين بالفشل الكلوي المزمن وتقييم العلاقة بين مصل انترليوكين-18 والفشل الكلوي المزمن. الدراسة اجريت في مستشفى تكريت التعليمي للفترة من الاول من شهر اذار ولغاية شهر تموزعام 2019, وتضمنت جمع 150 عينة دم من مرضى يعانون من قصور كلوي و 50 عينة دم من اشخاص اصحاء (مجموعة سيطرة). بينت الدراسة ان اعلى نسبة لمستوى البرولاكتين 85% وجدت في النساء المصابات بالفشل الكلوي و 23% وجدت في الذكور, بينما لدى الاصحاء كانت اقل نسبة لمستوى البرولاكتين 7% كانت في الذكور و11% في الأناث.

اظهرت الدراسة الحالية ان هناك علاقة معنوية بين الانترليوكين – 18 والفشل الكلوي المزمن, اذ تزداد مستوى الانترليوكين – 18 عند المرضى الذين يعانون من الفشل الكلوي المزمن مقارنة بالمرضى الأصحاء الذين تم الاعتماد عليهم كمجموعة سيطرة (27±49.5 vs. 49.6±66.5).