Plant Archives Vol. 19 No. 1, 2019 pp. 418-420 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

EVALUATION OF LEVELS OF CYSTATIN C AND INTERLEUKIN 18 AS A MODERN BIOMARKERS OF ACUTE KIDNEY INJURY (AKI) IN KIDNEY STONE PATIENTS

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Abstract

A new biomarkers to recognize AKI more sensitively, specifically, and earlier are needed. Cystatin C and Interleukin 18 are a modern biomarkers of acute kidney injury (AKI) .In the current study, the levels of cystatin C and IL -18 were determined in kidney stone patients .the results reveled a significant increase in the levels of cystatin C and IL -18 in stone patients when compared with the healthy controls ($P \leq 0.05$), these results suggest that Cystatin C and Interleukin 18 consider as promising biomarker for diagnosis, clinical progression and investigations for AKI induced by kidney stone diseases.

Key words: Cystatin C, AKI, Interleukin 18.

Introduction

Due to known limitations in the current gold standard for AKI (creatinine and urea), new biomarkers to recognize AKI more sensitively, specifically, and earlier are needed, Cystatin C is a cysteine protease inhibitor that is released at a constant rate by all nucleated cells into the plasma, is freely filtered by the glomerulus, and is completely reabsorbed in the tubules. Several studies reported that cystatin C appears to predict renal function (i.e. GFR) as well as creatinine in CKD, and even better than creatinine in AKI. Moreover it seems that cystatin C predicts the risk of cardiovascular morbidity and mortality in patients with AKI as well as patients with CKD (Vigil *et al.,* 2014; Carlsson *et al.,* 2014).

Interleukin 18 (IL-18) is a member of the IL-1 cytokine family. It occurs intracellulary as an inactive precursor in monocytes and epithelial cells of the gastrointestinal tract (Dinarello *et al.,* 2013).. The inactive form is activated by caspase-1, and then secreted mainly by macrophages or dendritic cells (Sugawara *et al.,* 2001). Free IL-18 in the cells is normally bound by IL-18 binding protein. The amounts of free IL-18 in the circulation are elevated with increasing imbalance between IL-18 and its binding protein after excess IL-18 production. IL-18 promotes inflammation (Dinarello *et al.,* 2013), and has a role in many autoimmune diseases (Sedimbi *et al.,* 2013).

IL-18 is involved in ischaemic tubular necrosis as shown by animal studies in which IL-18- blocked mice were protected against ischaemic AKI (Melnikov *et al.,* 2002). IL-18 is shown to rise significantly in patients with acute tubular necrosis compared to healthy controls, and patients with various other renal diseases (urinary track infection, prerenal azotaemia, chronic renal diseases, renal transplant patients) (Parikh *et al.,* 2004). In cardiac surgery patients, IL-18 started to rise 4-5h after cardiopulmonary bypass (CPB) and peaked at 12h (Parikh *et al.,* 2006). IL-18 levels have been elevated in patients with sepsis, and especially in patients with gram positive infections (Tschoeke *et al.,* 2006).

The prognostic value of IL-18 in the prediction of AKI in an adult has been investigated in many studies these studies all used urine IL-18 (Siew *et al.,* 2010).

This study aimed to evaluate the levels of Cystatin C and IL-18 as amodern bio markers of AKI in kidney stone patients.

Patients and Methods

"A cross section study done in Tikrit city for the period

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from September 2017 to January 2018. The current study included 75 patients with kidney stone diseases 49 were males and 26 were females there ages range was 35-50 years. All patients were screened and followed up in out-patients clinics in Salah-Aden general hospital. Also, 15 healthy volunteers (5 females and 10 males) served as controls.

"A blood and first morning urine sample was obtained from all patients and healthy volunteers."

"Blood and urine was centrifuged at 3000 RPM for 10 min at 4°C. Aliquots were transferred into tubes, snap frozen and stored at- 20°C until further use. Cystatin C levels was determined in the blood while IL-18 was determined in the urin using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions.

Statistical Analysis:

Statistical analysis the results was performed using *Statistical Package for the Social Sciences* soft ware (SPSS), for windows 7. All data were presented as mean ± S.D. (standard deviation)." Paired T test were used to compare between means of variables between males and females and, *p* values less than 0.05 were used as significant value.

Result and discussion

Cystatin C levels were significantly increased in stone patients when compared with the healthy controls ($P \leq 0.05$).

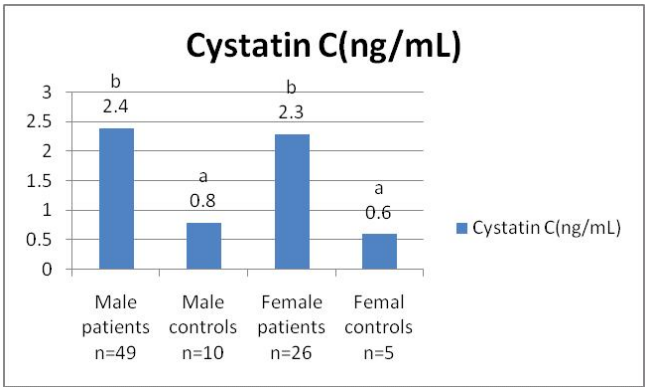

Fig. 1: Cystatin C levels in Healthy Controls and renal calculi patients. (the deferent lettering mean there is a significant differences at $p \leq 0.05$).

Cystatin C is an endogenic marker used for GFR determination because its serum level is dependent to almost whole of Estimated Glomerular Filtration Rate (eGFR) particularly it is seen more valuable in normal and mild decreased eGFR (Harmoinen *et al.,* 1999).

Laterza *et al.* (2002) have attributed cystatin C to be an important reagent in early stage kidney damage to its stabile production, muscle mass, not being dependent to age and gender or not showing reverse tendency to kidney secretion or blood circulation. In our study, the difference in cystatin C levels showed that even in normal buminuria stage, the diabetic renal disease can be identified.

In early kidney disease, there are contradictory results related to the role of cystatin C. As pursuant to our study, two studies show that cystatin C is not more sensitive than creatinine (Perlemoine *et al.,* 2003). Contrary to our results, in the study where cystatin C based equations and creatinine based equations like Schwartz, MDRD and CG formulas are compared and in a meta-analysis where 46 studies included, cystatin C is considered superior than creatinine in determination of decreased GFR. (Herget-Rosenthal *et al.,* 2007; Dharnidharka *et al.,* 2002).

Mumtaz *et al.,* (2016) stated that Although a negative weak relation is detected in cystatin C and eGFR in our study, it was not statistically significant. We think that this situation might be due to the limited number of cases in the patient group. In the study where Mussap and colleagues have examined 52 type 2 diabetic patients, (Mussap *et al.,* 2002) eGFR has decreased from 120 ml/ m/ 1.73 m^2 to 20 ml/m/1.73 m^2 and cystatin C has increased more than the serum creatinine has. The association between Cystatin C and eGFR was detected stronger than the serum creatinine.

In the study of Surendar et al. in Indians who have glucose intolerance, it was determined that cystatin C levels have increased as comparative with glucose intolerance and the highest cystatin C levels were found in the group which had micro albuminuria and retinopathy. (Surendar *et al.,* 2009).

Fig. 2 shows no significant changes within patients groups while shows that the Interleukin 18 levels were significantly increased in stone patients when compared with the healthy controls ($P \leq 0.05$).

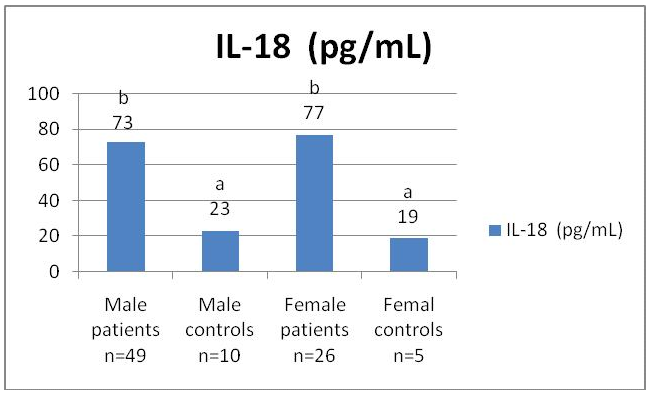

Fig. 2: IL-18 levels in Healthy Controls and renal calculi patients. (the deferent lettering mean there is a significant differences at $p \leq 0.05$).

Our result was graded with Endre *et al.,* (2011), *Siew et al.* (2006) and disagreed with Nisula (2014) who stated that IL-18 yielded an AUC of 0.586 in predicting new AKI during the next 48 hours .some colleagues also reported an independent association of IL-18 with development of AKI . The recent meta-analysis on urine IL-18 by Liu and colleagues reached a pooled AUC of 0.66 for IL-18 in prediction of AKI in critically ill patients (Liu *et al.,* 2013).

It has been previously reported that IL-18 is an early marker of kidney injury that starts to rise in 2-4 hours, peaks at 12 hours, and stays elevated for 24-48 hours after the initial insult to the kidneys 1 (Krawczeski *et al.,* 2011).

With most ICU patients there is significant delay between the onset of illness and admission to the ICU, and the early onset of the IL-18 rise might be one factor explaining its poor performance as a kidney injury marker in this group of patients. This hypothesis is supported by the finding in study III that the median concentration of IL-18 in AKI patients was decreasing from admission to 24 hours suggesting an earlier peak in IL-18. (Endre *et al.,* 2011).

The study by Siew and colleagues presented a composite end point of death or dialysis during 28 days with only 17 patients fulfilling this end point. The adjusted OR for IL-18 was 1.76 (Siew *et al.,* 2010) but IL-18 was not significant for predicting dialysis alone. The AUC (0.655) for IL-18 in prediction of RRT in study doesn't support the use of IL-18 for this purpose (Siew *et al.,* 2010).

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