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Study the Association of Asprosin and Dickkopf-3 with KIM-1, NTpro-BNP, GDF-15 and CPP among Male Iraqi with Chronic Kidney Disease.

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ABSTRACT
In chronic kidney disease (CKD), kidneys develop injured over time and don't work properly as in the kidneys for healthy people. At what time the kidneys cannot blood clean, further liquids stay and wastes in the body and which leads to many problems in health, such as high blood pressure (BP) and cardiovascular disease (CVD). In current study, we attempt to examine the association of asprosin (APN) and dickkopf-3 (DKK-3) with kidney injury molecule-1 (KIM-1), N-terminal pro-brain natriuretic peptide (NTpro-BNP), growth differentiation factor 15 (GDF-15) and copeptin (CPP) among male Iraqi with CKD.
Methods: serum APN, DKK-3, KIM-1, NTpro-BNP, GDF-15 and CPP were determined by ELISA technique in 40 healthy controls (HCs) and 44 male patients with CKD, from the Al-Fallujah teaching hospital were recorded in this paper, serum concentrations of urea, creatinine and estimated glomerular filtration rate (eGFR) were measured by colorimetric methods
Results: serum APN and DKK-3 were importantly greater in CKD males than in HCs (P<0.0001) and they positively associated with KIM-1, NTpro-BNP, GDF-15 and CPP (P<0.01), also serum concentration of ANP was positively associated DKK-3 (P<01). Studied variables presented the following descending order of area under the receiver operating characteristic (AUROC) curve urea, creatinine and e GFR (1for all, P<0.0001), KIM-1(0.9896), APN (0.939), CPP (0.8966), DKK-3 (0.893), NTpro-BNP (0.8558) and GDF-15 (0.8375) respectively (P<0.0001for all).
Conclusion: serum levels APN, DKK3 KIM-1, NTpro-BNP, GDF-15 and CPP may be a biomarker of renal damage in CKD development in Iraqi males.
Key words: Asprosin, Dickkopf-3, Copeptin, Chronic Kidney Disease.
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INTRODUCTION
Chronic kidney disease (CKD) is an advanced situation which consists of several diseases with heterogeneous pathways, and leads to permanent variations of kidney structure and function [1]. CKD may cause severe problems for example heart failure, metabolic bone disease and anemia [2].
Asprosin (APN) secreted by white adipose tissue (WAT) has been discovering as a new hormone. It is protein consist of 140-amino acid [3]. APN levels are augmented in many situations such as type 2 diabetes mellitus and obesity, and are linked with concentrations of triglycerides and fasting glucose [4]. Until now, the clinical research on relationship between CKD and APN is very limited and does not exceed the fingers of one hand globally. No previous study has evaluated the APN concentration in males with CKD. Also, the correlation among other cytokine with APN has studied very limitedly.
Dickkopf-3 (DKK-3) member of glycoproteins group (DKK1–4) which controls the pathway of Wnt signalling [5]. Recent data showed sign that DKK-3 is expressed in the evolving kidney, repressed in life of adult and neo-expressed under conditions of renal pathology, such as tissue damage of renal [6]. It appears to be an element of gene clusters for evolutionarily preserved, which are stimulate in progressions of evolving, afterward quieted and reexpressed in statuses of infection. So, it is important that former experiments *in vitro* discovered that DKK-3 may activate or inhibit canonical signalling of Wnt/b-catenin [7].
Despite the stated roles of KIM-1 in damage of acute kidney, many signs observed for its function in CKD [8]. Previous study reported that urinary and serum KIM-1 concentrations augmented after many days in unilateral ureteral obstruction mice, however serum levels of creatinine did not alteration. Concentration of KIM-1 in urine had been established to be strictly linked to KIM-1 concentration in urine and to relate with injury of kidney tissue [10]. It was revealed KIM-1 to be up-regulated in many nephropathy of allograft and in human primary and secondary diseases of kidney [11]. KIM-1 expression was related with inflammation and fibrosis of kidney [11].
N-terminal pro-Btype natriuretic peptide (NT-proBNP) is excreted from the ventricles of heart in reply to tension and wall stretch of ventricular [12]. It was described to be associated to occurrence of CKD in the common populace of USA, but contributors in this research were restricted to individuals more than 65 years in age [13]. Previous paper in CKD patients was conformed a strong relationship between NTproBNP to adverse results of renal. Serum concentrations of NT-proBNP was raised and strongly related with CKD in advanced stages [14]. Yet, no studies have tested relations of NT-proBNP with decline renal function in a males Iraqi with CKD, which may explain the impact of CVD to negative results of renal and recognize chances for primary interferences. Thus, in this paper, we studied the NTproBNP relationship with renal function decline in males Iraqi without and with CKD.
Growth differentiation factor15 (GDF15) is belonging to the cytokine superfamily called TGF-β, which augmented their expression in reply to neurohormones, other proinflammatory cytokines and ischemia of tissue [15]. Limited papers have studied of GDF-15 relationship with development of CKD. Previous study stated an important relationship among GDF-15 raises with fast renal function decline and increase of CKD occurrence [16].

Copeptin (CPP), is glycoprotein consist of 39 amino acid, it is precursor of arginine vasopressin (AVP) by part of carboxyl-terminal and is secreted synergistically with AVP from the hypothalamus. Due to its superior stability it is easier to estimate serum level of CPP instead of AVP, one study confirmed strong relationship among mature AVP with CPP, that means we can use CPP as new instead of AVP [17]. CPP is removed relatively via the renal so that, CPP concentration is greater in patients with CKD, than others conserved function of renal [18]. In T2DM patients and CKD, greater concentration of CPP was related to greater risk of sudden cardiac death, all-cause mortality and stroke [19].

The central goal of this paper was to explore effects of APN and DKK-3 on KIM-1, NTpro-BNP, GDF-15 and CPP concentrations, in addition to urea, creatinine and eGFR concentrations in CKD Iraqi males and HCs, also to detect links among APN and DKK3 concentrations with KIM-1, NTpro-BNP, GDF-15 and CPP concentrations.

MATERIALS AND METHODS

This data contain of 44 Iraqi males with CKD (not include stage 5) and 40 HCs who enrolled at the nephrology unit at the Al-Fallujah Teaching Hospital between July 2019 and December 2019. Samples of blood were taken after fasting for 8-12 hours. Serum urea and creatinine were determined via colorimetric methods by kits equipped from the Spanish company linear. Serum levels of APN, DKK-3, KIM-1, NTpro-BNP, GDF-15 and CPP were estimated by an ELISA technique using kits equipped from the MyBioSource company (USA), estimated GFR calculated through the modification of diet in renal disease study (MDRD) equation, which is the one endorsed via the renal association (UK) and national institute for clinical excellence (NICE).

All CKD patients did not appear important history of CVD depending on radiography of chest, clinical examination and recording of electrocardiography. The criteria of rejection were firstly age less than 35 or more than 70 years, secondly eGFR less than 20 ml/min/1.73 m^2, end stage renal disease (ESRD) and high or low blood pressure. The search followed to the Helsinki declaration, and was permitted by committee of local ethics in University Of Anbar. All CKD patients donated printed agreement before being joined into the study.

STATISTICAL ANALYSIS

Data in this study were done by GraphPad Prism version 7 and SPSS version 25. Results were stated as mean (standard deviation [SD] and standard error of mean [SEM]). Unpaired Student's t test was done to estimate differences in biomarkers among control and patients group. The Pearson correlation test was calculated to explore all correlations between APN and DKK3 with other studied biomarkers. Receiver operating characteristic (ROC) curve investigation with area under curve (AUC) determination was done to estimate the prognostic value of all studied biomarkers in CKD. Significance of statistical analysis was supposed for a p value less than 0.05.

RESULTS

The laboratory data and general characteristics of this paper were established in Table 1. There was no difference in age between HCs and CKD group ($p>0.05$), but HCs had lower concentrations of urea (29.3 *vs* 55.12 mg/dL; figure 1), creatinine (0.8736 *vs* 2.238 mg/dL; figure 2), APN (4.741 *vs* 12.06 ng/mL; figure 4), DKK-3 (10.97 *vs* 21.22ng/mL; figure 5), KIM-1 (2.172 *vs* 6.157 ng/mL; figure 6), NTpro-BNP (2.454 *vs* 4.749 ng/mL; figure 7), GDF-15 (693 *vs* 1919 pg/mL; figure 8) and CPP (1.772 *vs* 4.034 ng/mL; figure 9) than the patients with CKD ($p<0.0001$). There was a significant upsurge of eGFR in HCs (97.18 *vs* 33.39 ml/min/1.73m^2; figure 3) as regarded to patients with CKD ($p<0.0001$).

Table 1: Distribution of Studied Biomarkers in healthy control and CKD patients group

Parameter	Healthy controls			CKD Patients			
	Mean	SD	SEM	Mean	SD	SE	p-value
Age years	55.43	9.61	1.173	57.87	11.42	1.371	>0.05
Urea mg/dL	29.3	7.91	1.251	55.12	16	2.499	<0.0001
Creatinine mg/dL	0.8736	0.2554	0.04038	2.238	0.6801	0.1062	<0.0001
eGFR (ml/min/1.73m^2)	97.18	12.13	1.918	33.39	9.752	1.523	<0.0001
APN ng/mL	4.741	2.416	0.382	12.06	4.213	0.6579	<0.0001
DKK-3 ng/mL	10.97	4.975	0.7867	21.22	6.691	1.045	<0.0001
KIM-1 ng/mL	2.172	0.9518	0.1505	6.157	1.652	0.2581	<0.0001
NTpro-BNP ng/mL	2.454	1.195	0.189	4.749	1.74	0.2717	<0.0001
GDF-15 pg/mL	693	470.6	74.41	1919	1095	171.1	<0.0001
CPP ng/mL	1.772	0.7639	0.1208	4.034	1.474	0.2303	<0.0001

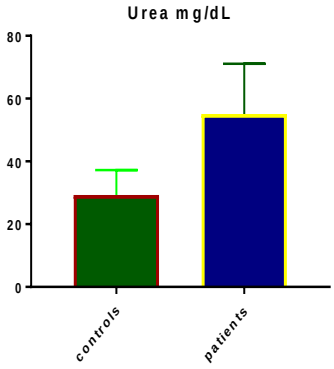

Fig. (1): mean+ S.D for Urea

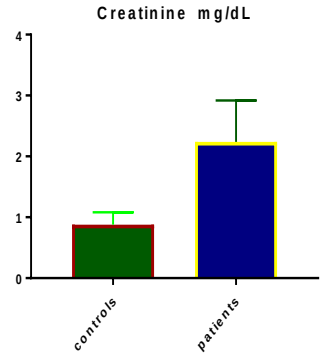

Fig. (2): mean+ S.D for creatinine

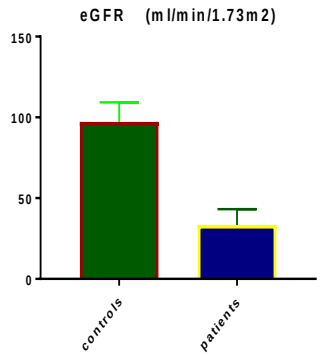

Fig. (3): mean+ S.D for eGFR

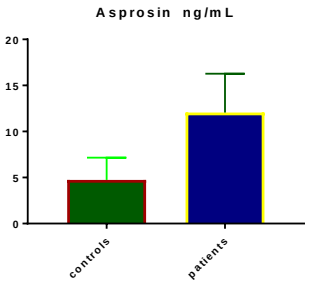

Fig. (4): mean+ S.D for Asprosin

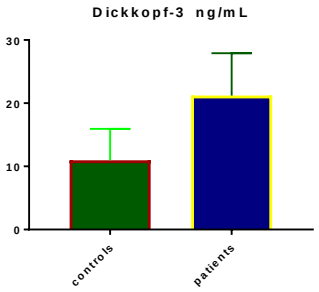

Fig. (5): mean+ S.D for Dickkopf-3

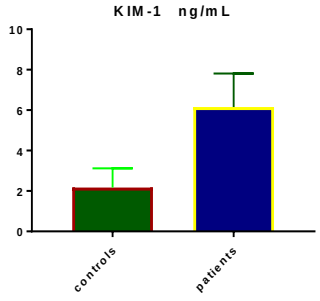

Fig. (6): mean+ S.D for KIM-1

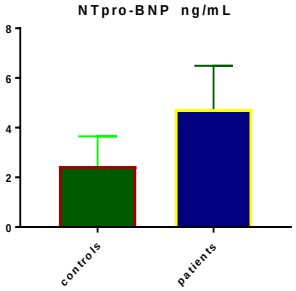

Fig. (7): mean+ S.D for NTpro-BNP

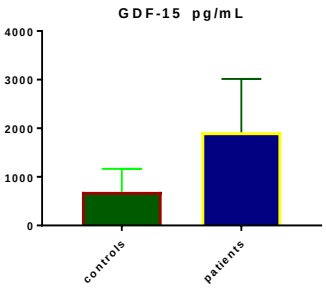

Fig. (8): mean+ S.D for GDF-15

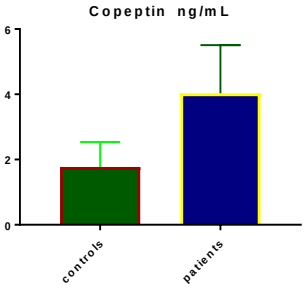

Fig. (9): mean+ S.D for Copeptin

Spearman's correlation examination exhibited that serum APN and DKK-3 concentrations were positively related with KIM-1 (r=0.610 and r=0.529), NTpro-BNP (r=–0.301 and r=0.627), GDF-15 (r= 0.524 and r= 0.405) and CPP (r= 0.519 and r= 0.305) and negatively related with serum eGFR (r=–0.683 and r=–0.594) with p-value less than 0.01 for all these relationships as presented in table 2.

Furthermore, an important but weak positive relationship was established among APN and DKK-3 concentrations (r=–0.362; p<0. 01). A strong positive association was similarly detected among APN and DKK-3 concentrations with urea (r=0.775 and r=0.635) and creatinine(r=0.573 and r=0.578) with p-value less than 0.01 for all these relationships as presented in table 2.

Table 2: The Association of Asprosin and Dickkopf-3 with all studied biomarkers

Biomarker		Asprosin ng/mL	Dickkopf-3 ng/mL
APN	ng/mL	1	0.362*
DKK-3	ng/mL	0.362*	1
KIM-1	ng/mL	0.610*	0.529*
NTpro-BNP	ng/mL	0.301*	0.627*
GDF-1	pg/mL	0.524*	0.405*
CPP	ng/mL	0.519*	0.305*
Urea	mg/dL	0.775*	0.635*
Creatinine	mg/dL	0.573*	0.578*

eGFR (ml/min/1.73m^2)	-0.683*	-0.594*
*P is significant; it was less than 0.01 for all variables.		

A ROC curve investigation for serum urea, creatinine and eGFR in patients with CKD (Figures 10-12 respectively and Table 3) exhibited that the AUC was excellent and very perfect with value equal 1 (95% CI 1-1) and this was expected because these three parameters are very specialized for kidney function. A ROC curve examination for other studied variables in patients with CKD (Figures 13-18 and Table 2) displayed the following values of AUCs 0.939 (95% CI 00.8928 to 0.9853) of ANP, 0.893 (95% CI 0.8279 to 0.9581), DKK3 0.9896 (95% CI 0.9737 to 1.006), KIM-1 0.8558 (95% CI 00.777 to 0.9346), NTproBNP 0.8375 (95% CI 0.7536 to 0.9214) and GDF-15 0.8966 (95% 0.8312 to 0.9621), p value for all studied parameters was less than 0.0001.

Table 3: Diagnostic Criteria of the ROC Curves for Tested Variables in Patients with CKD

Variable	AUC	Std. Error	95% confidence interval (CI)	P-value
Urea mg/dL	1	0	1 to 1	<0.0001
Creatinine mg/dL	1	0	1 to 1	<0.0001
eGFR (ml/min/1.73m^2)	1	0	1 to 1	<0.0001
APN ng/mL	0.939	0.02359	0.8928 to 0.9853	<0.0001
DKK-3 ng/mL	0.893	0.03322	0.8279 to 0.9581	<0.0001
KIM-1 ng/mL	0.9896	0.008145	0.9737 to 1.006	<0.0001
NTpro-BNP ng/mL	0.8558	0.04019	0.777 to 0.9346	<0.0001
GDF-15 pg/mL	0.8375	0.04281	0.7536 to 0.9214	<0.0001
CPP ng/mL	0.8966	0.0334	0.8312 to 0.9621	<0.0001

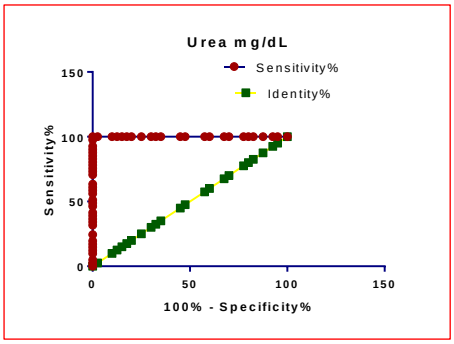

Fig. 10: ROC curve displaying AUC of Urea in CKD patients

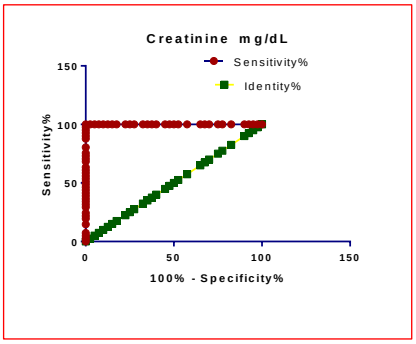

Fig. 11: ROC curve displaying AUC of Creatinine in CKD patients

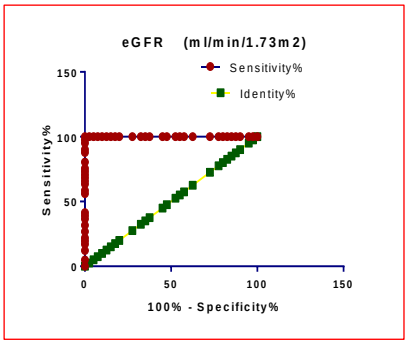

Fig. 12: ROC curve displaying AUC of eGFR in CKD patients

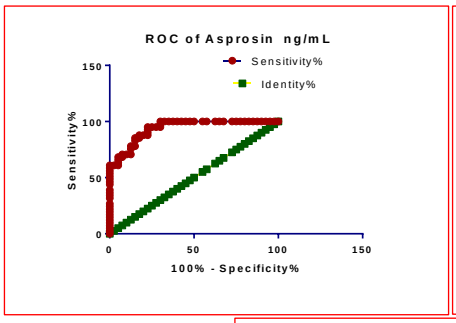

Fig. 13: ROC curve displaying AUC of APN in CKD patients

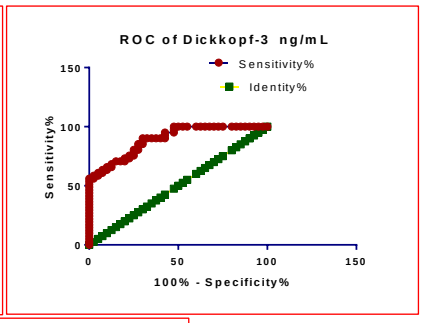

Fig. 14: ROC curve displaying AUC of DKK-3 in CKD patients

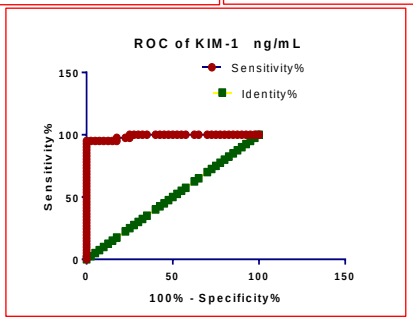

Fig. 15: ROC curve displaying AUC of KIM-1 in CKD patients

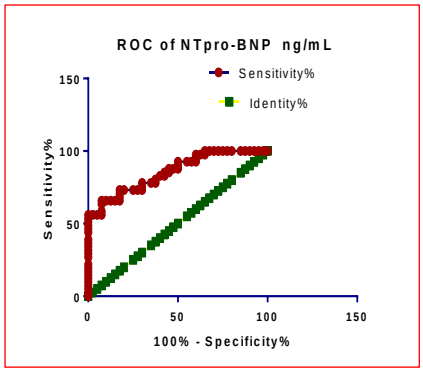

Fig. 16: ROC curve displaying AUC of NTproBNP in CKD patients

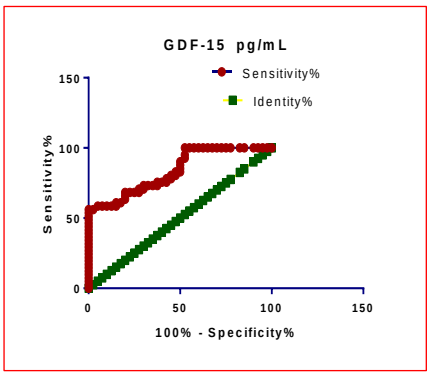

Fig. 17: ROC curve displaying AUC of GDF-15 in CKD patients

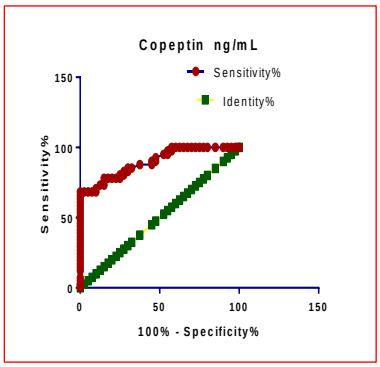

Fig. 18: ROC curve displaying AUC of CPP in CKD patients

DISCUSSION

At this time, there is a main task in the medical controlling of CKD, which is the requirement for prior identification of CKD, exactly prior ESRD incidence, which is necessary and irrevocable, quick identification makes it probable for a well result and quick medicinal interference.

Serum concentrations of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP were extremely increased in CKD patients than in HCs group. This may clarify the ease of making these variables for the early identification of CKD in Iraqi men.

Very recent paper stated antiasprosin may importantly inhibit the biological development and pathophysiological of diabetic nephropathy in rats with T2DM, that showing, it may use as a new renoprotective mediator in patients with CKD [20]. The mechanism that causes development of renal disease with increase APN serum levels not completely predictable.

In the present search, we detected a positive relationship between APN with urea, creatinine, DKK-3, KIM-1, NTpro-BNP, GDF-15, and CPP, but this relationship was altered into a strong negative relationship with eGFR. APN is reported to exert a strong function in PCOS progress by having a linkage with pathophysiological pathways for example inflammation and insulin resistance [21]. For the reason of APN glycogenic function in production of glucose [22], it may contribute in all forms of diabetes pathogenesis and problems of diabetic for example nephropathy and retinopathy [23]. Diabetic nephropathy considers first cause of CKD in the world, so, in the current paper; the possible influence of APN on CKD was investigated.

Present study indicated that DKK-3 levels have important changes in HCs as compared to CKD patients; potent positive associations of DKK3 was revealed with urea, creatinine, APN, KIM-1, NTpro-BNP, GDF-15, and CPP, while eGFR presented a potent inverse association with DKK3. It acts as calcineurin inhibitors, immunosuppressive and, molecule of profibrotic [24]. T cells are significant

participates to a nonresolving, chronic inflammation may causes kidney fibrosis advanced [25]. Hence, it is interesting that preserving function and morphology of kidney in the lack of DKK3 was associated with T cell augmented and increase in the interstitium of kidney with tendency toward producing Th1, Tregs and IFNγ. While previous study indicated that IFNγ and Th1 cells, especially, may play a useful function in fibrosis of kidney [26].

Kidney injury molecule-1 as significant variable for the diagnosis of CKD patients which examined in many papers in the world. Previous data containing CKD patients with stage 4 and 3, estimated serum KIM-1 concentrations as significant variable for the diagnosis increase of CKD in people in England [27]. KIM1 may also reflects features injury of proximal tubular which detecting the degree of proximal tubule injury, whereas KIM-1 existence in the blood stream may be assisted via tubular cell polarity loss with damage [28]. Another study indicated that chronic expression of KIM-1 may causes fibrosis of tubule interstitial and inflammation, endogenous mutant of KIM-1 mice was saved from fibrosis in a CKD model [29].

Function of kidney affects the concentrations of plasmatic NT-pro-BNP and may reduce their efficacy as biomarkers of hemodynamic in CKD. As well, NT-proBNP was related with a greater CKD risk when NTproBNP was used as a significant biomarker. This proposes that the NT-proBNP concentration, can strongly guess occurrence of CKD. A number of mechanisms are suggested to clarify the association between NT-proBNP increasing and occurrence CKD. It is improved by volume overload, congestion of venous and stretch of ventricular wall [30]. Furthermore, NT-proBNP increasing proposes a decreased rate of clearance produced by dysfunction of kidney, because secretion of kidney is the chief way for clearance of NT-proBNP [31]. Parallel to this data, previous study indicated robust relations between in failure of renal function and high levels of NT pro BNP [32].

The current search detects concentration of GDF-15 was very higher in patients with CKD as compared to HCs group. GDF15 is an induced cytokine as inflammatory states of stress response, after damage of tissue and oxidative stress response [33]. New study demonstrated strong correlation between high levels of GDF15 with decline function of kidney [34]. Another previous search of TIDN was indicated high level of GDF-15 was correlated with quicker drop in eGFR but not ESRD development [35]. GDF15 is likely to be a new variable to diagnosis progression of CKD in men Iraqi patients.

The significance of CPP in CKD has been demonstrated in many studies. In those with CKD, high level of CPP was related with an augmented sudden cardiac death, all causes of mortality and stroke risk [36]. High level of CPP was related to decrease in GFR and increase reduce of kidney function in with renal transplant patients, New data presented the correlation for serum concentration of CPP with many biomarkers of CKD, results of this study were consistent with the results of our study [37]. Present study showed a probable pivotal function of high levels of CPP in CKD development. Supposing relationship between progressions of CKD with increasing CPP concentrations, for example low level of CPP through augmented influence of pharmacological or intake of water is likely to be a target for cure encouraging. This study explains useful properties of reducing CPP levels by augmented hydration in the development of CKD men Iraqi patients.

In ROC investigation, KIM-1 and APN was the best indicator of diagnosis CKD in Iraqi males with values of AUCs more than 0.9 which means these biomarkers very specific to predicate and diagnosis CKD, in second place came CPP, DKK-3, GDF-16 and NTpro-BNP respectively, with values of AUCs more than 0.8.In this study, higher levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP were related with an augmented risk of adverse kidney results in CKD patients. Nonetheless, the power of urea, creatinine and eGFR as predictors of CKD was more than expellant and very perfect with values of AUCs equal to one. Our data confirm that serum ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP were excellent variables to diagnosis progression of CKD in men Iraqi. Nonetheless, more analysis is wanted to detect the clear role of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP in CKD pathogenesis of. To our knowledge, this search is the first to evaluate the function of APN in CKD patients in world.

The main limitations of this search consist of, firstly, this data was built on men Iraqi patients therefore the outcomes may have narrow generalizability, thus, the outcomes should be widespread with care, and more searches are wanted to measure the medical significance of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP in many people from other countries in the world. Secondly, eGFR was not estimated from samples of patients, but it was calculated by MDRD equation. Thirdly, collect of samples were from single center only with inadequate size of samples and any cure that was taken by patients with CKD not calculated which may declining the relationship between of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP with occurrence of CKD. Fourthly, other diseases information for example, myocardial infarction, angina pectoris and cardiovascular diseases was collected through a questionnaire analysis or reviewing medicinal records in the current paper, the limited number of patients with CKD involved in the search did not permit investigation and classifications of results regarding to estimation of kidney disease stage for patients. Cutoff values of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP didn't calculate whereas this requires very large numbers of CKD patients to be endorsed. Fifthly serum levels of urea, creatinine ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP was determined one time only, which may have not permitted us to precise assessment, unluckily, our data can't to compare serum levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP to reference values, whereas no information obtainable of serum normal values for these biomarkers from a reliable sources. With all this our search, very important where it is the first study try to explore the association between serum levels of APN with eGFR in patients with CKD.

In conclusions this search studied the possible functions for serum levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP in CKD Iraqi men and HCs and we confirmed that serum levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15

and CPP augmented in CKD patients as compared to HCs, also this study identify robust positive relationship of ANP with DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP. Furthermore, serum levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP may exert a key function in CKD cure and progress. Hence, results of our study suggest that serum levels of ANP, DKK3, KIM-1, NT-pro-BNP, GDF-15 and CPP can be used as an important variable of CKD. Similarly we determine, serum level of APN is a very suitable test to identify CKD in Iraqi men. Serum levels of APN maybe a new variable to determine CKD in Iraqi men. Furthermore, great serum concentrations of APN show an elevated of CKD risk and further decline of renal function. We also confirmed that elevated APN and DKK-3 concentrations are inversely linked with eGFR in CKD Iraqi men.

The current paper is the first which determine the relationship between APN and raised CKD risk in Iraqi men. Serum levels of ANP, DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP are not only CKD screening variables but likewise may be important predictors for occurrence of CKD in Iraqi men. Our data may be a chance to detect novel parameters for dysfunction of kidney in Iraqi men. New studies may be necessary to more find out of the essential pathophysiology for dysfunction of kidney which associated with high serum levels of ANP, DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP in patients with CKD. Nonetheless, bigger studies in future with larger sample size are necessary with the aim of endorsing our clarifications and to more certify the biological efficacy and use of ANP, DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP in diagnosis or treatment of CKD in Iraqi men. This study showed that serum levels of NT-proBNP are related with quick weakening of renal function and CKD occurrence. These data propose that cardiovascular disease patients are at great risk for CKD in future. All of the examined variables were importantly increased in CKD patients and negatively associating with eGFR. Additional investigations are required to determination whether serum levels of ANP, DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP are basically variables or exert main roles in the patients with CKD.

Finally serum levels of ANP, DKK3 KIM-1, NT-pro-BNP, GDF-15 and CPP could be possible and dependable variables for the quick diagnosis of CKD. More, multicenter, multiethnic and multination prospective cohort studies are necessary to create the evidence more forceful.

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CONFLICT INTEREST

No conflicts of interest

REFERENCES

1. Webster, A.C.; Nagler, E.V.; Morton, R.L *et al.* Chronic Kidney Disease. *Lancet (*2017), 389: 1238–1252.
2. Saran, R.; Robinson, B.; Abbott, K.C.; *et al.* US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am. J. Kidney Dis.* (2018), 71: A7.
3. Romere, C., Duerrschmid, C., Bournat, J., *et al.,* Asprosin, a fasting-induced glucogenic protein hormone. *Cell* (2016), 165: 566–579.
4. Zhang L, Chen C, Zhou N, *et al.* Circulating asprosin concentrations are increased in type 2 diabetes mellitus and independently associated with fasting glucose and triglyceride. *Clin Chim Acta*. (2019), 489:183–8.
5. Grone EF, Federico G, Nelson PJ *et al.* The hermetic functions of Wnt pathways in tubular injury. *Pflugers Arch Eur J Physiol* (2017);469: 899–906.
6. Federico G, Meister M, Mathow D *et al.* Tubular Dickkopf-3 promotes the development of renal atrophy and fibrosis. *JCI Insight* (2016); 1: e84916.
7. Nakamura RE, Hackam AS. Analysis of Dickkopf3 interactions with Wnt signaling receptors. *Growth Factors* (2010); 28: 232–242.
8. Humphreys BD, Xu F, Sabbisetti V, *et al.* Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. *J Clin Invest.* (2013); 123: 4023–4035.
9. Sabbisetti VS, Waikar SS, Antoine DJ, *et al*. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. *J Am Soc Nephrol.* (2014); 25: 2177–2186.
10. Luo QH, Chen ML, Sun FJ, *et al.* KIM-1 and NGAL as biomarkers of nephrotoxicity induced by gentamicin in rats. *Mol Cell Biochem*. (2014); 397: 53–60.
11. van Timmeren MM, van den Heuvel MC, Bailly V, *et al.* Tubular kidney injury molecule-1 (KIM-1) in human renal disease. *J Pathol. (2007);* 212: 209–217.
12. Martinez-Rumayor A, Richards AM, Burnett JC, *et al.* Biology of the natriuretic peptides. *Am J Cardiol* (2008); 101: 3 – 8.
13. Bansal N, Katz R, Dalrymple L, *et al.* NT-proBNP and troponin T and risk of rapid kidney function decline and incident CKD in elderly adults. *Clin J Am Soc Nephrol* (2015); 10: 205 – 214.
14. Desai AS, Toto R, Jarolim P, *et al.* Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. *Am J Kidney Dis*. (2011), 58: 717–728.
15. Preusch MR, Baeuerle M, Albrecht C, *et al.* GDF-15 protects from macrophage accumulation in a mousemodel of advanced atherosclerosis. *Eur J Med Res* (2013), 18: 19.
16. Ho JE, Hwang SJ, Wollert KC, *et al.* Biomarkers of cardiovascular stress and incident chronic kidney disease. *Clin Chem* (2013), 59: 1613–1620.
17. Bankir L, Bouby N, Ritz E: Vasopressin: a novel target for the prevention and retardation of kidney disease? *Nat Rev Nephrol* (2013); 9: 223–239.

18. Morgenthaler NG, Struck J, Jochberger S, *et al.* Copeptin: clinical use of a new biomarker. *Trends Endocrinol Metab* (2008); 19: 43–49.
19. Fenske W, Wanner C, Allolio B, *et al.* Copeptin levels associate with cardiovascular events in patients with ESRD and type 2 diabetes mellitus. *J AM Soc Nephrol* (2011); 22: 782– 790.
20. . El Kattawy H.A; Ashour W.M.R. Anti- Asprosin: A Potential Protective Role Against the Progression of Diabetic Nephropathy in Type 2 Diabetic Rats. *Am. J. Biomed. Sci.* (2019), 11(3): 183-199.
21. Alan M, Gurlek B, Yilmaz A, *et al.* Asprosin: a novel peptide hormone related to insulin resistance in women with polycystic ovary syndrome. *Gynecological Endocrinology*, (2018):1-4.
22. Romere C, Duerrschmid C, Bournat J, *et al.* Asprosin, a Fasting-Induced Glucogenic Protein Hormone. *Cell* (2016); 165(3): 566-579.
23. Gheith O, Farouk N, Nampoory N, *et al.* Diabetic kidney disease: worldwide difference of prevalence and risk factors. J Nephropharmacol (2016); 5(1): 49-56.
24. Federico G, Meister M, Mathow D, *et al.* Tubular Dickkopf-3 promotes the development of renal atrophy and fibrosis. *JCI Insight*. (2016); 1(1): e84916.
25. Nikolic-Paterson DJ. CD4+ T cells: a potential player in renal fibrosis. *Kidney Int.* (2010);78(4): 333–335.
26. Oldroyd SD, Thomas GL, Gabbiani G, *et al.* Interferon-γ inhibits experimental renal fibrosis. *Kidney Int.* (1999); 56(6): 2116–2127.
27. Alderson HV, Ritchie JP, Pagano S *et al.* The Associations of Blood Kidney Injury Molecule-1 and Neutrophil Gelatinase–Associated Lipocalin with Progression from CKD to ESRD. *Clin J Am Soc Nephrol.* (2016); 11(12): 2141–49.
28. Nowak N, Skupien J, Niewczas MA *et al.* Increased plasma kidney injury molecule-1 suggests early progressive renal decline in non-proteinuric patientswithtype1diabetes.*KidneyInt* (2016); 89: 459–467.
29. Humphreys BD, Xu F, Sabbisetti V, *et al.* Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. *J Clin Invest*. (2013); 123: 4023–4035.
30. Koratala A, Kazory A. Natriuretic peptides as biomarkers for congestive states: The cardiorenal divergence. *Dis Markers* (2017); 2017: 1454986.
31. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* (2004); 6: 257 – 260.
32. Patel UD, Garg AX, Krumholz HM, *et al.* Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium: Preoperative serum brain natriuretic peptide and risk of acute kidney injury after cardiac surgery. *Circulation* (2012), 125: 1347–1355.
33. Adela R, Banerjee SK. GDF-15 as a Target and biomarker for diabetes and cardiovascular diseases: a translational prospective. *J Diabetes Res*. (2015); 2015: 490842.
34. Nair, V., Robinson-Cohen, C., Smith, M, *et al.* Growth differentiation factor-15 and risk of CKD progression. *J.Am.Soc.Nephrol*. (2017), 28: 2233–2240.
35. Lajer M, Jorsal A, Tarnow L, *et al.* Plasma growth differentiation factor-15 independently predicts all-cause and cardiovascular mortality as well as deterioration of kidney function in type 1 diabetic patients with nephropathy. *Diabetes Care* (2010), 33: 1567–1572.
36. Fenske W, Wanner C, Allolio B, *et al.* Copeptin levels associate with cardiovascular events in patients with ESRD and type 2 diabetes mellitus. *J AM Soc Nephrol* (2011); 22: 782– 790.
37. Ponte B, Pruijm M, Ackermann D, *et al.* Copeptin is associated with kidney length, renal function, and prevalence of simple cysts in a population-based study. *J Am Soc Nephrol* (2015), 26:, 1415–25.