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Assessment of Proenkephalin (PENK) and Interleukin-18 (IL-18) Biomarkers for Detection of Acute Kidney Injury in Patient with Acute Heart Failure

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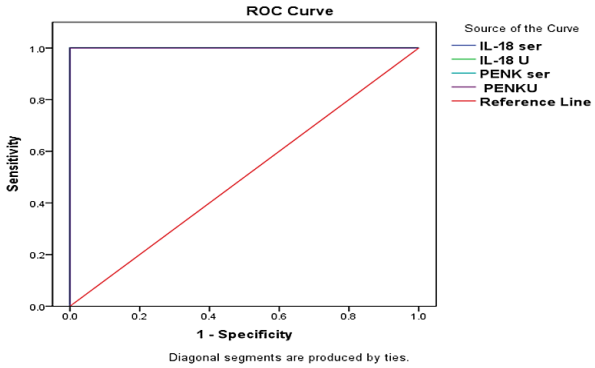
ABSTRACT

Acute kidney injury (AKI) is a reiterated kind of organ injury in acute heart failure (AHF). As for data collection, AKI markers of serum and urine were applied for both proenkephalin (S-PENK and U-PENK) and interlocune-18(S-IL-18 and U-IL-18) in AHF. The study aimed to evaluate the competency of (S-PENK and U-PENK) and (S-IL-18 and U-IL-18) to prognosticate acute kidney injury in AHF patients. Modern studies indicate that Proenkephalin (PENK) is produced in kidneys, muscles, lung, intestine, heart, and central nervous system. The cytokine interleukin-18 (IL-18) is involved in the detection of AKI in AHF patients. Serum and urine PENK and IL-18 levels for all healthy and AHF patients were tested via enzyme-linked immunosorbent assay (ELISA). The results notably revealed that serum PENK and urine PENK level increased considerably with disease severity and were quite compatible with those who reported higher mean serum PENK and urine PENK in patients diagnosed with AHF in comparison to the healthy control group. The results of this study suggest that S- PENK, U PENK, S-IL-18, and U-IL-18 can be useful potential biomarkers for diagnosis of AKI in patients AHF. In conclusion, the level of PENK and IL-18 is significantly increased in AHF, suggesting that PENK and IL-18 are a good indicator for detection of AKI in patients AHF.

GRAPHICAL ABSTRACT



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Introduction

Zinc oxide (ZnO) is an inorganic metal oxide that Acute kidney injury (AKI) that occur during heart failure (HF) has been categorized as a cardio renal syndrome (CRS) type 1 [1]. CRS was first presented by Ronco *et al*. (2008) as an endeavor to expound the discourse between the heart and kidneys, recognized as a pathophysiologic illness of the heart and kidneys in which chronic or acute dysfunction of one organ may result in chronic or acute dysfunction of the other. CRS has five categories. The first, third and fifth types of CRS [2-4**]** Proenkephalin (PENK) have lately been utilized as a precise biomarker for kidney function and heart failure [5-6]. Also, IL-18 has been identified as a robust biomarker for cardiovascular disease and acute heart Failure [7-8].

Proenkephalin is an endogenous opiate peptide that has cardiac depressant impacts, such as lessening heart rate and restraining norepinephrine secretion, as well as reforming kidney function by increasing urinary output and renal blood flow. It is a stable alternative to enkephalin [9-10]. The biologically active enkephalin is hard to measure because of its short half-life and the lack of stability after collation. PENK possesses a long half-life in vivo, is stable after collation, and its levels are not affected by gender or age, acting as a befitting alternative to its biologically active counterparts for critically poor patients. [11].

Proenkephalin (PENK) is an internal mono peptide spilled from preproenkephalin A that is associated with enkephalin peptides. Enkephalins are connected with opiate receptors, and they are yielded in the central nervous system, kidneys, intestine, muscles, lung, and heart. PENK has many characteristics of an exemplary Glomerular filtration (GFR) biomarker; it is endogenous and freely filtered by the glomeruli due to its little molecular size (4.5 k Da) [9].

Research has highlighted a method to measure patients with acute coronary syndromes, and to identify strong predictor of cardiovascular death, Cytokines happen through the effects on atherosclerotic plaque destabilization. Circulating interleukin (IL)-18 levels can be identified as an important mediator of the innate immune response. High circulating levels of IL-18 can be found in patients with acute coronary syndromes, and can be identified as a potent predictor of acute heart failure and cardiovascular death [12- 13]. More lately, the plant with serum IL-18 levels are correlated with metabolic risk factors, including waist circumference, body mass index (BMI), and fasting triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and insulin levels and glucose as well as systolic and diastolic blood pressure (BP) [12].

Interleukin (IL)-18, originally identified as an interferon (IFN)-ɤ–inducing factor in Kupffer cells and macrophages, plays a major role in the inflammatory cascade and in the processes of innate and acquired immunities owing to its ability to stimulate IFN-ɤ production in T natural killer cells and lymphocytes that is deemed to play a pivotal role in atherosclerotic plaque rupture. Moreover, IL-18 has a part in upholding IL-12 to boost the development of T helper 1 (TH1) responses [14].

Materials and methods

Subjects

The research was carried out with 45 control subjects and also 45 acute heart failure (AHF) patients with the age ranging 35 to 68 years old. The control group was considered as non-diabetic. There was also no record of drinking or consuming alcohol. Patients were selected randomly selected from those who attended Baghdad Teaching Hospital/Medical City and Yarmouk Hospital. Blood and urine samples were collected and a well-structured questionnaire, including age, gender, smoking and BMI, was filled in after a full clinical examination by the consultants. Acute heart failure patients were determined.

Methods

Blood samples (8 ml) were collected from 90 people; after being placed in a centrifuge at 3500 rpm for 10 minutes, the serum was frozen at 80 °C for detection and the same condition was taken for urine samples (8 ml) from 90 people, taken on the first morning in a clean container free of any detergents. And. IL-18 and PENK levels in serum

and urine samples were examined by enzyme-linked immunosorbent assay kits supplied by Melsin (China). A spectrophotometer was used to measure lipids and renal creatinine.

Statistical analysis

To analyze the data, SPSS-22 was used. The data were expressed as means ±SD. Statistical significance the difference in the mean of a normal distribution quantitative variable was evaluated through an analysis Fisher exact. P-value ≤ 0.05 was considered as significant. Receiver operating characteristic (ROC) curves were utilized to analyze the early diagnostic value of urine IL-18 and PENK levels for AHF.

Results and Discussions

Description of the groups of AHF and healthy control

Table 1 shows the mean values (± SD), the extent and distribution of the studied groups (number and percentage), age (in years), gender, and smoking and disease stages.

The mean values of ± SD for age for the healthy group and the AHF were 50.689 ± 7.954 and 51.200 ± 7.497, respectively. The results were not significant between the groups (P> 0.05) between the mean values of (± SD) for age in the studied groups. However, we noticed that patients with AHF were the most common among the elderly.

The Gender ratio of the two groups was 40.54% for male and 56.603% for female and 59.46% for male and 43.396% for female for the healthy group and the AHF, respectively. The results showed no significant (P>0.05) difference between the gender ratio in the studied groups; men were higher than women in general. Smoking results were not significant (P> 0.05), and considering this variable, we noticed that it was higher in the group of patients.

The stage percentage in the studied groups was the result of highly significant differences (P< 0.05) between the stages shared by the studied groups. The stages depend on the result of the eGFR test and how well the kidneys are filtering waste and extra fluid from the blood.

Table1: The mean (± SD) values and Distribution (number and percentage) for some epidemiological variables and healthy groups with AHF

Variables	Cats.	G1			G2		Total		P value
		N		%	N	%	N	%	
Age (years) b		50.689± 7.954 (37-67)			51.200±7.497 (40-68)		(50.94±7.69) 37-68		0.755NS^
Gender a		M	15	40.54	22	59.46	37	41.11	0.134NS^
		F	30	56.603	23	43.396	53	58.89	
Smoking a		0	35	53.030	31	46.97	66	73.33	0.340NS^
		1	10	41.67	14	58.333	24	26.667	
Stage C		I	45	100.00	0.00	0.00	45	50.00	0.000Sig*
		II	0	0.00	42	100.00	42	46.67	
		IIIa	0	0.00	1	100.00	2	1.11	
		IIIb	0	0.00	2	100.00	1	2.22	

a=chi square b =Two sample T test C=Fisher exact

Also, as presented in Table 2, the results were significant (P < 0.05) for (BMI and WHR). The body mass index (BMI) is higher in AHF than the healthy ones, also Waist-to-hip Ratio **(**WHR**).**

Table 2: Mean values (±SD) and distribution (number and percentage) of BMI and WHR variables for patient group and healthy group

	Groups	Min	Max.	Mean	±SD	P value
BMI	Healthy	17.306	39.136	27.524	6.160	0.001 Sig*.
	AHF	22.173	44.259	32.036	6.301	
WHR	Healthy	0.700	1.010	0.832	0.118	0.038 Sig*.
	AHF	0.743	0.992	0.880	0.097	

*=significant at p<0.05., ^=not significant at p >0.05

As can be seen in Table 3, the results were significant (P < 0.05) for uric acid, urea, s.cr, ACR and eGFR. The mean in AHF group is higher than that of healthy group except for eGFR which is higher in healthy group than that of AHF group.

Table 3: Mean ± SD and range of renal function parameter for the Healthy group and acute kidney injury (AKI) in patients' acute heart failure (AHF) group and healthy group

		Minimum	Maximum	Mean	±SD	P value
Uric acid	Healthy	3.100	6.120	4.377	1.186	0.000*
	AHF	1.020	8.830	5.060	1.530	
Urea	Healthy	17.000	32.000	22.867	4.855	0.000*
	AHF	10.000	43.000	26.933	7.703	
s.cr	Healthy	0.510	0.840	0.661	0.114	0.000*
	AHF	0.780	2.560	0.966	0.359	
Albumin- Creatinine ratio (ACR)	Healthy	4.545	27.397	14.143	8.926	0.000*
	AHF	22.883	364.078	63.649	74.379	
e GFR	Healthy	90.749	145.860	113.768	19.821	0.000*
	AHF	27.492	90.544	77.979	13.616	

*=significant at p<0.05., ^=not significant at p >0.05

Lipid profile

Based in Table 4, the result serum lipid profile is significant (p<0.05) except for HDL with no significance (p >0.05). The mean in AHF group was higher than that of the healthy group.

Table 4: Mean ± SD value and their range of serum lipid profile for acute kidney injury (AKI) in patients' acute heart failure (AHF) group and healthy group

		Minimum	Maximum	Mean	±SD	P value
CHO	Healthy	141.000	288.000	172.400	36.053	0.000 Sig*.
	AHF	112.000	274.000	204.333	31.210	
HDL	Healthy	25.000	70.000	44.467	12.185	0.416 NS^
	AHF	31.000	58.000	46.222	7.693	
LDL	Healthy	66.000	130.000	103.467	17.078	0.012 Sig*.
	AHF	40.000	169.000	117.222	31.798	
VLDL	Healthy	8.000	65.000	23.267	13.317	0.000 Sig*.
	AHF	19.000	70.000	41.889	12.824	
TG	Healthy	40.000	324.000	115.933	66.251	0.000 Sig*.
	AHF	96.000	351.000	209.333	64.166	

*=significant at p<0.05., ^=not significant at p >0.05.

PENK (Serum and Urine) and Il-18 (Serum and Urine) levels

Table (5) shows that the result of PENK (serum and urine) and IL-18(serum and urine) is significant (p<0.05); the mean in AHF group was higher than that of healthy group.

Table 5: Mean ±SD value and their range of PENK (serum and urine) and IL-18(serum and urine) for acute kidney injury (AKI) in patients acute heart failure (AHF) and Healthy

	Groups	Minimum	Maximum	Mean	±SD	P value
IL-18 Ser	Healthy	3.574	48.328	16.793	10.219	0.000*
	AHF	117.460	802.700	305.575	161.551	
IL-18 U	Healthy	4.521	47.335	18.257	9.333	0.000*
	AHF	118.000	802.800	306.630	162.858	
PENK ser	Healthy	22.810	66.494	42.500	8.964	0.000*
	AHF	377.830	808.300	609.180	162.753	
PENK U	Healthy	22.477	69.103	46.919	9.031	0.000*
	AHF	399.860	802.800	610.944	151.708	

*=significant at p<0.05., ^=not significant at p >0.05.

ROC area under the curve

Based on Table 6, ROC analysis showed that PENK (serum and urine) (AUC) is (1) specificity =%100 and sensitivity=%97.8. Considering the value of PENK by 800 pg/ml, test value higher than 800 Pg/ml is considered abnormal case whereas above this value points to the healthy subjects as shown in Figure 1 and Table 6. IL-18 (serum and urine) (AUC) is (1) specificity =%100 and sensitivity = %95.6. Considering the value of IL-18 by 320 pg/ml, test value higher than 320 Pg/ml is considered abnormal case whereas above this value represents the healthy subjects as shown in Figure 1 and Table 6 as sensitive indicators of AHF, suggesting that PENK (serum and urine) and IL-18 (serum and urine) may be a potentially useful biomarker in early diagnosis of AKI for patients AHF.

Table 6: ROC for PENK (serum and urine) and IL-18(serum and urine) between AHF group and healthy group

Groups	Area Under the Curve					
	Test Result Variable(s)	Area	%sensitivity	%specificity	P value	
Control from AHF	PENK ser (pg/ml)	1	97.8	100	0.000	Sig*.
Control from AHF	PENK U (pg/ml)	1	97.8	100	0.000	Sig*
Control from AHF	of IL-18 ser (pg/ml)	1	95.6	100	0.000	Sig*
Control from AHF	of IL-18 U (pg/ml)	1	95.6	100	0.000	Sig*

*=significant at p<0.05., ^=not significant at p >0.05.

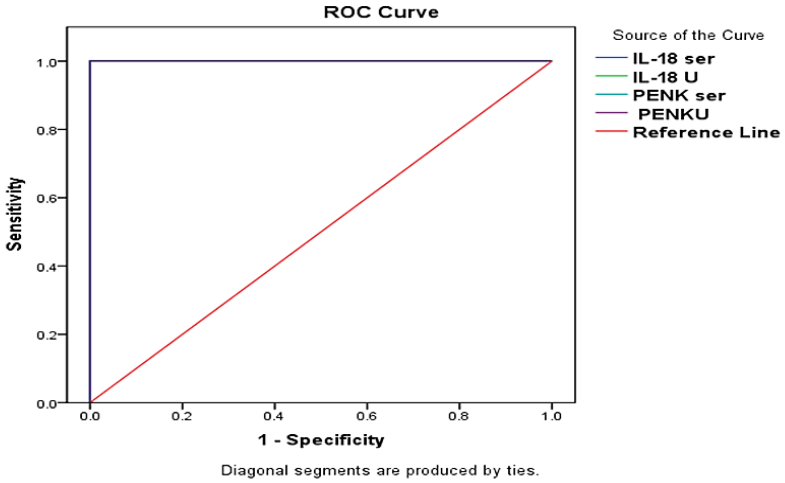

Figure 1: ROC curve displaying the trade-off between sensitivity (rate of true positive) and rate of false positive (1-specificity) for PENK (serum and urine) and IL-18 (serum and urine) concentration when used to acute kidney injury (AKI) in patients' acute heart failure AHF with healthy controls

As clear from Table 1, the result is no significant (P >0.05) but considering that patients were older than healthy people, they are more susceptible to diseases [15]. Also, the gender ratio in the studied groups was not significant (P > 0.05), but the results were slightly higher in men than in women, suggesting that men and women are more likely to develop heart diseases, also women are more likely to develop heart diseases [16]. Further, men are more likely to die from heart disease [17]. Note that the samples were not equal. The result for the smoking was no significant (P >0.05) but we noticed that the percentages of patient groups who smoke were higher compared with healthy people. Smoking is the main cause of heart disease [18]. While the stage ration in the studied groups the result was highly significant (p <0.05) as anticipated, the incidence increased in patients with eGFR < 60mL/min/1.73 m^2 due to the lower renal functional reserve produced by the HF itself or due to co-morbidities and age, which increased the risk of renal functional deterioration. [19- 20].

As can be seen in Table 2, the result was significant ($p < 0.05$) in BMI and WHR; the more people gain weight, the more susceptible they are to diseases [21-22]. In Table 3, the kidney function results were significant ($p < 0.05$); when a person suffers from heart failure, the kidneys are affected, thus kidney function is affected, leading to the rise in the level of uric acid, urea, serum creatinine, and ACR [23-26]. As for eGFE, the level of renal clearance was low in case of the kidneys and heart diseases [20].

Based on Table 4, the results of serum lipid profile were significant ($p < 0.05$) except HDL whose result was not significant ($P > 0.05$) which was higher in patients groups than in healthy groups [27- 28]. Lipids causes the heart disease that lead to the kidney disease. Clinical studies strongly suggest that hyperlipidemia can cause glomerulosclerosis and tubulointerstitial fibrosis and induce renal injury harm [29]. As illustrated in Table 5, the results were significant ($p < 0.05$) as the level of PENK increased compared with healthy levels, since PENK (serum and urine) is a biomarker of the renal heart [6- 30]. IL-18 (serum and urine) was significant ($P < 0.05$) as the level of IL-18 in AHF patients was higher compared with healthy groups [8- 31].

As clear from Table 6, the result of the significant level of PENK was obtained at ($P < 0.000$). ROC analysis showed that PENK was a sensitive indicator of AHF, suggesting that serum and urine may be an advantageous biomarker for diagnosis of AKI in AHF patients [30, 32-33]. The results were also significant ($P < 0.000$) for IL-18 (serum and urine) [8, 34, 35].

Conclusion

In summary, as far as the research to screen for acute kidney injury (AKI) in patients with acute heart failure (AHF) is considered, the available evidence indicates that PENK and IL-18 are a more accurate biomarkers for detecting acute kidney injury than the current methods. However, further investigations with a large number of patients enrolled for a longer noting period are required to confirm previous findings in AHF.

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