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The Role of Omentin-1 in Cardio-renal Syndrome

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ABSTRACT

Acute heart disease patients often go on to develop worsening renal function, termed as a cardiorenal syndrome(CRS). Cardiorenal syndrome is defined as "disorders of the heart and kidneys where by acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. Methods: Omentin-1 were measured in 144 subjects including: 50 samples with cardiorenal syndrome, 25 samples with heart disease, 25 samples with kidney disease and 44 normal healthy . Results: A highly significant increase ($p<0.0001$) in the levels of omentin-1 with cardiorenal syndrome patients, a highly significant decrease in patients with heart disease and significant decrease ($p<0.05$) in patients with kidney disease group when compared with control group. There is no significant differences between males and females, while significant increase ($p<0.05$) in <50 years age groups in patients with heart cardiorenal syndrome and significant decrease ($p<0.05$) in <50 years age groups in patients with kidney disease when compared with 38-50 years age group. Conclusions Omentin-1 have higher diagnostic validity values in the current study, which may be useful as a diagnostic tool to identify recurrence of the cardiorenal syndromes.

Keywords : *Cardiorenal syndrome, Omentin-1, Heart disease, Kidney disease.*

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دور هرمون الاومنتين-١ في المتلازمة القلبية الكلوية

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الملخص

إن الهدف من الدراسة الحالية هو تقييم دور هرمون الاومنتين-١ في أمراض القلب التي يصاحبها مضاعفات كلوية (متلازمة قلبية كلوية) وأمراض القلب وأمراض الكلى. تم قياس هذا الهرمون في مصل دم 144 عينة :-50 عينة لمرضى المتلازمة القلبية الكلوية و25 لمرضى القلب و25 عينة لمرضى الكلى و٤٤ عينة للأصحاء تم استخدامها كمجموعة سيطرة للمقارنة.

أن النتائج التي تم الحصول عليها من هذه الدراسة أظهرت وجود ارتفاع معنوي عالي ($p<0.0001$) في تركيز هرمون الأومنتين-١ في مصل دم مرضى المتلازمة القلبية الكلوية وانخفاض معنوي عالي ($p<0.0001$) في مصل دم مرضى القلب وانخفاض معنوي ($p<0.05$) في مصل دم مرضى الكلى مقارنة مع مجموعة السيطرة (الأصحاء) ، لا توجد فروقات معنوية بين الذكور والاناث ولكن يوجد ارتفاع معنوي ($p<0.05$) في الفئة العمرية (<50) في مصل دم مرضى المتلازمة القلبية مقارنة مع الفئة العمرية (38-50)، كما يوجد انخفاض معنوي ($p<0.05$) في الفئة العمرية (<50) في مصل دم مرضى الكلى مقارنة مع الفئة العمرية (38-50). الاستنتاجات :- ان الاومنتين-1 في الدراسة الحالية يمتلك قيم صحة تشخيص عالية، والتي ربما يمكن استخدامها كأداة تشخيص لتحديد تكرار حدوث المتلازمة القلبية الكلوية.

الكلمات الدالة: المتلازمة القلبية الكلوية ، الاومنتين-1، امراض القلب ، امراض الكلى.

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List of Abbreviation:- CRS= Cardio-renal syndrome**,** CAD = coronary artery disease , ROC =Receiver operating characteristics, AUC =The area under the curve.

1.Introduction

Cardiorenal syndrome is defined as "disorders of the heart and kidneys where by acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other" [1]. The exact cause of deterioration of kidney function and the mechanism underlying this interaction are complex, multifactorial in nature, and still not completely understood. Renal dysfunction is one of the most important comorbidities in heart failure. Reduced estimated glomerular filtration rate seems to be a potent predictor of cardiovascular complications and mortality. Patients with renal dysfunction have a significantly increase risk of developing an adverse outcome after acute myocardial infarction[2]. The most common underlying risk factors that account for renal dysfunction in the setting of heart failure or cardiac dysfunction include hypertension, diabetes mellitus, severe atherosclerotic disease, elderly age and a prior history of renal insufficiency or heart failure[3].

Omentin-1 has been identified as a major visceral (omental) fat secretory adipokine. The mature omentin is a secretory glycoprotein consisting of 295 amino acids and N-linked oligosaccharides, and its basic structural unit is a 120-kD homotrimer in which 40-kD polypeptides are bridged by disulfide bonds. Omentin-1 is a 32 kD adipokine that is primarily secreted by stromal vascular cells in visceral adipose tissue, and is expressed to a lesser extent in the heart, lung, and placenta and heart and highly abundant in human plasma[4]. This fat depot-specific protein is synthesized by visceral stromal vascular cells, but not adipocytes[5]. Omentin-1 is a new type of Ca^{2+}-dependent lectin with affinity for galacto furanosyl residues (constituents of pathogens and dominant inmunogens). It is suggested, therefore, that a biological function of omentin/intelectin is the specific recognition of pathogens and bacterial components, an important role in the innate immune response to parasitic infections**.** Moreover, several studies have shown that omentin gene expression is altered by inflammatory states and obesity[6]. The aim of this is to find levels of omentin-1, and their relationship with cardiorenal syndrome.

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2.Materials and Methods

Blood samples were collected from one hundred fourty four subjects (ages range from (38–70) years) , they divided into four groups:

Group 1: Included a total of 50 patients (30 males and 20 females); their ages ranged from 40-65 years for females and (38-70) years for males. All of them are suffering from heart with kidney diseases.

Group 2: Included a total of 25 patients (13 males and 12 females); their ages ranged from 38 to 70 years for males and for 40 to 65 years for females. They are suffering from heart disease.

Group 3: Included a total of 25 patients (13 males and 12 females); their ages ranged from 38 to 68 years for males and 40 to 65 years for females . They are suffering from kidney diseases.

Group 4: This group is including 44 apparently healthy controls (22 males and 22 females); their ages ranged from 38 to 70 years.

The omentin-1 assay employs the quantitative sandwich enzyme immunoassay technique suppliers by GenAsia companies[7].

Statistical analysis:- The significante of difference between mean values were estimated by student T-test. The probability $P < 0.0001$=highly significant , $P < 0.05$ = significant, $P > 0.05$ = non-significant. Also the data were processed with the software package SPSS (statistical package for social science) Ver. 22 (SPSS Inc. Chicago IL) and Microsoft Excel XP version to estimated the ROC and cut off values .

3. Results and Discussion

The mean (±SD) of omentin-1 concentration in the sera of control group (healthy control), patients with cardiorenal syndrome group, patients with heart disease group and patients with kidney disease group are illustrated in Table (1) .

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Table (1): Mean ±SD of omentin-1 ng/ml concentration in the all studied groups according to gender.

Omentin-1	Healthy control n=44	CRS n=50	Heart diseases n=25	Kidney diseases n=25
Total	414.29±86.12	536.84±55.6*	298.56±56.3*	344.85±85.37#
Males	412.95±94.61	534.84±61.42	298.46±51.54	346.27± 49.62
Females	415.6±78.94	538.84±50.5	298.66±63.39	342.58± 63.54

* high Significant $p<0.0001$ compared with healthy control

Significant $p<0.05$ compared with healthy control

There is a highly significant increase ($p<0.0001$) in serum levels of omentin-1 in cardiorenal syndromes group, a highly significant decrease ($p<0.0001$) in heart disease group and significant decrease ($p<0.05$) in kidney disease group when compared with the control group, no significant differences between males and females, while significant increase in >50 years age groups in cardiorenal syndromes group and significant decrease in >50 years age groups in kidney disease group when compared with (38-50) age group, as shown in the Table (2).

Table (2): Mean (±SD) omentin-1 ng/ml concentration in the all studied groups according to age.

Omentin-1	Healthy control n=44	CRS n=50	Heart disease n=25	Kidney disease n=25
38-50years	433.4±93.1	506.55±52.3	299±44.6	384.37± 39.33
>50years	398.3±78.1	557.03±48.9*	298.21±65.7	304.4± 72.24#

** high Significant $p<0.05$ compared with age group > 50

Significant $p<0.05$ compared with age group > 50

There is a highly significant increase ($p<0.0001$) in the sera levels of omentin-1 in cardiorenal syndromes group when compared with (heart and kidney) diseases groups, a significant decrease ($p<0.05$) in the sera levels of omentin-1 in heart disease group when compared with kidney disease group.

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Receiver operating characteristics (ROC) curves were used to compare the performance of the biochemical diagnostic methods of diseases in this study and to determine the appropriate cut off values for the omentin-1. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to analyze the diagnostic value of hormone. The area under the curve (AUC) was commonly used as a summary measure of diagnostic accuracy. Table (3) shows the criteria of statistical diagnosis validity of omentin-1 level in cardiorenal syndrome group compared with control by using 431 ng/ml as cut-off value (The optimal cut-off value for omentin-1 in all groups estimated from ROC curves). According to these results, test is positive if test > threshold value (cut off values). Fig. (1) explained the ROC curve for omentin-1 concentration in cardiorenal syndrome group, sensitivity and specificity shown in fig. (2).

Table (3): Predictive values of serum omentin-1 level in in cardiorenal syndrome group using 431 ng/ml as cut-off value.

Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
98%	68%	77%	96%	84%	0.868

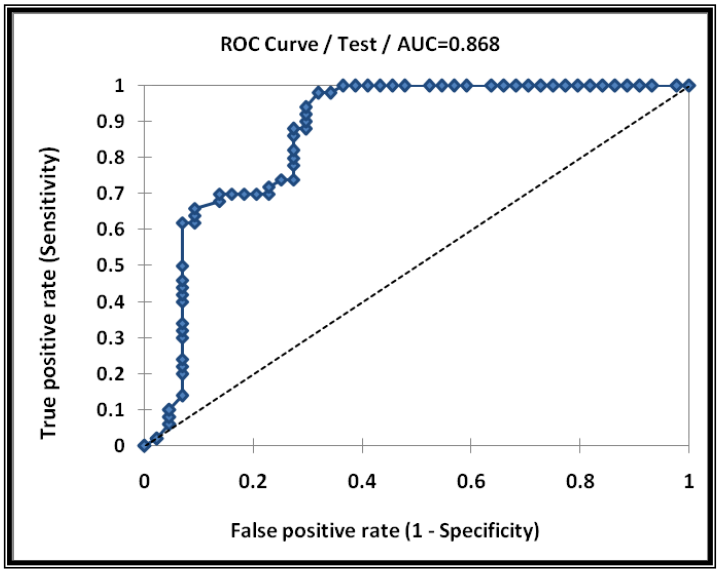

Fig. (1): ROC curve for omentin-1 concentration in cardiorenal syndrome group

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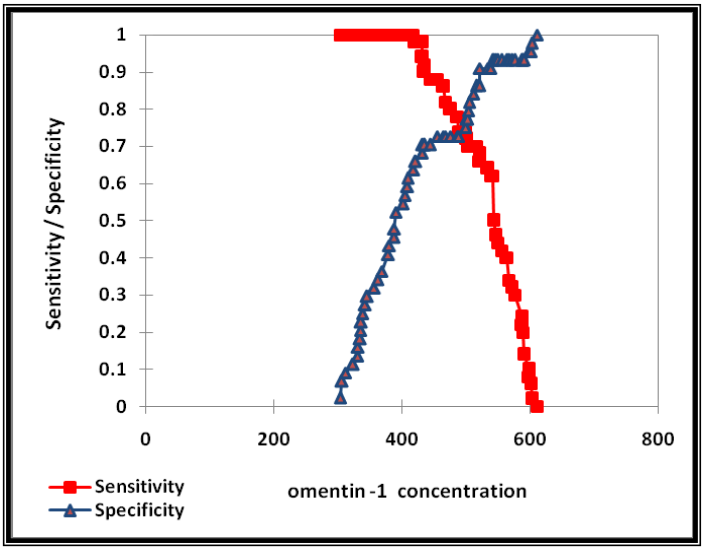

Fig.(2): Sensitivity and specificity test for omentin-1concentration in cardiorenal syndrome group

Table (4) shows the criteria of statistical diagnosis validity of omentin-1 level in heart disease group compared with control by using 3.12 ng/ml as cut-off value. Fig. (3) explained the ROC curve for omentin-1 concentration in heart disease group, sensitivity and specificity shown in Fig. (4). According to these results , test is positive if test < cut off values.

Table (4): Predictive values of serum omentin-1 level in heart disease group using 3.12 ng/ml as cut-off value.

Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
99%	97%	90%	86%	92%	0.987

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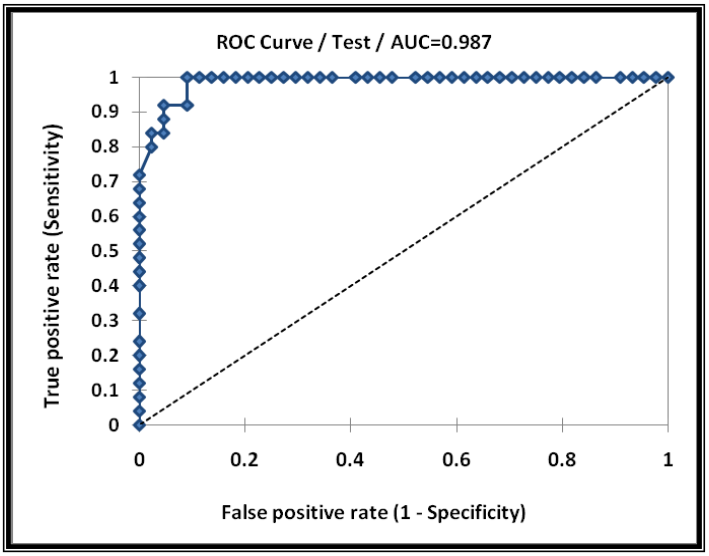

Fig. (3): ROC curve for omentin-1 concentration in heart disease group

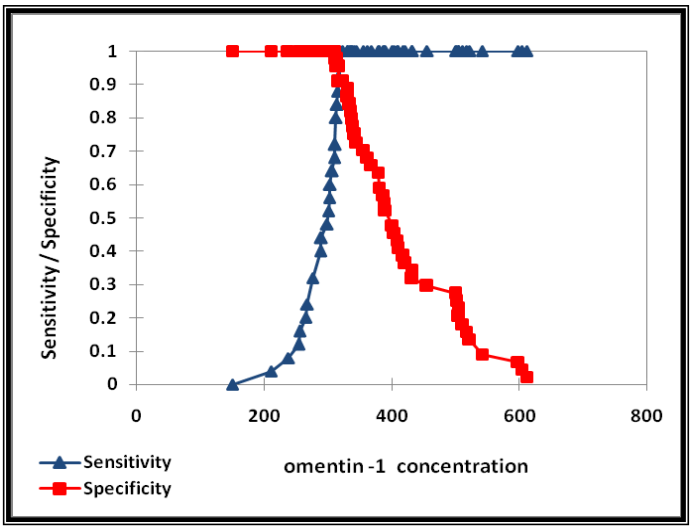

Fig. (4): Sensitivity and specificity test for omentin-1 concentration in heart disease group

Table (5) shows the criteria of statistical diagnosis validity of omentin-1 level in kidney disease group compared with control by using 323 ng/ml as cut-off value. Fig. (5) explained the ROC curve for omentin-1 concentration in kidney disease group, sensitivity and specificity shown in Fig. (6). According to these results , test is positive if test < threshold value (cut off values).

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Table (5): Predictive values of serum omentin-1 level in kidney disease group using 323 ng/ml as cut-off value.

Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
60%	63%	73%	53%	50%	0.756

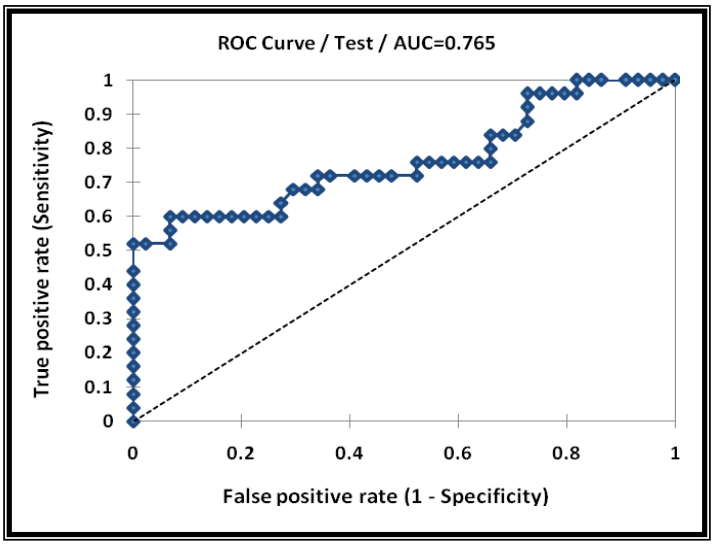

Fig. (5): ROC curve for omentin-1 concentration in kidney disease group

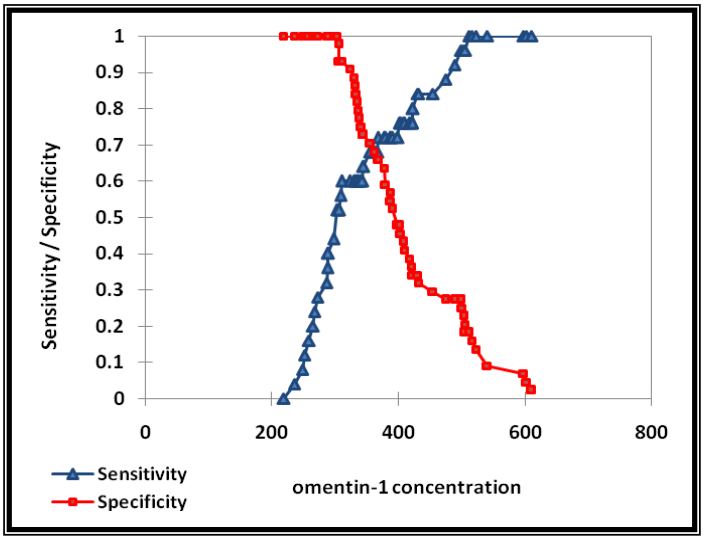

Fig. (6): Sensitivity and specificity test for omentin-1 concentration in kidney disease group

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Omentin is expressed in visceral adipose tissue and it has anti-inflammatory effects[8]. The relationship between circulating omentin-1 with cardiovascular health were investigated in several clinical studies. *Moreno-Navarrete et al*.(2011) and others demonstrated that omentin was independently associated with endothelial dysfunction after controlling for adiposity, age, and inflammation[9]-[11]. This study showed that serum omentin-1 levels were lower in patients with heart and kidney disease, than in control participants, and this was concomitant with other studies. more importantly, they found that serum omentin-1 levels were independently associated with coronary artery disease (CAD) prevalence. Mechanisms of the association of omentin-1 with CAD have not been elucidated; however, one could consider several possibilities. Omentin induces endothelium-dependent relaxation via endothelium-derived nitric oxide through phosphorylation of endothelial nitric oxide synthase in rat isolated aorta[12]. Coronary artery disease may also be associated with impaired endothelium dependent coronary dilatation. Therefore, omentin may participate in CAD development at least in part through regulation of coronary contractility. In one study, decreased insulin sensitivity was associated with increased incidence of myocardial infarction and death, even after adjusting cardiovascular risk for smoking and low physical activity. As a result, decreased omentin-1 levels may contribute to the development of CAD by modulating insulin action. The present data showed that decreased omentin expression is implicated in a variety of chronic inflammatory diseases[13]. In *Narumi et al (2014)* study, they found that serum omentin-1 level appears to be a novel prognostic marker for the risk stratification of patients with heart failure[14].

Adiponectin has been suggested to play a role in the prevention of cardiovascular diseases via its anti-inflammatory, anti-oxidant, and antiapoptotic properties. Reports have shown several adipokines to have beneficial effects on cardiovascular diseases[15],[16]. Unlike to adiponectin, serum omentin-1 was reported to decrease with chronic inflammation and oxidative stress in patients with heart failure. Nonetheless, there was a significant relationship between serum omentin-1 levels and cardiac events[14],[17]. Systemic inflammation, accelerated atherosclerosis and insulin resistance are common pathogenic features of end stage renal disease. Low omentin levels are associated with endothelial dysfunction, atherosclerosis and cardiovascular diseases. When we neglect the possible effects of chronic kidney disease on omentin, the expected result was the reduced levels of omentin in hemodialysis patients due to inflammation, insulin resistance and accelerated atherosclerosis.

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We found unexpectedly, significantly higher levels of omentin-1 in the cardiorenal syndrome group than in the control group, and this disagrees with its role as anti-inflammation. The reason of increased levels of omentin-1 in our opinion might be related to impaired renal clearance , and defective degradation and excretion, and this agreed with few studies which found higher levels of omentin in end stage renal disease patients. This may due to the size of omentin which is relatively large protein, which during hemodialysis may not be significantly cleared from plasma. Currently there is no study supporting our estimation related to omentin excretion, but generally most adipokines such as adiponectin, visfatin and resistin are elevated in patients with chronic kidney disease, likely owing to decreased renal excretion[18]-[20]. But similarly, another important adipokine, adiponectin, has been shown to be eliminated or biodegraded through the renal route. also, increased levels of adipokine were shown in parallel with deterioration of renal function[18],[21]. An increase in inflammation and malnutrition components was correlated with a decrease in the serum level of omentin[22].

4. Conclusion

Omentin-1 levels measurement showed a significant of variety in the cardiorenal syndrome, heart disease and kidney patients, and it is more sensitive in cardiorenal syndrome which give: valuable information for diagnosis, good monitoring disease status and progression of the disease.

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