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Cardio-Renal Syndrome

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ABSTRACT

The cardio-renal syndrome (CRS) can be generally defined as a pathophysiologic disorder includes a broad spectrum of diseases in which heart and kidney are both involved, the CRS classification essentially recognizes two main groups, cardio-renal and Reno-cardiac syndromes, on the basis of ‘‘premium moves’’ of disease (cardiac or renal); both cardio-renal and Reno-cardiac syndromes are then divided into acute and chronic, according to the disease’s onset, Five subtypes of the syndromes were identified, abrupt worsening of cardiac function that lead to acute kidney injury called Acute Cardio-renal Syndrome or Type 1 CRS, this appears to be a syndrome of worsening renal function that frequently complicates hospitalized patients with acute heart failure and acute coronary syndrome. When Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) cause progressive and potentially permanent chronic kidney disease this condition called chronic cardio-renal syndrome or Type 2 CRS, CKD has been observed in 45-63% of CHF patients24, 25, 26, [10].

The number of participants in the questionnaire is 100 and the questionnaire was distributed in two ways. In the first way, the questionnaire was published on social media and the number of participants was 79 and the number of pharmacists participating in the electronic questionnaire was 51 and the number of participating physicians was 28. In the second way, the questionnaire was distributed to a group of private pharmacies in Baghdad, which numbered 21 and purpose of the questionnaire was to find out if the participants had any information about Cardio-renal Syndrome.

Heart and kidney interactions are complex and the subject of immense clinical and scientific interest and debate. In this article, we argue that without consensus on definitions and classification, clinicians will not be able to precisely phenotype the various forms of cardio- renal syndrome. Such phenotyping, in turn, forms the basis for in vitro and animal studies, as well as small translational studies in patients. Through the ADQI consensus on CRS, other processes will now be facilitated, including a better or clearer understanding of the epidemiology of these conditions, opportunities for early diagnosis through biomarkers, the development of preventive strategies and application of evidence-based management strategies

Keywords: *Kidney failure, cardiovascular disease, cardio-renal syndrome, Reno-cardiac syndrome*

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INTRODUCTION

Kidney failure occurs when the kidneys partly or completely lose their ability to filter water and waste from the blood, the buildup of toxic substances normally removed from the body by the kidneys can cause dangerous health problems [1].

Acute renal failure or acute kidney disease (AKD) occurs when your kidneys suddenly become unable to filter waste products from your blood, dangerous levels of wastes may accumulate, and your blood & chemical makeup may get out of balance. It can be fatal and requires intensive treatment. However, it may be reversible, if you & otherwise in good health, you may recover normal or nearly normal kidney function, it occurs in about 5% of people who are hospitalized for any reason. It is even more common in those receiving intensive care [2].

Abnormality of the kidney structure or function, present for more than 3 months called chronic kidney disease; it is not unusual for people to realize that they have chronic kidney failure only when their kidney function is down to 25% of normal [3]. Chronic kidney failure, unlike acute kidney failure, is a slow and gradually progressive process even if one kidney stops functioning the other can carry out normal functions. It is not usual for signs and symptoms to be noticeable until the disease is fairly well advanced and the condition has become severe, by which time most of the damage is irreversible, earlier stages of CKD are based on the combination of kidney damage and decreased kidney function [4].

Cardiovascular diseases are divided into two parts, cardiomyopathy disease (disease of the heart muscle that makes it harder for your heart to pump blood to the rest of your body) and vascular disease (any abnormal condition of the blood vessels [5].

Cardiovascular diseases (CVDs) are the leading cause of illness and death globally, estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke, out of the 17 million premature deaths (under the age of 70) due to non-communicable diseases, 82% are in low- and middle-income countries, and 37% are caused by CVDs [6] [7].

The cardio-renal syndrome (CRS) can be generally defined as a pathophysiologic disorder includes a broad spectrum of diseases in which heart and kidney are both involved, the CRS classification essentially recognizes two main groups, cardio-renal and Reno-cardiac syndromes, on the basis of ‘‘premium moves’’ of disease (cardiac or renal); both cardio-renal and Reno-cardiac syndromes are then divided into acute and chronic, according to the disease’s onset, Five subtypes of the syndromes were identified, abrupt worsening of cardiac function that lead to acute kidney injury called Acute Cardio-renal Syndrome or Type 1 CRS, this appears to be a syndrome of worsening renal function that frequently complicates hospitalized patients with acute heart failure and acute coronary syndrome. In the US, over one million patients are hospitalized each year with acute decompensated heart failure, and it is estimated that 27% to nearly 40% of these patients will develop acute kidney injury and those who experience worsening renal function have higher mortality and morbidity and increased length of hospitalization [9] [11].

When Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) cause progressive and potentially permanent chronic kidney disease this condition called chronic cardio-renal syndrome or Type 2 CRS, CKD has been observed in 45-63% of CHF patients24, 25, 26, [10].

Important pathophysiological triggers of renal disease progression include chronic increases in renal venous pressure, maladaptive activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system, as well as a chronic inflammatory state. Intra-renal oxidative stress and pro-inflammatory signaling precipitate structural injury, including glomerulosclerosis and tubulointerstitial fibrosis. One clear example of CRS2 would be congenital heart disease and ‘cyanotic nephropathy', in which heart disease temporally precedes any kidney disease. [11] [12]. When acute kidney injury (AKI) contributes to precipitates the development of acute cardiac injury this called acute Reno-cardiac syndrome (type 3). AKI may directly or indirectly produce an acute cardiac event; triggered by the inflammatory surge, oxidative stress, and secretion of neurohormones following AKI.

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Other triggers for cardiac injury and dysfunction include AKI-related volume overload, metabolic acidosis, and electrolytes disorders such as hyperkalemia and hypocalcemia. Acute, left ventricular dysfunction and accelerated fibrosis have been also described in patients with AKI. [13] Type 4 CRS or chronic cardio-renal syndrome describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of cardiovascular diseases including coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death are the primary contributors to morbidity and mortality in patients with chronic kidney disease (CKD). Arteriosclerosis and disorders of left ventricular (LV) structure and function are common in patients with CKD, the incidence and mortality rates associated with CVD tend to increase following a decline in renal function, CVD is a common cause of morbidity and mortality in chronic kidney disease patients among whom it is (5–20) times higher than in the general population, Major cardiac events represent almost 50 % of the causes of death in CKD patients, the incidence of cardiovascular mortality is much higher than the incidence of end-stage renal disease, the effect is more marked with end-stage renal disease than with milder levels of renal insufficiency, and more than 50% of patients with end-stage renal disease on renal replacement therapy die of cardiovascular causes. [14] Type-5 CRS is a clinical and pathophysiological entity to describe the concomitant presence of renal and cardiovascular dysfunction, the heart and the kidney are both targets of a strong systemic inflammatory reaction [5] and there are marked cellular and molecular changes in these organs with a time-specific pattern. Type-5 CRS can be acute or chronic, examples of diseases that cause systemic inflammation include sepsis, systemic lupus erythematosus, and amyloidosis. Inflammation and microvasculature alterations form the basis of the pathogenesis for the involvement of both the kidneys and the cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction [16], Septic cardiac dysfunction is multifactorial, Cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70% to 90% compared with 20% in patients without cardiovascular impairment. AKI is a common complication of patients with sepsis and carries a poor prognosis. It occurs in 20% of critically ill patients and in 51% of patients with septic [17] The mortality rate of sepsis-induced AKI is high at approximately 70%, whereas the mortality of AKI alone is 40%-45%. [18] [19] A systemic amyloidosis is an uncommon group of disorders characterized by the extracellular deposition of amyloid in one or more organs. Cardiac and renal deposition leading to restrictive cardiomyopathy and proteinuria renal disease, among many types of amyloidosis, AL (primary) and AA (secondary) amyloidosis is the most frequently encountered type in clinical practice. AL amyloidosis (amyloid is derived from monoclonal light chains) is associated with clinical cardiac involvement in about 50% of all cases [20]. Renal involvement occurs in 30%-40% of all AL cases [21]. In contrast, the AA type is characterized by predominant renal involvement in 60%-100% of all cases [22-23-24-25]. Cardiac involvement is less frequent and varies from 0% to 39.5%, the predominant manifestation of amyloid heart disease is congestive heart failure. In patients with small vessel involvement and minimal or no myocardial infiltration, the presenting complaint may be angina. In addition, atrial arrhythmias are frequently seen [20], the majority of patients with renal amyloidosis present with proteinuria, which can vary from minimal asymptomatic proteinuria to nephrotic syndrome, hematuria is present in about one-third of patients, chronic renal insufficiency with little proteinuria can also be seen in patients with extensive vascular deposits. [26]

Heart is very commonly involved in systemic lupus erythematosus (SLE). Any cardiac structure, including the pericardium, myocardium, endocardium, conduction tissue, and even coronary arteries, are involved in SLE, Pericarditis is the most frequent cardiac manifestation of SLE, and pericardial involvement is seen in 11%-54% of patients in echocardiographic studies, Myocardial involvement was seen in 40% of SLE cases in postmortem examinations and 20% of cases on echocardiography [27].

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Classification of heart and kidney failure

Clinical classification of a disease serves a number of different purposes [18]. First, it can serve to create labels to establish clear communication about a clinical entity. This clarity would also enable quantification of the disease via measures of prevalence and incidence. Classification can also be used for the analysis of etiologies and prediction of outcome. A good example in the cardio-renal field is how classification of patients with heart failure and elevated versus normal central venous pressure has led to the clinical recognition of the link between central venous pressure and renal function impairment in patients with heart failure.19–21 Second, the method of classification can be based on temporal patterns (acute versus chronic, reversible versus irreversible), on simultaneous occurrence of signs and symptoms (that is, symptoms that define syndromes) and on particular diagnoses. Third, when disease mechanisms are well understood, classification can be based on structural and/or functional analysis. A recent proposal for cardio-renal syndrome based on this premise is an excellent first step towards such a functional classification. Finally, a good classification is based on unambiguous and measurable criteria that are discriminatory in terms of clearly defining the disease and, preferably, map to disease mechanisms and therapeutic options for a given patient. [8] The few currently available classifications of cardio-renal syndrome do not comply with such requirements for a valid classification. In the acute setting, there is no agreement among cardiologists, intensivists and nephrologists with respect to the diagnosis of worsening of renal function that is AKI. Worsening of renal function in the context of heart failure has been diagnosed by an absolute change in serum creatinine levels [8-20] or a change in plasma creatinine levels of >20%.23.

The RIFLE criteria (acronym indicating Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) use a multilevel classification, and incorporate urine flow as parameter of renal function. [9] The rate of decline in renal function is considered by criteria used by the AKI Network, but not by the other criteria. [10] To illustrate how easily a classification can become ambiguous, the aetiology and recognition of groups two (chronic cardio-renal syndrome) and four (chronic Reno-cardiac syndrome) of the Acute Dialysis Quality Initiative (ADQI) cardio-renal syndrome classification should be considered. [11]. If the patient is first diagnosed with CKD, cardiac investigations would likely follow and could reveal heart failure, and vice versa. This situation has been recognized by the ADQI group. [12] Clinical situations that could provide data for the compilation of a robust classification of CRS occur in critical care, nephrology and cardiology settings, and a combined effort might be required to achieve this goal.

Coupling between the heart and kidneys

Haemodynamic factors In 1931, an association between increased renal venous pressure and reduced renal blood flow was reported in dogs.8 In 1956, the consequences of an increase in renal venous pressure for peritubular capillary and intratubular pressure were assessed in rats.28 A slight increase in renal venous pressure (0–15mmHg) had little effect on either peritubular capillary or intratubular pressures; however, further increases caused linear increases in both these parameters. The transmission of increased renal venous pressure to increased intratubular pressure is important, since every 1mmHg increase in intratubular pressure directly reduces net ultrafiltration pressure—which is normally only ~20 mmHg29—thereby decreasing glomerular filtration rate (GFR). Heart failure induces a decline in cardiac output and arterial blood pressure that activates the sympathetic nervous system (SNS) and the renin–angiotensin system (RAS).30,31 This activation leads to volume expansion which, in turn, restores renal perfusion.30,31 Interestingly, these haemodynamic factors provide bidirectional coupling in patients with heart failure, such that the renal failure induced by heart failure leads to sodium and water retention, further aggravating heart failure, and potentially further decreasing arterial pressure and elevating renal venous pressure.

This bidirectional coupling is quite profoundly illustrated in patients with untreated heart failure, who show large increases in extracellular fluid and plasma volumes.32 Indeed, drugs that reverse this vicious cycle (such as inhibitors of the RAS, β-blockers, digoxin, nitrates, aldosterone inhibitors and loop diuretics) are successfully used as therapeutic agents in patients with heart failure.

However, this therapeutic approach is not successful in a number of conditions, suggesting that other underlying disturbances have a role.33 A detailed discussion of all haemodynamic factors that could potentially drive heart and/or kidney failure is beyond the scope of this Review, and such information can be found elsewhere.34,35 The reader should note, however, that information about renal haemodynamics and segmental sodium handling in patients with combined heart and renal failure is extremely limited.

Non-hemodynamic factors

It is proposed that several Cardio-renal connectors—the RAS, SNS, inflammation, and the balance between nitric oxide (NO) and reactive oxygen species (ROS)—underpin all nonhaemodynamic Cardio-renal interactions.1 This hypothesis forms an extension to the haemodynamic model of Cardio-renal interaction, but does not replace it. However, for each of these factors, interactions have been described with all the other factors, which make this concept quite complicated.

The RAS can be considered a prototypical Cardio-renal connector, since it fulfils the prerequisite of a bidirectional response and is induced by both heart failure and by renal failure. Renin release is triggered by decreased renal artery pressure,36 increased renal venous pressure,37,38 decreased delivery of sodium to the distal nephron39 and increased activity of the SNS,36 which all occur in heart failure and/or CKD. Activation of the RAS is associated with myocardial remodelling40 and fibrosis.41 these structural consequences of RAS activation seem to happen in conjunction with activation of other cardio-renal connectors. Angiotensin II-induced ROS production by NADPH oxidase is present in patients with cardio-renal syndrome and is implicated in inflammation. Angiotensin II stimulates pro-inflammatory cells through their type-1 angiotensin II receptors as part of the physiological response to stress. RAS inhibitors can prevent AKI (or worsening of renal function) in patients during acute heart failure is not known. In fact, RAS inhibitors are frequently discontinued in such patients, since they are held to be responsible for the deterioration of renal function, which might not be true. Nevertheless, some arguments and data suggest that, for instance, aggressive diuresis would have increased efficacy during RAS inhibition. The SNS, similarly to the RAS, also fulfils the prerequisites of bidirectional cardio-renal coupling and activation in both heart failure and CKD.45–47 Again; multiple connections link the SNS with other cardio-renal connectors.

The last two connectors are of an even higher complexity, NO and ROS are both involved in renal sodium handling, systemic haemodynamics49 and renal haemo-dynamics,50–54 generally in opposing ways. Moreover, the balance between NO and ROS has complex consequences for the regulation of cardiac function.55, Both renal failure and heart failure are associated with decreased NO bioavailability 56,57 which in turn can lead to aggravation of renal failure and heart failure.58

SUBJECTS AND METHODS

The number of participants in the questionnaire is 100 and the questionnaire was distributed in two ways. In the first way, the questionnaire was published on social media and the number of participants was 79 and the number of pharmacists participating in the electronic questionnaire was 51 and the number of participating physicians was 28. In the second way, the questionnaire was distributed to a group of private pharmacies in Baghdad, which numbered 21 and purpose of the questionnaire was to find out if the participants had any information about Cardio-renal Syndrome.

RESULTS AND DISCUSSION

When publishing the questionnaire about CRS, the questionnaire was directed to health care providers to know their knowledge about CRS. 100 health care providers participated in the questionnaire, including physicians and pharmacists, the number of participating pharmacists was 72 and number of physicians that participated was 28.

when the participants were asked about Knowing about CRS, 48 of the participants answered yes, 24 said no, and the rest answered that they had insufficient information on the topic, and when asked whether all heart failure patients had kidney disease, the respondents' answer was 19 yes and 47 No.

We asked the health care provider about if there any difference between CRS and RCS, the answer was 64 of the participants knew the difference, 26 did not know, and 10 answered Yes, but not sure of that and perhaps this is due to the novelty of the topic, but the largest percentage knows the difference between the two.

One of the questions that were asked to the participants about the effect of using the herbal remedy on CRS, if it contradicted its use or not, 26 answered Yes, 49 answered No, and the rest answered that it may affect its use negatively, but not significantly.

We asked the health care provider about whether there are warnings about the risk of using certain treatments during CRS in Iraq, 33 answered Yes, 42 said No, and 25 had little knowledge about this topic, and when asked about the importance of monitoring and following up the issue by the pharmacists Syndicate, 71 answered yes and 29 answered no or had little knowledge about the subject.

Through the results shown in the questionnaire, it was found that there is good knowledge about CRS although the topic is recent, as the research and evidence were presented starting in 2008. Despite the lack of studies and researches, the percentage of knowledge of health care providers about CRS was more than those who do not have sufficient knowledge about the topic. It may return by virtue of their work, knowledge and clinical follow-up, as the percentage of those who differentiated between the two syndromes was good, from the results of the questionnaire, we conclude that the participants do not have sufficient knowledge about drug use warnings, and this may also be due to the lack of studies and research, as mentioned earlier.

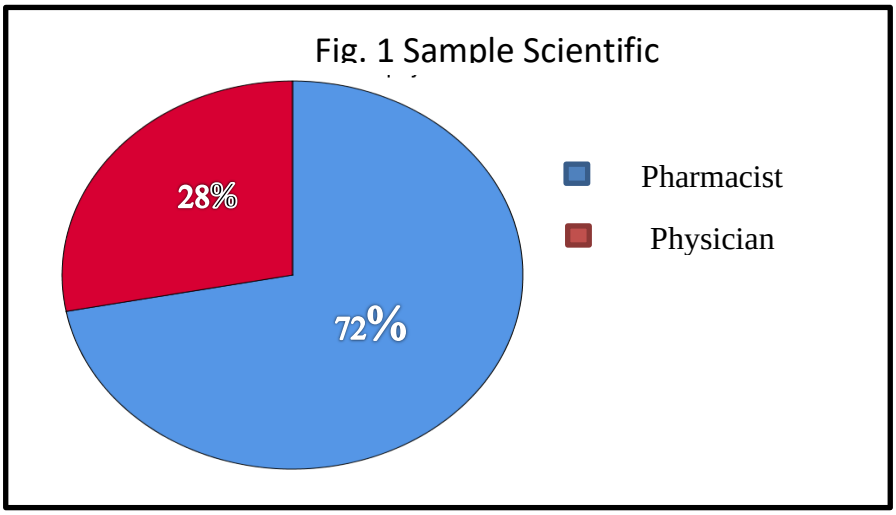

TABLE 1: Sample scientific specializing

	Frequency	**Percent**
Pharmacist	72	72 %
Physician	28	28 %
Total	100	100 %

TABLE 2 : Reliability Statistics

Cronbach's Alpha	N of Items
0.953	6

TABLE 3: Pearson correlation of the axiom and its statements

	Pearson correlation	**Sig.**
Do you have any pervious information about the cardio- renal syndrome CRS?	0.244*	0.007
In your opinion, all patient with heart failure have kidney disease	0.073**	0.023
In your opinion, is there any difference between cardio – renal and Reno – caradiac syndromes	0.290**	0.038
Do you think it is safe to use any herbal drug in CRS?	0.091**	0.046
According to your knowledge, the warning of medication during CRS applied in Iraq.	0.123**	0.021
In your opinion, the subject needs follow- up From the pharmacist syndicate.	0.240**	0.047

*Correlation is significant at the 0.01 level (1-tailed)
**Correlation is significant at the 0.05 level (1-tailed)

TABLE 4: Trends of the sample opinions toward the statements of the questionnaire

The statements	**Yes**	**No**	**Little bit**	**Mean**	**SD**
Do you have any pervious information about the cardio- renal syndrome CRS?				1.74	0.799
• Frequency	48	30	22		
• Percent	48%	30%	22%		
In your opinion, all patients with heart failure have kidney disease.				2.04	0.650
• Frequency					
• Percent	19	58	23		
	19%	58%	23%		
In your opinion, is there any difference between cardio – renal and Reno – caradiac syndromes.				1.46	0.673
• Frequency					
• Percent	64	26	10		
	48%	26%	10%		
Do you think it is safe to use any herbal drug in CRS?				1.99	0.717
• Frequency	26	49	25		
• Percent	26%	30%	25%		
According to your knowledge, the warning of medication during CRS applied in Iraq.				1.97	0.758
• Frequency	30	43	27		
• Percent	30%	43%	27%		
In your opinion, the subject needs follow- up From the pharmacist syndicate.				1.42	0.713
• Frequency	71	16	13		
• Percent	71%	16%	13%		

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TABLE 5: Descriptive the difference between the sample opinions according to their scientific specializing

Descriptive								
The Dimensions	**N**	**Mean**	**Std. Deviation**	**Std. Error**	**95% confidence interval for Mean**		**Minimum**	**Maximum**
					Lower Bounded	**Upper Bounded**		
Pharmacist	72	1.808	0.663	0.078	1.652	1.964	1.00	3.00
Physician	28	1.672	0.608	0.114	1.437	1.908	1.00	2.83
Total	100	1.770	0.648	0.065	1.642	1.899	1.00	3.00

TABLE 6: Comparison of basic parameters according to their scientific specializing

ANOVA					
The Dimension	**Sum of Squares**	**Df**	**Mean Square**	**F**	**Sig**
Between Groups	0.369	1	0.369	0.878	0.351
Within Groups	41.175	98	0.420		
Total	41.543	99			

CONCLUSION

Heart and kidney interactions are complex and the subject of immense clinical and scientific interest and debate. In this article, we argue that without consensus on definitions and classification, clinicians will not be able to precisely phenotype the various forms of cardio-renal syndrome. Such phenotyping, in turn, forms the basis for in vitro and animal studies, as well as small translational studies in patients.

Through the ADQI consensus on CRS, other processes will now be facilitated, including a better or clearer understanding of the epidemiology of these conditions, opportunities for early diagnosis through biomarkers, the development of preventive strategies and application of evidence-based management strategies, The application of these consensus definitions will also allow the identification of gaps in the literature, and provide direction for future research including clinical trials. This classification indeed represents a tool to promote new interaction between cardiology and nephrology in the attempt to build a new pathway of collaboration and a new holistic approach to patients suffering from combined heart and kidney disorders.

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