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Obesity: A Growing Risk Factor for Cardiorenal Syndrome

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Abstract
Obesity and its associated comorbidities like diabetes, hypertension are among the significant risk factors for heart failure and kidney disease. Visceral obesity is robustly associated with a greater risk of cardiorenal morbidity than subcutaneous obesity. Cardiac impairment in obesity is caused by hemodynamic changes, endothelial dysfunction, RAAS activation, neurohormonal dysregulation, oxidative stress and adipokines causing inflammation. Obesity impairs kidney function by hyper-filtration, increased glomerular capillary wall tension, podocyte dysfunction and finally causing CKD. This review article discuss the relationship and significance of smoking, hypertension, alcohol intake, diabetes mellitus, obesity and anemia in cardio renal syndrome in acute heart failure patients.

Introduction

Cardiorenal syndrome is defined by the ADQI as a pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

Table 1: Components of cardiorenal syndrome

CRS components
1 Central obesity
2 Insulin resistance
3 Hypertension
4 Metabolic dyslipidemia (low HDL, high triglycerides and increased small, dense LDL particles)
5 Albuminuria
6 Reduced glomerular filtration rate (<60 ml/min)

Table 2: Types of Cardiorenal syndrome (Adapted from Ronco, C. (2010). Cardiorenal syndromes: definition and classification. In Fluid Overload (Vol. 164, pp. 33-38). Karger Publishers.)

TYPE	
Acute CRS (Type 1)	Acute worsening of cardiac function leading to renal dysfunction
Chronic CRS (Type 2)	Chronic abnormalities in cardiac function leading to renal dysfunction
Acute Renocardiac Syndrome (Type 3)	Acute worsening of renal function causing cardiac dysfunction
Chronic Renocardiac Syndrome (Type 4)	Chronic abnormalities in renal function leading to cardiac disease
Secondary CRS(Type	Systemic conditions causing simultaneous dysfunction of the heart and kidney

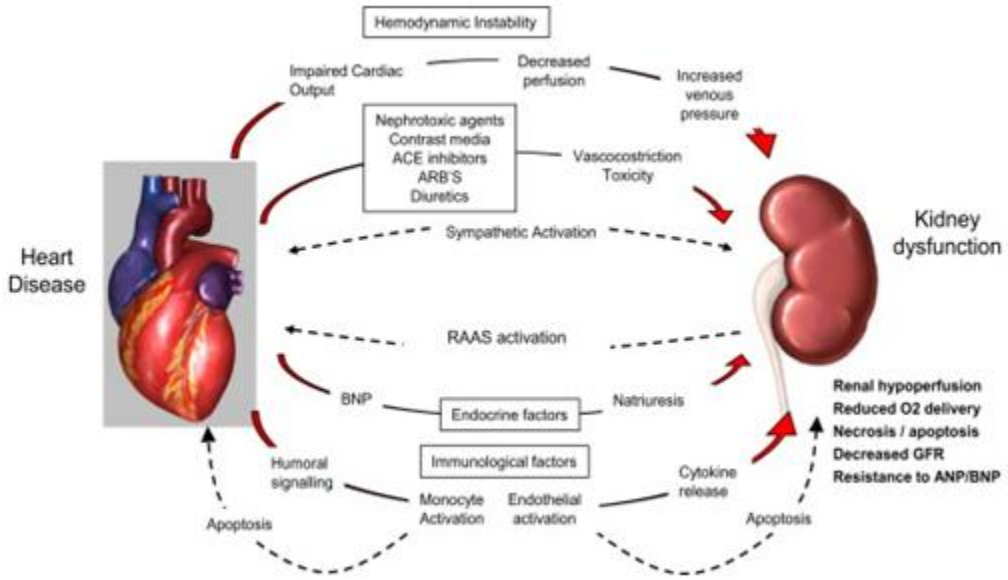

Figure 1: The pathophysiological interactions in cardiorenal syndrome (Adapted from Soni, S. S., Barnela, S. R., Saboo, S. S., et al (2014). Cardiorenal syndrome. Clinical Queries: Nephrology, 3(1), 30-37)

Multiple studies have shown that the predictors of cardiorenal syndrome (type 1) include baseline eGFR, older age, female sex, increased baseline blood pressure and increased central venous pressure. Hypertension targets both the heart and the kidney and there is impairment in their function and structure with chronic hypertensive heart disease. Therefore, both HF and renal failure commonly results in the same patient as a sequence of hypertension[(1)]. The prevalence of LVH and GFR is inversely related. In a study, the echocardiographically determined LVH was twice more common in similarly aged patients with creatinine clearance < 25 ml/min[(2)]. Patients with diabetes have high rates of mortality contributed maximally by cardiovascular disease, which accounts for nearly 50% of their mortality[(3)]. The pathophysiological mechanisms underlying cardiorenal syndrome among diabetics include hyperglycemia, glycated proteins and oxidative injury causing hemodynamic impairment induction of growth factors in the kidney[(4)]. Diabetic patients had twice the predisposition to develop renal parameter worsening than in patients with no similar risk factors[(5)].

The global prevalence of obesity among children is 5% and 12% among adults. Obesity peaks by the age between 50-64 years. The prevalence of obesity has increased dramatically in the last decade. The amount and distribution of adiposity is found to be a risk factor for hypertension, heart failure, CKD and global mortality[(6)]. South Asians

have a higher incidence of mortality from CAD and CKD compared to the East Asians and Whites[7]. The cardiovascular events arising from the cardiometabolic risk factors increases with greater BMI values. Severe/morbid obesity worsens the cardiometabolic risk factors by increasing triglycerides, hs-CRP, diastolic blood pressure[8]. Further, obesity leads to endothelial dysfunction, reduced NO bioavailability, metabolic syndrome induced oxidative stress exerting adverse effects on heart and kidneyfunction[9].Chang et al found that BMI of 30,35,40 kg/m2 causes a decline in glomerular filtration rate by 18%, 69% and 102% respectively[10]. RAAS activation, pro inflammatory adipokines, reducednitric oxide bio availability in obesity might influence the progression of glomerular to tubule interstitial fibrosis, nephron loss and ESRD[11].

Anemia was found to be associated with HF and with impaired renal function this was known as cardio-renal anemia syndrome, which is defined as the concurrent occurrence of anemia, renal failure and CHF, with non-occasional pathophysiologic correlations [12]. The prevalence of anemia was found to be high among patients with cardio-renal syndrome but was not associated with increased mortality. Increased serum creatinine and low EF were variables associated with death[13].

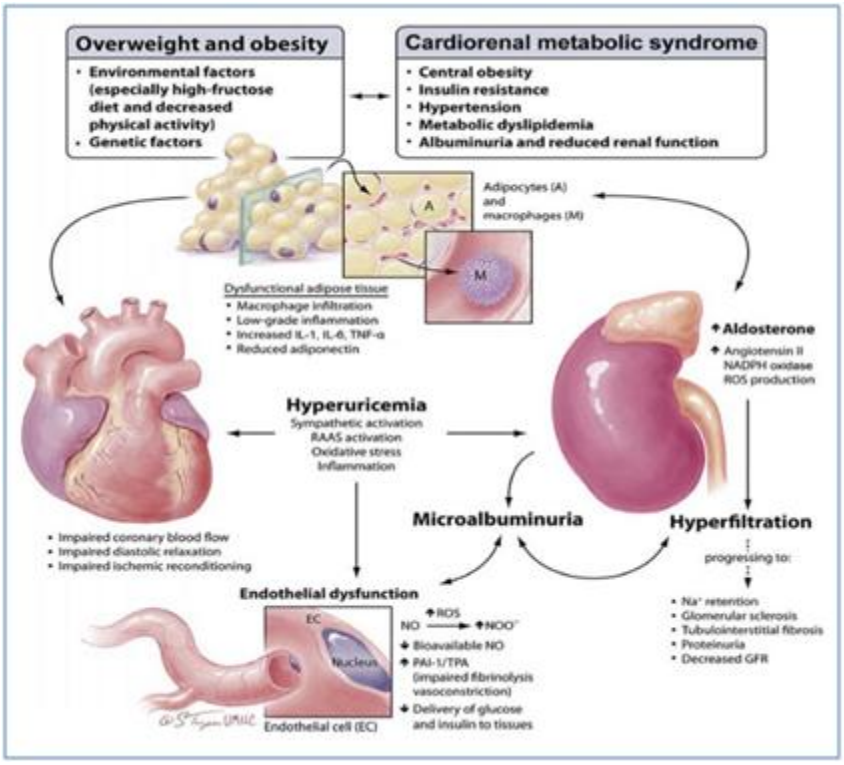

Figure 2: Obesity and cardiorenal syndrome pathophysiological interactions

In adults, both current and past cigarette smokers had increased HF risk[14]. Heavy alcohol consumption was implicated in the development of cardiac diseases more commonly so in chronic, heavy drinkers than those consuming small to moderate amounts of alcohol. In a recent meta-analysis investigating the association between alcohol intake and kidney disease researchers reported that the pooled risk ratios of chronic kidney disease, proteinuria, and end-stage renal disease in alcoholics were 0.83, 0.85, and 1.00, respectively, indicating decreased risk or no risk of kidney disease in heavy alcohol consumers[15]. However research suggests several potential mechanisms by which alcohol may directly or indirectly affect the kidneys, they have not yet been validated experimentally[16].

Aims

The present study was done to evaluate the association between cardiorenal syndrome and smoking, alcohol intake, anemia, obesity, hypertension and diabetes mellitus.

Methods

The cross sectional study included 100 cases of heart failure consisting of 40 cases of cardiorenal syndrome admitted at Rajah Muthiah Medical College Hospital. Ethical committee clearance was obtained. All patients were subjected to thorough history taking and necessary blood investigations after obtaining consent.

Inclusion Criteria

Patients with acute decompensated heart failure and having elevated renal parameters post admission (elevation of serum creatinine 0.3mg/dl from baseline within 48 hours of hospital stay/1.5 to 1.9 times baseline or urine output <0.5 mg/ kg/hour for 6-12 hours).

Exclusion Criteria

- Systemic illness with underlying nephropathy
- Nephrotoxic drug intake history
- Known case of renal arterystenosis
- Patients with ADHF and elevated baseline renalparameters
- Patients with sepsis
- Patients with liverdisease
- Patients with elevated serum uricacid

Method of Collection of Data

In the present work, a total of one hundred patients with acute heart failure and admitted at Rajah Muthiah Medical College Hospital were analyzed. The patients who developed acute cardiorenal syndrome amongst these patients were taken and the association of cardiorenal syndrome with the risk factors such as obesity (BMI> 25, according to Asia- Pacific guidelines), diabetes (based on ADA diagnostic criteria), hypertension (based on JNC 8 guidelines) and personal habits such as smoking, alcohol intake were evaluated. The association of cardiorenal syndrome with anemia (Hemoglobin of less than 12 g/dL in females and less than 13 g/Dl in males). The quantitative variables were compared between the two categories (with and without cardio renal syndrome) using independent sample test whereas the non-quantitative variables were analyzed using non parametric, Mann-Whitney 'U' test. The entire statistical analysis was carried out by the statistical packages of the social sciences (SPSS-2).

Observations

Table 3-A: Hypertensive individuals – comparison between the two study populations

Risk factors	Cardiorenal syndrome		Without cardiorenal syndrome		Overall	Mann Whitney 'U' Test	
	N	%	N	%	%	Z	P
DM	20	50	28	46.7	48	0.325	0.745

The percentage of patients who were previously diagnosed as hypertensives was 62.5% in the cardiorenal syndrome group and was 58% in those with heart failure but without cardiorenal syndrome. There was no significant difference while comparing the proportion of diagnosed hypertensives among those with and those without cardiorenal syndrome.

Table 3-B: Blood Pressure measurement-analysis of the study patients

BP	Cardiorenal syndrome		Without cardiorenal syndrome		Overall		T	P
	Mean	SD	Mean	SD	Mean	SD		
Systolic BP	103.5	11.67	110.67	15.61	107.80	14.53	2.48	0.015
Diastolic BP	68.50	7.69	71.67	8.06	70.40	8.03	1.98	0.051

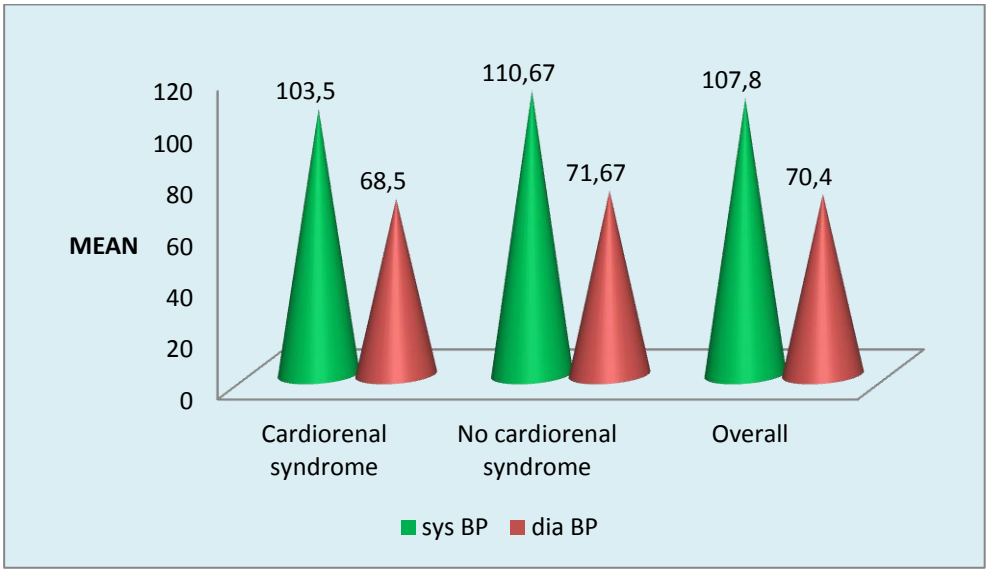

Figure 3: Blood Pressure measurement-analysis of the study patients

The mean overall systolic and diastolic BP was 107.80±14.53 mm Hg and 70.40±mm Hg respectively. The mean systolic BP of the patients with cardiorenal syndrome was 103.45±11.67 mm Hg and mean systolic BP of the patients without cardiorenal syndrome was 110.67±15.61mm Hg. The difference in the systolic BP between the two categories was statistically significant, t=2.48, p=0.015<0.05. The mean diastolic BP of the patients with cardiorenal syndrome and without cardiorenal syndrome were 68.50±7.69 mm Hg and 71.67±8.06mm Hg respectively. Although the mean diastolic BP of the cardiorenal syndrome patients was comparatively lower, the difference was statistically insignificant.

Table 4: Proportion of diabetics among the study groups

Risk factors	Cardiorenal syndrome		Without cardiorenal syndrome		Overall	Mann Whitney 'U' Test	
	N	%	N	%	%	Z	P
HTN	25	62.5	33	55	58	0.741	0.459

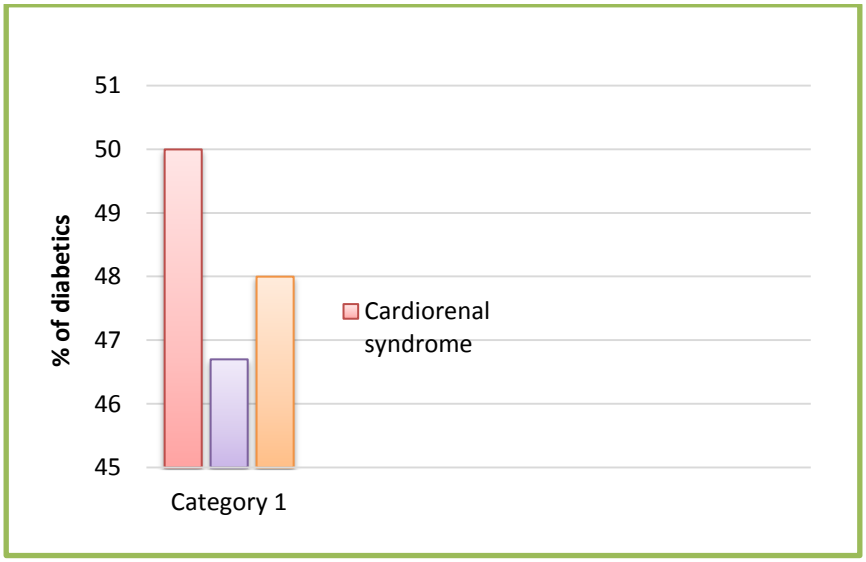

Figure 4: Proportion of diabetics among the study groups

There was no significant difference in the proportion of diabetics between the two groups.

Table 5: Comparison between smokers/ non-smokers and alcoholics/ non-alcoholics of the two groups

Risk factors	Cardiorenal syndrome		Without cardiorenal Syndrome		Overall	Mann Whitney 'U' Test	
	N	%	N	%	%	Z	P
Smokers	17	42.5	25	41.7	42	0.082	0.934
Alcoholic	15	37.5	24	40	39	0.250	0.803

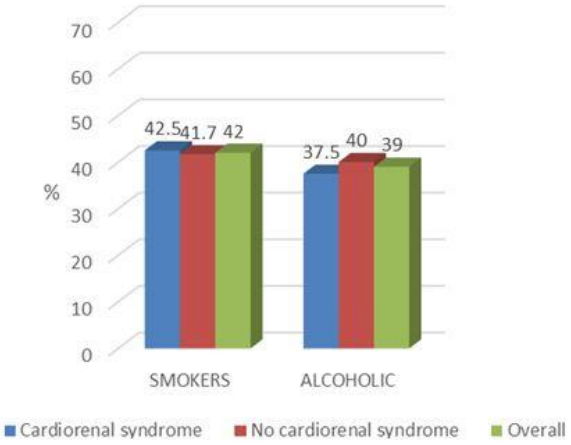

Figure 5: Comparison between smokers/ non-smokers and alcoholics/ non-alcoholics of the two groups

Overall 42 % of the patients were smokers. The proportions of the smokers in patients with and without cardiorenal syndrome was 42.5% and 41.7% respectively. There was no significant difference in the percentage of smokers proportions among the two groups. There was no significant difference in the proportion of alcoholics in those with cardiorenal syndrome 42.5% and in those without cardiorenal syndrome 41.7%.

Table 6(i): Obesity among the study patients

BMI	Cardiorenal syndrome		Without cardiorenal syndrome		Overall	Mann Whitney 'U' Test	
	N	%	N	%	%	Z	P
<25	6	15	34	56.7	20	3.88	0.001
>25	34	85	26	43.3	80		
Total	40	100	60	100	100		

It is inferred that, 85% of the patients with the cardiorenal syndrome had BMI >25kg/m2 and only 43.3% of the patients without cardiorenal syndrome had BMI more than 25kg/m2. This difference in BMI distribution between the two categories was statistically significant (z=3.88, p=0.001).

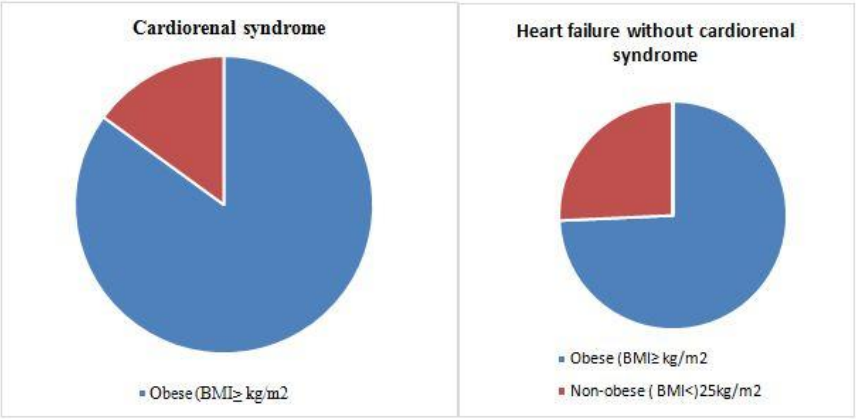

Figure 6 (i): Proportion of obese among the study groups

Table 6(ii): BMI distribution of the study patients

BMI (kg/m^2)	Mean	SD	T	P
Cardiorenal syndrome	27.56	2.21	4.19	0.001
Without cardiorenal syndrome	23.22	2.48		
Overall	25.39	2.39		

It is observed from the above study table, that the mean overall BMI of the study patients was 25.39±2.39 kg/m2. The mean BMI was 27.56±2.48 kg/m2 among the patients with cardiorenal syndrome is and 23.33±2.48 kg/m2 among the patients without cardiorenal syndrome and difference is statistically significant (p=0.001).

Table 7: Analysis of the Hemoglobin values of the study patients.

	Cardiorenal syndrome		Without cardiorenal syndrome		Overall		T	P
	Mean	SD	Mean	SD	Mean	SD		
Hb (gm)	12.38	1.51	12.39	1.61	12.39	1.56	0.044	0.965

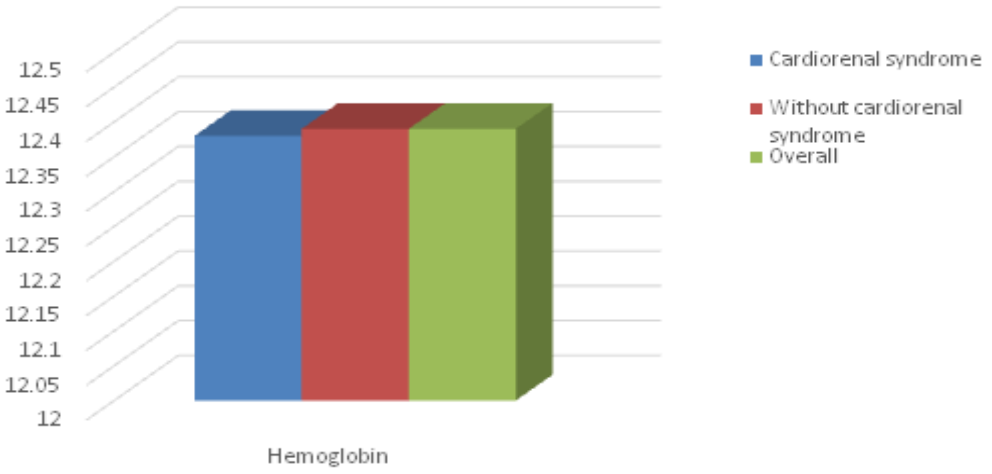

Figure 7: Analysis of the Hemoglobin values of the study patients.

It is inferred from the table that the mean overall Hb of the study patients was 12.37±1.51 for cardiorenal syndrome and 12.39±1.61 for the patients without cardiorenal syndrome. The difference was statistically insignificant.

Discussion

Adiposity measured by BMI worsens renal function by hyper filtration, increased glomerular capillary wall tension, podocyte stress and indirectly through diabetes and hypertension, the two most common causes of ESRD [17]. Adiposity causes inflammation by oxidative stress, altered lipid metabolism, endothelial dysfunction, RAAS activation, and increased production of aldosterone[18]. Renal plasma flow deterioration begins in the early stages of obesity itself. In this setting GFR is maintained by afferent arteriolar dilation and efferent arteriolar constriction leading to increased glomerular pressure and hyper filtration. In our study we could note obesity as a strong risk factor for development of cardiorenal syndrome among those with heart failure, also we can note an increased BMI in 80% of the study population including both the study groups which tells us that obesity predisposes to heart failure in the first place. Thus obesity is a risk factor for heart failure and also even among those with heart failure obesity increases the risk of cardiorenal syndrome.

In our study we also noted that patients with cardiorenal syndrome had a significantly lower systolic and diastolic blood pressure at presentation than those with heart failure but without cardiorenal syndrome. This indicates how hypoperfusion can play a role in the pathogenesis of cardiorenal syndrome.

In our study however we were not able to demonstrate an association between those who were known hypertensives, diabetics and cardiorenal syndrome. Also smoking, hypertension and anemia could not be established as risk factors for cardiorenal syndrome.The reasons might include lack of a more detailed analysis on the frequency, type of alcohol/cigarette consumed and also a lack of credibility of history provided.

It has been suggested that an underlying cause of obesity is a prolonged positive energy balance[19]. Setting a reasonable target weight is the crucial step in the approach to any weight loss treatment. National Institute of Health (NIH) published the following guidelines for obesity treatment in adults[20].

1. A low calorie diet (800-1200kcal/day).
2. Aerobic exercises results in modest weight loss and improved cardio respiratory fitness
3. Behavior therapy
4. Pharmacological therapy for obese patients with BMI >30 or BMI >27 with comorbidities.
5. Bariatric surgery is suggested for severely obese patients having BMI >40 or BMI>35 with comorbidities.

Conclusion

Obesity and obesity related diabetes and hypertension plays a major role in the onset of CRS. RAAS activation, inflammation, oxidative stress and other neurohormonal mediation of adipokines acting systemically and locally induce ventricular remodeling and glomerular hyper-filtration in the early stages of obesity. This leads to heart failure and renal fibrosis in long term. Acute and chronic cardiovascular events increases the risk of renal failure and vice versa. From this study we can propose obesity as a single significant risk factor in the cardiorenal umbrella that includes cardiac and renal failure, obesity induced neurohormonal inflammation, endothelial and fibrotic consequences. GLP-1 agonists. SGLT-2 inhibitors have better cardiovascular and renal outcomes in obese diabetic patients. Life style modifications, pharmacotherapy, bariatric surgery have been shown to be a new and promising therapeutic strategies in patients with obesity and obesity related cardiorenal syndrome.

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