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Research Article

Early Clinical Manifestations of Type 5 Cardiorenal Syndrome in Patients with Type 2 Diabetes and Hypertension

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Abstract

The Cardiorenal Syndrome (CRS) type 5 is characterized by the simultaneous presence of cardiac and renal dysfunction associated to acute or chronic systemic disorders. The detection in early stages is difficult because of the complexity pathophysiological in addition that the majority of patients are often oligo-symptomatic.

Methods: Study longitudinal, observational and cross-sectional study, conducted in a community in the state of Mexico. We studied patients of 82 years with diabetes type 2 (DM) and/or hypertension ≥ 5 years of evolution without kidney or heart disease. Is somatometrics and biochemical parameters were analyzed. The results are presented as simple frequencies and proportions for categorical variables, and as mean ± standard deviation for scalar variables. The correlations were analyzed using the Student t test (95% CI).

Results: 30 patients (mean age 57.3 [33 - 82] years) were studied, 18 were women (60%), 26 patients had a diagnosis of DM/Hypertension, 20 patients presented some type of dyslipidemia. 15 patients (50%) had higher levels of HbA1c above the therapeutic goal (≤ 6.5%), 9 patients (30%) fulfilled the therapeutic goal of glucose (90 - 130 mg/dL). The glycosylated hemoglobin (HbA1c) level declined 1.93% of the total population and increased 3.92% in patients with DM/Hypertension. The plasma levels of creatinine levels were 0.87 ± 0.20 mg/dL with an increase of 10.34%. The GFR (Glomerular filtration rate) estimated average was 94.06 ± 21.80 mL/min/1.21m^2 showing a decrease of 11.15%. The average RR interval was significantly shorter (845 ± 98.82 ms) and corrected QT interval (QTc) longer (428 ± 24.34 ms) in patients with DM. The estimated GFR showed a progressive decrease in spite of the reduction of HbA1c (p=0.03). The estimated GFR showed a directly proportional relationship to the QTc interval showing an increase for both variables of 14.03% and 10.61%, respectively (p = 0.03).

Conclusions: Early clinical manifestations are nonspecific in these diseases, however, in our study group renal alterations were more frequent, and the progressive renal failure in our population was independent to the adequate metabolic control, being able to infer that the kidney damage precedes the heart damage in patients with diabetes and/or hypertension.

Keywords: *Cardiorenal Syndrome; Diabetes; Hypertension; Kidney Injury*

Abbreviations

CRS: Cardiorenal Syndrome; DM: Diabetes Type 2; GFR: Glomerular Filtration Rate; QTc: Corrected QT Interval; HF: Heart Failure; SLE: Systemic Lupus Erythematosus; DBP: Diastolic Blood Pressure; HbA1c: Glycosylated Hemoglobin; GFR-e: Glomerular Filtration Rate Estimated; ADA: American Diabetes Association

Introduction

The correlation between renal failure and the heart has a high prevalence; however, until just a few years it has been recognized that association. In 2004, the National Heart Lung and Blood Institute coined the term cardiorenal syndrome (CRS) defining it as an extreme deregulation cardiac and renal failure, which leads to a syndromic entity in which the treatment to alleviate the symptoms of congestive heart failure (HF) is limited by the marked renal dysfunction [1]. Ronco., *et al*. established in 2008 a classification based on the initial organ dysfunction and the temporality [2]. Subsequently, Hatamizadeh., *et al.* proposed the two-way relationship of the damage through hemodynamic, neurohumoral and immunological [3].

CRS type 5: Secondary cardiorenal syndrome

The CRS type 5 is characterized by the simultaneous presence of renal and cardiac dysfunction associated with acute or chronic systemic disorders. There are limited data about the condition to other organ systems; however, there is evidence in systemic diseases such as DM, amyloidosis, systemic lupus erythematosus (SLE), and sarcoidosis [4,5]. The sepsis is the most common cause and serious that induces LRA and myocardial depression [6,7].

The feasibility and clinical applicability of this classification is difficult to establish. Despite an increased understanding of the pathophysiology and better diagnostic tools, the precursors of the syndrome are difficult to identify; often, the organizational and clinical consequences are detected simultaneously and it is almost impossible to determine which factor was the precursor.

Due to the fact that the CRS type 5 was recognized recently, there is no published literature enough about this syndrome. We have identified causes associated with the development of the acute and chronic form of this syndrome (Table 1) [8]. It should be noted that the main feature of this in acute situations is generally simultaneously, but in chronic conditions an organ (heart or kidney) may be affected first and then the other; in such situations, it may be difficult to establish the direct origin [9].

This syndrome has been recently defined so that there is a lack of information about its epidemiology. The heart condition and kidney in the conditions listed above may occur simultaneously or in different moments of appearance [8]. Still does not establish direct relations to find out whether the cardio-renal interactions contribute to the development of CRS in these pathologies [9]. The epidemiological data of this syndrome are nonspecific, so a general definition on the overall incidence and prevalence is not possible at this stage. We present in this paper the early manifestations in patients with diabetes and/or hypertension focused on cardiac and renal damage as part of this syndrome.

Materials and Methods

Study longitudinal, observational and cross-sectional study, carried out in the rural health center Cahuacan in the State of Mexico. We studied patients with age range of 82 years with diabetes and/or hypertension ≥ 5 years of evolution that had no diagnosis of kidney or heart disease. Somathometric parameters were analyzed, glucose (mg/dL), glomerular filtration rate (mL/min/1.21 m2) using formula CKD-EPI and total lipids (mg/dL) The results are presented as simple frequencies and proportions for categorical variables, and as mean ± standard deviation for scalar variables. The correlations were analyzed using the Student t test (95% CI).

Results and Discussion

The total population that suffers from a chronic disease is of 66 patients, of whom only 30 were selected to be included in the study, due to the fact that some of them had no studies or time required to homogenize the sample of study (Figure 1). Baseline Characteristics (Table 2), show similar demographic characteristics, including nutritional conditions and socio-economic level.

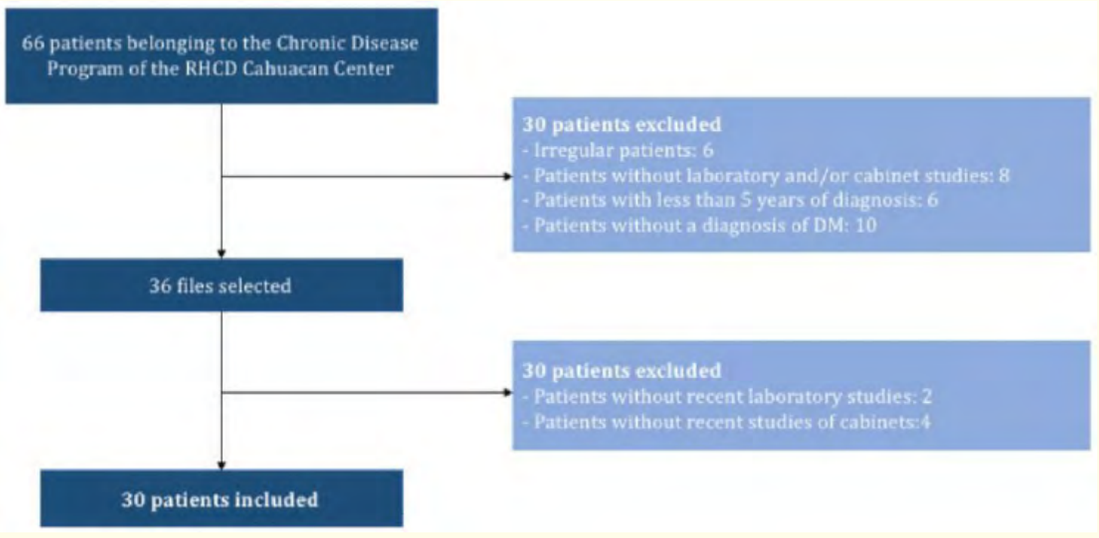


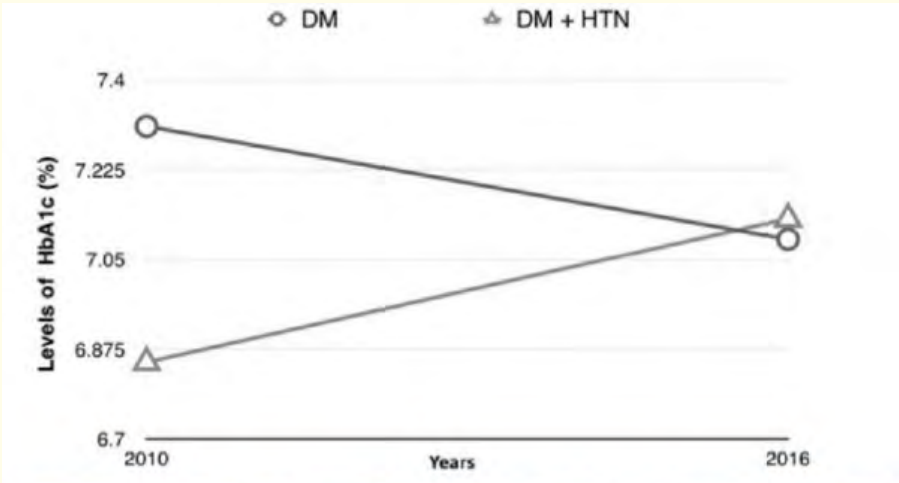
Figure 1: *Flow diagram of the selection of patients.*
RHCD: Rural Health Center Dispersed; DM: Diabetes Mellitus

Characteristics	DM (n = 4)	DM/HTN (n = 26)	Total (n = 30)
Gender			
Male - No. (%)	1 (25)	11 (42.30)	12 (40)
Female - No. (%)	3 (75)	15 (57.7)	18 (60)
Age - Years			
Media	45.5	59.19	57.36
SD	10.27	10.28	11.15
Range	32 - 57	39 - 82	32 - 82
Weight - Kg			
Media	76.6	76.13	76.19
SD	4.56	15.02	14.02
Range	70 - 80.5	47 - 109.5	47 - 109.5
Size - Mts			
Media	1.59	1.56	1.56
SD	0.033	0.099	0.093
Range	1.55 - 1.63	1.40 - 1.76	1.40 - 1.76
BMI - Kg/ m^2			
Media	30.32	31.01	30.92
SD	1.19	5.04	4.70
Range	29.16 - 31.44	22.43 - 40.69	22.43 - 40.69
Systolic blood pressure - mmHg			
Media	125	124.61	124.66
SD	10	15.55	14.79
Range	110 - 130	100 -140	100 - 140

Table 2: *Clinical characteristics and demographics of the population.*

Of the total number of patients included in the study, 18 patients were female (60%), whose average age of the sample was 57.36 ± 11.15 years, 26 patients had a diagnosis of DM/hypertension (86.66%), the majority of patients had an average body mass index of 30.92 kg/m^2 (grade 1 obesity), and 20 patients have some degree of dyslipidemia (66.66%). All patients had more than 5 years of evolution in his suffering, and all had laboratory studies and current cabinet and at least 2 previous studies of 3 and 5 years ago. The systolic arterial pressure (SBP) in patients with binomial DM/hypertension was 126 (100 - 140) mmHg in patients with single diagnosis of DM was 125 (110 - 130) mmHg; diastolic blood pressure (DBP) was not significantly different between the two groups.

Of the 30 patients included, 15 (50%) had a glycosylated hemoglobin (HbA1c) above the reference values (< 6.5%), on the other hand 9 patients (30%) fulfilled with the therapeutic objectives of serum levels of glucose (90 - 130 mg/dL). From 2010 to 2016, the HbA1c levels decreased by 2.0% cent in the total population, however, it was observed an increase of 3.92% in patients with a diagnosis of DM/HA (p = 0.07), women had higher levels of HbA1c with respect to men (7.45% vs 6.4%, respectively); the mean plasma glucose levels decreased by 3.59% (p = 0.07) (Figure 2).



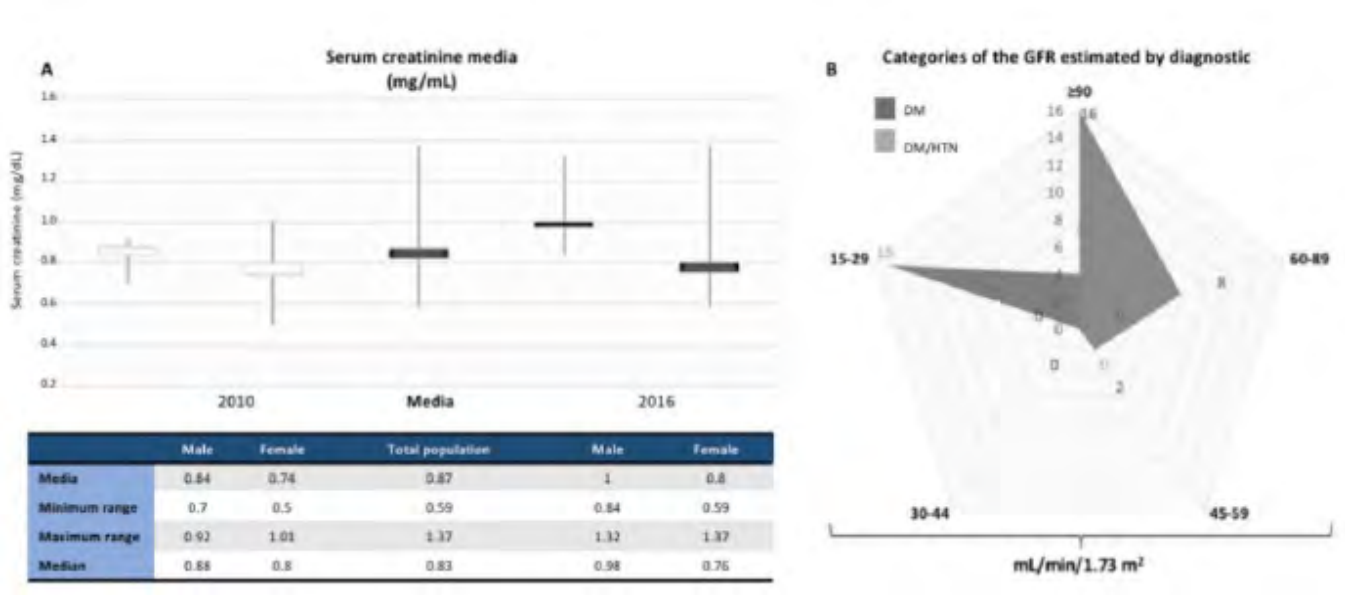
	Count	Media (%)	Minimum Range (%)	Q1 (%)	Median (%)	Q3 (%)	Maximum range (%)
HbA1c (2010)	30	7.24	4.95	5.65	6.48	8.54	10.59
HbA1c (2016)	30	7.10	4.98	5.68	6.15	8.48	11.52

Figure 2: *Distribution of the HbA1c levels in all patients by correlating with diagnosis and year. DM: Diabetes Mellitus; HTN: Hypertension; HbA1c: Glycosylated Hemoglobin A1c. (p 0.07).*

The average of the cholesterol levels for both groups was of 203.4 ± 43.68 mg/dL, having higher levels than women (2.99%); the average of triglycerides was 188.3 ± 81.69 mg/dL, noting higher levels in men (3.65%). From 2010 to 2016, the levels of cholesterol showed a decrease of 2.39% (p = 0.06), whereas in the triglyceride levels was observed a decrease of 26.99% (p = 0.01).

The plasma levels of creatinine had an average of 0.87 ± 0.20 mg/dL for patients with DM/hypertension, and the average for patients with DM2 was 0.82 ± 0.13 mg/dL. Men had higher levels of creatinine. From 2010 to 2016 there was an increase of 10.34% in both groups (p = 0.03). The mean plasma urea levels for both groups were 30.91 ± 8.00 mg/dL, with higher levels in men (0.76%). During the study period, there was an increase in the urea concentration of 5.27% (p = 0.04). The glomerular filtration rate (GFR) estimated for both groups

was obtained by means of the formula CKD-EPI, obtaining an average value of 94.06 ± 21.80 mL/min/1.73 m2. There was a decrease in GFR in women of 11.15% (Figure 3).



	Male	Female	Total population	Male	Female
Media	0.84	0.74	0.87	1	0.8
Minimum range	0.7	0.5	0.59	0.84	0.59
Maximum range	0.92	1.01	1.37	1.32	1.37
Median	0.88	0.8	0.83	0.98	0.76

Figure 3: *A. Distribution of the serum creatinine concentration by sex and year. B. Distribution of the estimated glomerular filtration rate for diagnosis.*

DM: Diabetes Mellitus; HTN: Hypertension; GFR: Glomerular Filtration Rate. (p 0,034).

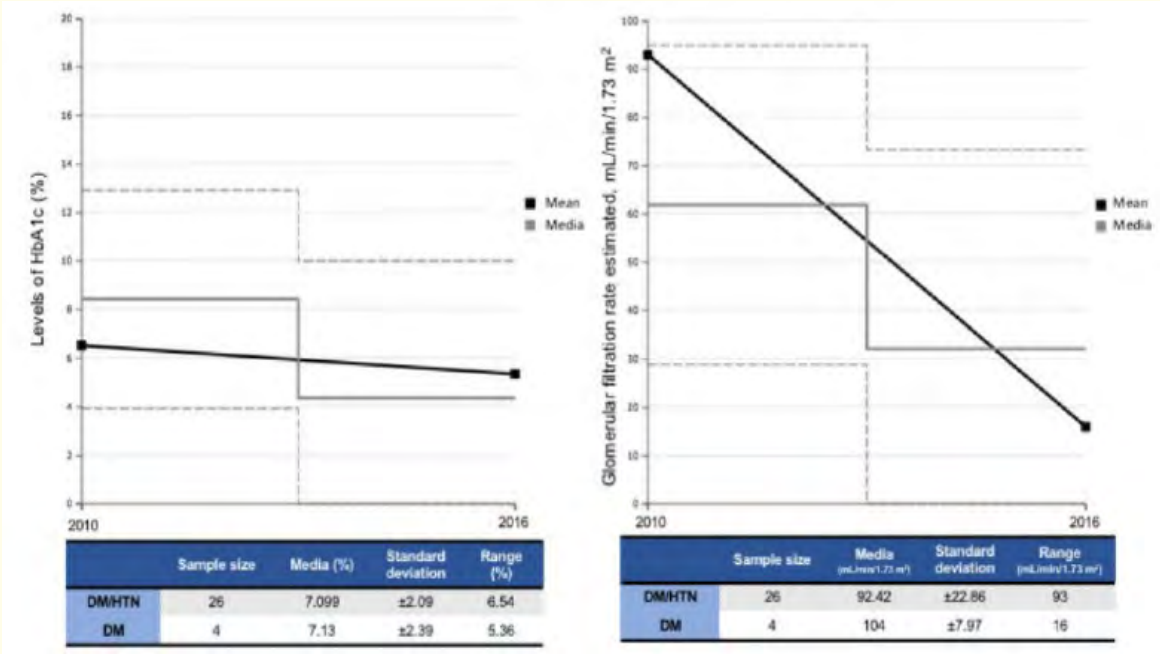
The results of the study showed various electrocardiographic changes as the resting heart rate, PR interval, QRS axis RR interval, and the corrected QT interval varied significantly between sex and diagnostics. The average resting heart rate was higher in patients with DM/hypertension (70.42 Core Return ± 11.86); similar values were observed in the PR interval. The average RR interval was significantly lower in patients with DM (845 ± 98.82). The corrected QT interval was higher in patients with DM (428.75 ± 24.34) (Table 3).

ECG Parameters	DM+HTN	DM	P
Resting Heart Rate (bpm)	70.42 ± 11.86	69.5 ± 8.85	0.08
RR interval (ms)	861.53 ± 113.23	845 ± 98.82	0.07
PR interval (ms)	171.34 ± 12.29	165 ± 20.81	0.03
QRS duration (ms)	85.73 ± 6.15	82.5 ± 6.45	0.03
QRS axis (º)	30.57 ± 5.77	27 ± 3.36	0.02
QTc Interval (ms)	423.42 ± 15.37	428.75 ± 24.34	0.05

Table 3: *Distribution of the electrocardiographic changes in patients with DM and DM/HTN.*

ECG: Electrocardiogram; DM: Diabetes Mellitus; HTN: Hypertension; bpm: Beats Per Minute; ms: Milliseconds.

The relationship between the levels of HbA1c and estimated GFR (CKD-EPI) to 5 years, showed a progressive decrease in the GFR-e of 10.61%, independent of the percentage of HbA1c, which decreased by 1.93%, being inside of therapeutic goals (p = 0.03) (Figure 4).



	Sample size	Media (%)	Standard deviation	Range (%)
DM/HTN	26	7.099	±2.09	6.54
DM	4	7.13	±2.39	5.36

	Sample size	Media	Standard deviation	Range
DM/HTN	26	92.42	±22.86	93
DM	4	104	±7.97	16

Figure 4: *Retrospective relationship between GFR estimated and the glycosylated hemoglobin by diagnosis. HbA1c: Glycosylated Hemoglobin A1c; GFR: Glomerular Filtration Rate. (p 0.039).*

The duration of the QTc interval (424.13 ± 16.38) had no significant difference with respect to the variation of the percentage levels of HbA1c (p = 0.05), being for both groups within physiologic range, although there was a greater extension in patients with DM (428.75 ± 24.34).

The estimated GFR showed a directly proportional relationship to the QTc interval for both groups, taking a slight increase for both variables of 14.03% and 10.61%, respectively (p = 0.03).

As already established, the CRS type 5 is characterized by the simultaneous presence of renal and cardiac dysfunction associated with acute or chronic systemic disorders, however, the information that you have about this pathology is limited, being the most studied the way doubt sepsis and DM in the chronic form4-5. Most of the times, to be both the renal or cardiac disease, therapeutic opportunities are very limited, so it is important to know what and at what time of the disease these changes start to become evident and be able to provide a timely treatment.

This study identified two groups of patients who suffer from chronic degenerative diseases, particularly DM and DM/Hypertension, through a cross-sectional longitudinal study, which sought to establish the incidence of CRS 5 as well as the relationship that exists between the levels of HbA1c, the Glomerular filtration rate estimated (GFR-e) and the electrocardiographic alterations, in this case the QTC interval. This relationship proved indirectly proportional to the expected results, since patients with HbA1c levels within therapeutic goals (7.10 ± 2.09%) were with lower levels of GFR-e (94.06 ± 21.80 mL/min/1.73 m^2, while the electrocardiographic changes did not have a significant clinical impact, however, begin to observe changes in early, which could be an indication of the early development of the SCR type 5.

Various studies establish that the glycemic control in patients with DM leads to kidney damage-mediated cytotoxicity by the end products of advanced glycosylation (AGEs) [10], however, in our study population, the renal function estimated using the GFR-e By the formula CKD-EPI, was independent to glycemic control, because despite the fact that the percentage of HbA1c was on average within the therapeutic goals (< 7.0%) established by the American Diabetes Association (ADA) [11], the GFR-e resulted in a progressive decrease of 10.61%, while the HbA1c decreased by 1.93% over the same period (2010 - 2016).

It was thought that the SCR began with cardiac dysfunction which caused a decrease of renal blood flow, with the resulting cardiac overload by water retention [12], however, in this study, it was noted that the earliest and obvious changes were at the renal level, which could corroborate the independent association of heart disease and kidney failure, and to the endothelial dysfunction [13]. In the early stages of both DM and you have, we can observe changes in the ECG, such as sinus tachycardia, elongation and/or of the QTc interval, changes in the variability heart rate and growth of cardiac cavities. In this population were observed mostly changes in the dispersion of the QTc interval, being more prolonged in patients with DM (428.75 ± 24.34), the other parameters did not show significant changes, however due to the fact that most of the patients presented tensional figures within the therapeutic range (PAS 124.66 ± 14.79 mmHg) and had a close attachment to their treatment, the results are consistent with the position that the maintain SBP < 140 mmHg and DBP < 90 mmHg, delayed cardiac manifestations in this group of patients [14].

The strengths of this study include the characteristics of the population, which have little variability, provide results with very little dispersion which helps an analysis more reliable, prospectively close monitoring that was carried out with each of the patients, performing a detailed record of your blood pressure, level of serum glucose, HbA1c, creatinine and urea during the study period, which prevents the loss of information or the intervention of external factors (change or suspension of treatment, changes of hygenic-diethetic habits, etc.) thus obtaining a close analysis and with very little variation of our population.

The limitations of this study were in the first place the sample such a small population, the age range in population has high variability, the main one being the aging, which represents physiologial changes such as increase of oxidative stress, endothelial dysfunction and worsening in the microcirculation, being an area of care of first and second level, resources for laboratory analysis are scarce in addition to not having all of the reagents necessary for a complete analysis of each patient (neutrophil gelatinase associated lipocalin, cystatin C, Kidney injury molecule-1, interleukin 18, natriuretic peptides and troponins, echocardiography, etc).

Conclusion

In conclusion, the SCR type 5 turns out to be an entity still very little studied, and even more so in patients with chronic degenerative diseases, so that it is of the utmost importance to have a high index of suspicion for any renal or cardiac disease in this group of patients, because when you have more serious problems such as heart failure or kidney disease, therapeutic opportunities are very limited. The set early relationships both glucose and/or blood pressure with the renal and cardiac function takes a very important role in the care of this group of patients, as at present, it is not known exactly which is the trigger that begins to deteriorate both organs, and know it would offer us a new and comprehensive overview in the treatment and prevention of complications of these diseases.

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