

Review Article

Cardiorenal Syndrome Type 4—Cardiovascular Disease in Patients with Chronic Kidney Disease: Epidemiology, Pathogenesis, and Management

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The term cardiorenal syndrome refers to the interaction between the heart and the kidney in disease and encompasses five distinct types according to the initial site affected and the acute or chronic nature of the injury. Type 4, or chronic renocardiac syndrome, involves the features of chronic renal disease (CKD) leading to cardiovascular injury. There is sufficient epidemiologic evidence linking CKD with increased cardiovascular morbidity and mortality. The underlying pathophysiology goes beyond the highly prevalent traditional cardiovascular risk burden affecting renal patients. It involves CKD-related factors, which lead to cardiac and vascular pathology, mainly left ventricular hypertrophy, myocardial fibrosis, and vascular calcification. Risk management should consider both traditional and CKD-related factors, while therapeutic interventions, apart from appearing underutilized, still await further confirmation from large trials.

1. Introduction

The term cardiorenal syndrome has been introduced recently in an attempt to emphasize the tight interaction between the cardiovascular and renal systems in acute or chronic disease settings and to expand our knowledge regarding its pathogenesis, prevention, and potential treatment [1].

The definition encompasses different syndromes, all involving the heart and the kidney, “whereby acute or chronic dysfunction of one organ may induce an acute or chronic dysfunction of the other” [2]. According to the site of the initial injury and the acute or chronic nature of the process five distinct syndromes (types) are defined. In acute cardio-renal syndrome (Type 1), acute worsening of heart function leads to acute renal dysfunction. In chronic cardiorenal syndrome (Type 2), chronic cardiac dysfunction leads to chronic renal dysfunction. In acute renocardiac syndrome (Type 3), acute renal dysfunction causes cardiac dysfunction, and in chronic renocardiac syndrome (Type 4), chronic renal dysfunction leads to cardiovascular disease

and increased cardiovascular mortality [1]. Finally, type 5, or secondary cardiorenal syndrome, involves systemic conditions such as diabetes mellitus, amyloidosis, systemic lupus erythematosus, or sepsis, which simultaneously affect both the heart and the kidney [2].

This paper will focus on cardiorenal syndrome type 4 (chronic renocardiac syndrome) presenting epidemiologic evidence of excess cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) as well as current knowledge on the pathogenesis and management of this syndrome.

2. Epidemiologic Evidence Linking CKD and Cardiovascular Disease (CVD)

CKD is defined as either a reduction in the glomerular filtration rate (GFR) to values below $60 \text{ ml/min}/1.73 \text{ m}^2$, or the presence of kidney damage as reflected in an abnormal urine sediment (proteinuria, hematuria, and casts) or

abnormalities in renal architecture (e.g., polycystic kidney disease) even if the GFR is preserved within normal levels. GFR may be directly measured by renal clearance of specific substances (e.g., creatinine, inulin) and radioactive markers (e.g., ^{99m}Tc -DTPA) or it may be estimated (estimated GFR-eGFR), by the application of formulas incorporating serum creatinine and demographic parameters (Cockcroft-Gault, MDRD) [3].

Both proteinuria and the reduction of GFR have been associated with increased cardiovascular morbidity and mortality [4]. This association is so strong and clinically relevant that according to current guidelines the diagnosis of CKD places a patient into the highest cardiovascular risk level, irrespective of stratification according to traditional cardiovascular risk factors [3, 4]. Compared to the general population, CKD patients are still plagued by a frustratingly high mortality, which is mainly attributed to cardiovascular events, with death being far more probable than advancing into the final CKD stages and the need of renal replacement therapy (RRT) [5]. The high mortality afflicting patients on renal RRT, which for the ages between 25 and 35 may rise up to 375-fold compared to the general population [6], is derived almost by half of cardiovascular causes [7].

2.1. Proteinuria/Albuminuria and CVD. The abnormal quantities of protein in the urine (proteinuria) consist mainly of albumin (albuminuria) and can be semiquantitatively identified by urine dipstick testing, estimated by the urine protein-to-creatinine ratio (UPCR) or albumin-to-creatinine ratio (UACR) in a spot urine sample, or directly measured in a timed (usually 24 h) urine collection [3, 8]. The diagnosis of microalbuminuria (30–300 mg/day) and albuminuria (>300 mg/day) is mainly utilized in the evaluation of diabetic nephropathy, while proteinuria (>300 mg/day or UPCR >200 mg/g) is mostly used for nondiabetic CKD [8].

Whether considered a marker of systemic endothelial dysfunction or a result of renal damage [9], proteinuria has been associated with increased cardiovascular mortality in the general population, even at levels regarded as normal [10]. In repeated studies, the presence of micro- and macroalbuminuria and eGFR reduction were independent predictors of increased overall and cardiovascular mortality in diabetic [11] and nondiabetic individuals [12]. In a recently published large community-based study involving nearly one million adult subjects, the presence of proteinuria was assessed by urine dipstick or UACR. Higher levels of proteinuria were independently associated with an increased risk of myocardial infarction and all-cause mortality, as were decreased levels of eGFR. The severity of proteinuria was actually a stronger predictor of worse clinical outcomes than was eGFR reduction, a fact suggesting that levels of proteinuria may have a role in risk stratification of CKD patients, who are currently staged only according to their level of GFR [13].

2.2. GFR and CVD. Irrespective of the presence of proteinuria, GFR decline has been repeatedly associated with

increased cardiovascular morbidity and mortality. In a large community study involving more than one million adults, an independent and graded association was observed between eGFR reduction and increased risk of death and cardiovascular events including hospitalization for coronary artery disease, heart failure, stroke, and peripheral vascular disease [14]. In middle-aged adults participating in the Atherosclerosis Risk in Community (ARIC) study, a baseline eGFR of less than $60 \text{ ml/min}/1.73 \text{ m}^2$ was independently associated with an increased risk of developing peripheral arterial disease [15] or heart failure, irrespective of prevalent coronary artery disease [16]. According to United States Renal Data System 2007 annual report regarding incident dialysis patients, comorbidities included congestive heart failure in 34%, atherosclerotic heart disease in 22.5%, cerebrovascular disease in 10%, and peripheral vascular disease in 15% of cases [17].

2.3. Cardiovascular Outcomes in CKD. In patients with already established cardiovascular disease, renal impairment markedly worsens outcomes. An inverse relationship between eGFR and the extent of coronary stenotic lesions was shown [18], as well as increased probability of having three-vessel coronary artery disease with decreasing eGFR [19]. In a study of almost 15.000 patients, who had suffered myocardial infarction, even mild eGFR reduction at baseline was independently associated with increased overall mortality or a composite end point of death from cardiovascular causes, reinfarction, congestive heart failure, stroke, or resuscitation after cardiac arrest [20]. In patients undergoing coronary artery bypass grafting, a reduced baseline eGFR has also been associated with increased 30-day and long-term mortality [21]. Furthermore, in patients with advanced congestive heart failure, impaired renal function seems to be a stronger predictor of mortality than impaired cardiac function (left ventricular ejection fraction and New York Heart Association class) [22]. Finally, in a recent study also involving patients with heart failure, the presence of albuminuria significantly aggravated prognosis by exhibiting a strong and independent association with increased all-cause and cardiovascular mortality [23].

3. Cardiovascular Injury in CKD

Due to the vital importance for the rapidly growing population of CKD patients, the pathogenetic mechanisms leading to cardiovascular damage in renal disease are under constant investigation. More than a dozen of pathways have been identified including hyperactivity of the renin-angiotensin-aldosterone system, osmotic sodium retention, volume overload, endothelial dysfunction, dyslipidemia, coagulopathy, inflammation, and anemia [24], all leading to histomorphological alterations of the heart and vessels.

In addition, some key emerging topics in this field include sympathetic hyperactivity, cardiotonic steroids, nonosmotic sodium retention, and catalytic or labile iron. Sympathetic activation by the failing kidney leading to both renal disease progression and cardiovascular morbidity

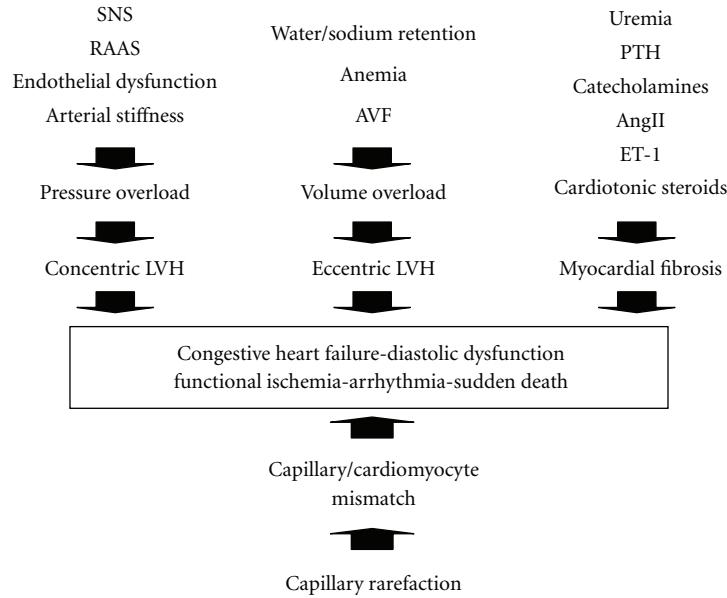


FIGURE 1: Heart alterations and their consequences in CKD. AVF: arteriovenous fistula, AngII: angiotensin II, ET-1: endothelin-1, LVH: left ventricular hypertrophy, PTH: parathormone, RAAS: renin-angiotensin-aldosterone system, SNS: sympathetic nervous system.

and mortality may provide a new target for therapeutic intervention [25]. Cardiotonic steroids are elevated in renal failure and have been linked to hypertension and to the development of uremic cardiomyopathy in animal models [26]. Nonosmotic sodium stores in the form of water-free Na⁺ accumulation in the skin have been proposed to contribute to the development of hypertension and thus might be associated to CKD progression and cardiovascular complications [27]. Finally, labile/catalytic iron is associated with oxidative stress in situations such as acute kidney injury after cardiac revascularisation and in diseases such as diabetes and may result in both kidney disease progression and cardiovascular complications [28]. However, an extensive analysis of all the above mechanisms lies outside the scopus of the present paper, and readers are referred to some excellent recent reviews [25–28].

3.1. The Heart in CKD. The mechanisms leading to cardiac alterations in CKD are depicted in Figure 1. Cardiac workload is increased in CKD. This increase is the result of two separate pathways both leading to left ventricular hypertrophy (LVH): pressure overload and volume overload. Pressure overload mainly derives from increased peripheral resistance and reduced arterial compliance due to sympathetic and renin-angiotensin system hyperactivity, hypertension, endothelial dysfunction, and vascular calcification/stiffening. It causes thickening of cardiac myofibres by parallel addition of sarcomeres, thus leading to concentric LVH. Volume overload is attributed to sodium and water retention, anemia, and the presence of an arteriovenous fistula in patients with end-stage renal disease (eGFR <15 ml/min/1.73 m² anticipating or on chronic dialysis). It results in lengthening of the cardiac myofibers by serial addition of sarcomeres thus causing eccentric LVH (left ventricular dilatation) [29, 30]. LVH in

renal disease is a pathologic process and, unlike physiologic adaptations to increased workload (e.g., “athletes heart”), is accompanied by fibrosis, which is also attributed to conditions related to the uremic milieu, including increased levels of parathyroid hormone, endothelin, aldosterone, catecholamines, and cardiotonic steroids [26, 30, 31]. In a study involving 432 ESRD patients, only 16% had a normal echocardiogram at initiation of dialysis, the rest exhibiting mainly features of concentric LVH (41%) and left ventricular dilatation (28%), both associated with increased risk of heart failure and death [32]. A more recent study demonstrated progression of concentric LVH in 576 new dialysis patients followed up by echocardiography [33].

In addition to fibrosis and cardiomyocyte hypertrophy, histological changes of the heart in uremia also include myocyte apoptosis/necrosis resulting in myocyte number reduction, and microvascular abnormalities such as arteriolar wall thickening and capillary rarefaction, the latter being specific to uremia [29, 34].

The functional consequences of all the aforementioned structural changes include diastolic dysfunction [35], increased oxygen demand and impaired, myocardial oxygenation unrelated to coronary obstruction [34, 36]. This may explain the angiographic finding of patent coronaries in 30%–40% of uremic patients with ischemic heart disease/angina pectoris [34], as well as their predisposition to arrhythmias, both atrial and ventricular, and sudden death, which account for more than half of the cardiovascular mortality of patients on RRT [37, 38]. Susceptibility to arrhythmias and sudden death may be further increased by coronary artery disease/myocardial infarction, left ventricular hypertrophy, congestive heart failure, electrolyte abnormalities, chronic fluid overload, anemia, autonomic imbalance, and inflammation [38].

3.2. Vascular Changes in CKD. Ever since early reports of aortic thickening in uremic patients by Richard Bright in 1827, renal disease has been associated with vascular pathology [39]. Pathologic features include reduced elasticity/compliance of large arteries, as reflected in an increase of the arterial pulse wave velocity (PWV) [40, 41], thickening of the arterial wall, leading to an increased intima-media thickness (IMT) [42], and, mainly, vascular calcification [43, 44].

Vascular calcification has recently been the focus of attention mainly because of its established association with cardiovascular mortality in CKD patients [45]. Moreover, in the last decade, research has shown that it is not simply the result of passive mineral precipitation but rather an active and highly regulated process, closely resembling osteogenesis [43, 46], and is orchestrated by the arterial smooth muscle cell after its genotypic transformation to an osteoblast-like cell [43]. Ossification of the arterial wall is favoured by conditions like ageing, diabetes, inflammation, and especially CKD. In renal disease, vascular calcification is linked to hyperphosphatemia, lack of calcification inhibitors (i.e., fetuin-A, matrix GLA protein, osteopontin, or pyrophosphate) and derangements in regulators of mineral metabolism (i.e., vitamin D, parathormone, osteoprotegerin, and bone morphogenetic proteins) [43], and abnormalities in bone turnover such as secondary hyperparathyroidism and adynamic bone disease [46–48].

In addition, recent studies implied a role for the phosphatonin Fibroblast Growth Factor-23 (FGF-23) in the pathophysiology of chronic kidney disease—mineral bone disorder (CKD-CMD) and in vascular calcification. FGF-23 levels are elevated in CKD patients both on dialysis and on conservative treatment and have been associated with increased mortality and left ventricular hypertrophy. Moreover, FGF-23 has been linked to increased arterial stiffness, endothelial dysfunction, and vascular calcification. However, a causative relation and its value as a marker of cardiovascular status and/or phosphate-related toxicity, as well as its potential role as a target for intervention, still await further clarification [49].

Calcium deposits may surround atheromatous plaques in the arterial intima (atherosclerosis) or involve the medial layer of the arteries (arteriosclerosis—Moenckeberg's sclerosis) [50]. They can be visualised in plain X-ray films [51, 52] and quantified by more sophisticated and more expensive techniques like electron beam computed tomography (EBCT) [53, 54], the latter regarding mainly coronary artery calcification (CAC).

Whether vascular intima and media calcification are really distinct entities still remains controversial. Because of the results from experimental models as well as their difference in histopathologic features, location in the arterial tree, and pathophysiologic consequences, they tend to be regarded as distinct [50] although this view has recently been challenged [55, 56]. Both types of vascular calcification appear early in CKD, run an accelerated course, especially after RRT initiation [53, 54], and lead to high cardiovascular morbidity and mortality [45]. More importantly, a recent metareview on treatments for vascular calcification in CKD

has demonstrated that no therapy to date, including statins and sevelamer, appears to influence their rate of progression [57].

In CKD patients, CAC score measurement as a tool for cardiovascular risk stratification may be affected by the unique presence of medial coronary calcification [58, 59] unrelated to obstructive coronary atherosclerosis, thus not necessarily leading to ischemia. Nevertheless, a high CAC score has been associated with increased mortality in CKD patients both before [60] and after the initiation of dialysis [61]. Apart from medial calcification, another feature characteristic of coronary artery disease (CAD) affecting CKD patients is the location of culprit atherosclerotic lesions. In renal patients with acute myocardial infarction, they were found to be located more proximal to the coronary ostia, which may account for the observed increased mortality [62].

Because CAD is highly prevalent in CKD patients, non-invasive screening tools for the prediction of asymptomatic coronary obstruction are needed. In recent studies, cardiac Troponin T (cTnT) has emerged as a powerful predictor of multiple-vessel CAD in asymptomatic hemodialysis patients [63, 64]. In addition, the acute kidney injury biomarker neutrophil gelatinase-associated lipocalin (NGAL) has recently been associated with both chronic renal impairment and cardiovascular complications and might potentially prove its worth as a cardiovascular risk predictor in CKD [65].

Aortic calcification assessed by lateral abdominal X-ray has also been associated with all-cause and cardiovascular mortality in dialysis patients and has been proposed as a simple tool for cardiovascular risk assessment and treatment guidance [52, 66].

4. Cardiovascular Risk Modification in CKD

Because of the heavy CVD burden affecting CKD patients, risk modification is vital in an effort to improve outcomes. Still CKD patients are usually excluded from large interventional trials [67] because of their expected adverse outcomes, thus hindering the evaluation of therapeutic interventions. Furthermore, interventions for traditional cardiovascular risk reduction already established in the general population have proved less effective in patients with CKD [24, 68, 69]. This seems to result into a kind of “therapeutic nihilism” [24], by denying treatment despite the presence of sound indications, for example, the underutilisation of antiplatelets, statins, β blockers, and ACE inhibitors in CKD patients with known CAD [70]. Furthermore, CKD patients are less likely to undergo coronary angiography, percutaneous coronary intervention, or bypass grafting, or to receive adjuvant treatments, such as GpIIb/IIIa inhibitors [67].

Strategies to reduce cardiovascular risk in CKD patients should target both traditional and non-traditional, that is, CKD-related factors. Traditional risk factors include hypertension, dyslipidemia, diabetes, obesity, physical activity, and smoking habit, while CKD-related factors refer to CKD progression, proteinuria, anemia, inflammation, mineral and bone disorder, LVH, oxidative stress, coagulopathy,

hyperactivity of the renin-angiotensin and the sympathetic nervous system, and dialysis dose and quality [67] (Table 1).

Setting of specific treatment targets is complicated, especially in patients on RRT, by findings of reverse epidemiology with a U-shaped curve associating mortality with blood pressure, BMI, cholesterol, and phosphate [71], possibly a result of the Malnutrition-Inflammation-Atherosclerosis (MIA) syndrome frequently encountered in this patient population [72, 73]. Further controversies also derive from recent results of increased morbidity and mortality in CKD patients associated with higher hemoglobin levels [74], intensive blood pressure [75] and glucose control [76], dual angiotensin II blockade [77] and suppression of parathyroid function, and bone turnover [47, 48], which question the safety of overaggressive intervention on specific laboratory and clinical parameters in this patient group. Rather than meticulously pursuing generalised targets, recent opinions suggest a potential benefit from a more individualised perspective, that takes into account patient-specific trends and distinctive dynamic features of the actual clinical situation [66, 78, 79].

Eagerly awaited is the publication of results from large randomised studies evaluating therapeutic interventions to lower cardiovascular morbidity and mortality in CKD patients, such as the ongoing EVOLVE (EVAluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) [80] and the concluded SHARP (Study in Heart And Renal Protection). The latter, a double blind placebo-controlled study involving almost 9500 CKD patients (a third of them on dialysis) in 18 countries, has been able to demonstrate a significant reduction in cardiovascular events, such as myocardial infarction, stroke, or need for coronary artery revascularization, with the use of a combination of ezetimibe plus simvastatin, according to most recent results presented during the American Society of Nephrology Renal Week 2010 [81].

Until further results are available, current recommendation for predialysis patients suggests regular exercise, where feasible, smoking cessation, blood pressure control to <130/80 mmHg with preference to angiotensin-II-targeted treatment, HbA_{1c} levels of <7.0%, Hb levels of 10–12 g/dL, LDL cholesterol levels as for the general population with high cardiovascular risk, sodium intake <2.4 g/day, maintenance of a BMI <25 kg/m², treatment of proteinuria, and avoidance of nephrotoxicity, aiming, apart from cardiovascular protection, at renal function preservation and slowing of CKD progression [3, 67, 82–84].

For patients on dialysis, blood pressure of <140/90 mmHg before and <130/80 mmHg after dialysis is recommended. Optimal levels of HbA_{1c} and LDL-C seem to be less clearly defined, since they may not accurately reflect glycemic status [85] and atherogenic potential [86], mainly because of the short erythrocyte lifespan [85] and the qualitative rather than quantitative lipid abnormalities in uremia [86]. Special consideration must be taken to mineral bone disorder aiming at normal phosphorus levels, avoiding hypercalcemia, and treating secondary hyperparathyroidism judiciously in order to maintain the mineral buffering ability of active bone turnover, in order to ameliorate vascular calcification [66].

TABLE 1: Targets for cardiovascular risk modification in CKD.

Traditional	CKD related
Physical activity	Proteinuria
Smoking	CKD progression
Obesity	Sympathetic nervous system
Blood pressure	Renin-angiotensin system
Glycemia	Left ventricular hypertrophy
Lipids	Mineral bone disorder
	Anaemia
	Inflammation
	Oxidative stress
	Coagulopathy
	Dialysis dose and quality

The latter is portrayed in recent recommendations regarding vascular calcification screening, phosphate binder choice, and target levels of parathormone [66, 87, 88]. Also of importance are dialysis adequacy, quality, and hemodynamic stability, as well as the optimization of conditions regarding inflammation and dialysis-related infections [89, 90].

The treatment and prevention of arrhythmias and sudden death remains a challenge. Apart from attention to electrolyte disorders and avoidance of low-potassium dialysate, whenever possible, the use of β blockers seems beneficial. ACE inhibitors and angiotensin II receptor blockers appear promising but have yet to prove their efficacy in prospective trials [38]. Implantation of cardiac defibrillators in dialysis patients is associated with increased risk for bleeding and infection. Compared to patients with normal renal function, their use for primary prevention in CKD patients confers a reduced survival benefit, possibly due to comorbid conditions or increased defibrillation thresholds. On the other hand, implantation for secondary prevention is underused in dialysis patients, despite a proven effect in reducing mortality [37, 38].

In summary, CKD patients carry a heavy cardiovascular burden leading to high morbidity and mortality. This can be attributed to the high prevalence of traditional risk factors, such as advanced age, diabetes, and hypertension but also derives from CKD-related morbidity, such as sympathetic and renin-angiotensin hyperactivity, sodium retention, fluid overload, anemia, dyslipidemia, mineral-bone disorder and inflammation, which lead to structural alterations of the heart and vessels (chronic renocardiac syndrome). Aggressive risk modification, high index of suspicion for cardiovascular morbidity, proper intervention, and secondary prevention are essential. Large high-quality trials involving CKD patients are urgently needed to provide results, which could support effective treatment strategies. Until such results are available, avoiding “therapeutic nihilism” and aiming at established treatment targets with an individualised patient-oriented approach appears sensible.

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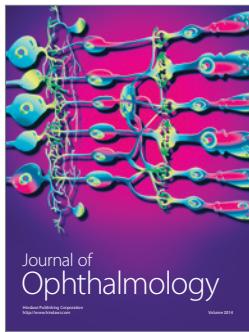
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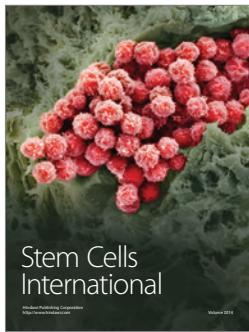
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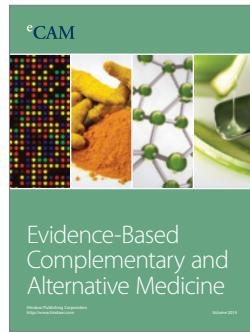
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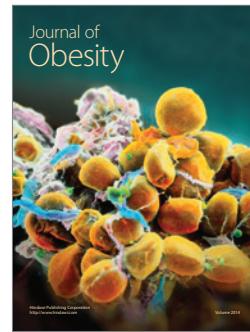
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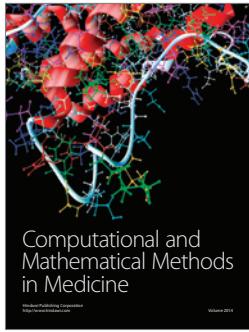
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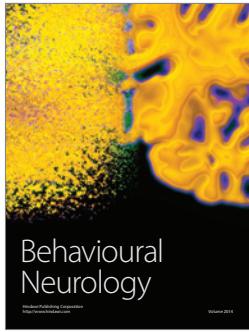
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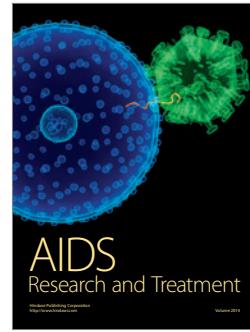
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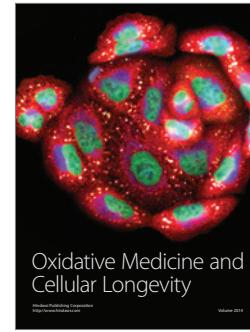
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