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“Intra-renal hemodynamic changes after habitual physical activity in patients with Chronic Kidney Disease”

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Chronic Kidney Disease (CKD) is considered a silent epidemic with a continuously growing prevalence around the world. Due to uremia many functional and morphological abnormalities occur in almost all systems. Mostly affected, the cardiovascular system, leads to diminished cardiac function that affects patients’ functional capacity and physical activity levels, reducing survival and increasing all-cause mortality. Systematic exercise training ameliorates uremia induced body deficits and significantly improves the survival of CKD patients. Intradialytic exercise training has been recommended as a complementary therapeutic modality equally important to hemodialysis. Thus the aim of this systematic review is to provide an update on recent advances in our understanding of how exercise training improves functionality of the cardiovascular system through the hemodynamic changes induced by habitual or intradialytic and/or home-based exercise training programs. Systematic exercise training induces beneficial adaptive responses and influences many sensitive physiological biomarkers, such as oxidative stress biomarkers that are implicated in the development of atherosclerosis. Additionally, exercise training decreases the cardiovascular risk by improving the autonomic nervous system activity and the left ventricular function and by reducing nontraditional risk factors such as epicardial adipose tissue. It seems that all these central and peripheral adaptations to exercise training significantly contribute to improvements in functional capacity and exercise tolerance among CKD patients and result in the risk reduction of CKD-associated disorders. In conclusion, exercise training could serve as a complimentary therapeutic strategy in CKD patients while health care providers should motivate patients to engage in any type of exercise training programs.

Keywords: chronic kidney disease, exercise training, uremia, habitual physical activity, intradialytic training, home-based exercise

INTRODUCTION

Chronic Kidney Disease (CKD) is characterized as a silent epidemic due to the continuously growing prevalence around the world and with a prevalence of 7.2% in patients aged >30 years old and ranging from 23.4% to 35.8% in patients aged >64 years, CKD is a major health problem [1]. In addition, it has been estimated that the percentage of people aged >60 years will increase from 11% to 22% in 2050, thus the prevalence of CKD will be increased [2] and this condition will have an enormous socio-economic impact. Thus, new strategies for CKD prevention and new complimentary treatments, which could ameliorate all the CKD consequences, should be found.

Aging, hypertension, diabetes, glomerulonephritis, cystic kidney disease and other diseases are responsible for the irreversible deterioration of kidneys structure and function. Unfortunately, the asymptomatic nature of CKD especially in the early stages does not allow the early diagnosis and many opportunities for prevention and treatments could be lost. Consequently, a significant loss of kidney function occurs which is accompanied from toxins accumulation in the plasma and progressively the clinical syndrome of uremia appears with numerous consequences. When the loss of kidneys function is significant to a level that less than 10% of kidneys function remains, this condition is characterized as end-stage renal disease (ESRD) and the renal replacement therapy of hemodialysis is necessary. Although the technology of hemodialysis therapy has improved all these years, it still induces numerous complications which are responsible for the significant clinical problems appeared in CKD patients and for the low levels of quality of life that are characterized them.

CKD patients and especially ESRD experienced several functional limitations such as fatigue, muscular weakness, low cardiorespiratory fitness, exercise intolerance, which induce disability and morbidity and contribute to the poor survival prognosis that these patients presents [3]. Moreover central and peripheral factors met in CKD patients are responsible for the exercise intolerance and especially cardiac dysfunction, metabolic abnormalities, impaired Autonomic Nervous System (ANS) activity, muscle wasting and muscular weakness are components of uremic myopathy and cardiomyopathy [4]. All these consequences lead CKD patients to inactivity and hypokinesis and accordingly increase the risk for cardiovascular mortality.

Cardiovascular disease (CVD) is remaining the most common cause of death in CKD patients [5]. As the kidneys function falls the cardiovascular risk increases [6], especially ESRD patients are in 40-50 times higher risk than the general population to die from cardiovascular events [7]. It has been found that 40% of the patients that have started hemodialysis therapy presents coronary artery disease, while the 85% of these patients manifested disturbances in left ventricular structure and function [8]. Several mechanisms have been proposed in the pathogenesis of CVD in CKD patients such as hypertension, dyslipidemia, activation of the renin-angiotensin system, endothelial dysfunction, oxidative stress and inflammation. Exercise training has proved to be an effective intervention, which have beneficial impact on cardiovascular and musculoskeletal system health. Moreover, exercise training has been recommended as a complementary therapeutic modality in the CVD prevention [9, 10].

Specifically, it has been found that systematic exercise training induces cardioprotective mechanisms by reducing traditional risk factors and can improve the low levels of cardiorespiratory fitness, which presents CKD patients and are irreversible connected with mortality. In order to increase the positive health effects of exercise and participant's compliance with the training programs different modalities of exercise training

programs have been applied to CKD patients such as intradialytic, home-based or habitual exercise training programs.

Thus the aim of this systematic review is to provide an update on recent advances in our understanding of how exercise training improves functionality of the cardiovascular system through the hemodynamic changes induced by habitual or intradialytic and/or home-based exercise training programs.

METHODS

A systematic review was conducted searching Pubmed and Scopus by using the Cochrane and PRISMA guidelines. A comprehensive literature search was conducted from June 2015 through October 2015. We used PubMed, Science Direct and Scopus or Google Scholar to search for studies that investigated the intra-renal hemodynamic changes induced by habitual or intradialytic and/or home-based exercise training programs on cardiovascular system in CKD patients. Eligibility of the studies based on titles, abstracts and full-text articles was determined by two reviewers. Studies were selected using inclusion and exclusion criteria. Figure 1 shows the progress of the literature screening. In the current review only studies that met the following criteria were included: studied CKD patients and patients on hemodialysis treatment, assessed cardiovascular system function in CKD patients; addressed randomized control trials or controlled trials or clinical trials or pilot studies designed to evaluate the intra-renal hemodynamic changes; lack of a drug or diet interventions on the cardiovascular system or lack of uremic animals' models, and full text articles written in English. Studies were excluded when they referred to patients on peritoneal dialysis and concerned low quality studies, namely studies with methodological flaws or lack of reporting.

RESULTS & DISCUSSION

Cardiovascular abnormalities in CKD patients

CKD is associated with increased risk for cardiovascular events and mortality. Especially ESRD who receive hemodialysis therapy experienced several cardiovascular complications such as coronary artery disease, congestive heart failure, arrhythmias and hypertension. High blood pressure, insulin resistance, dyslipidemia, vascular calcification, chronic inflammation, oxidative stress, endothelial dysfunction and other metabolic disturbances contribute to structural and functional changes in myocardium and accordingly lead to cardiac dysfunction and to increase cardiovascular events in patients with CKD.

Left ventricular hypertrophy (LVH), dilatation, systolic and diastolic dysfunction are components of the condition who is used to describe the effects of CKD on myocardium, termed as uremic cardiomyopathy leading to changes in the systemic hemodynamics affecting the structural and functional characteristics of the in myocardium. The main result of uremic cardiomyopathy is LVH which is manifested in the 26% of patients in stage 3 of CKD and in the 75% of patients on hemodialysis therapy [8] and is considered as an independent predictor of survival in CKD patients [11]. LVH is the result of hypertension and arteriosclerosis which occur due to pressure and/or volume overload that induced from anemia, arteriovenous fistula and hypervolemia in CKD patients [12] and it could be characterized as an adaptive response to these complications. Hypertension and increased volume overload, probably induce cardiomyocyte hypertrophy and vascular remodeling [13]. Additionally, an excessive activation of the renin-angiotensin-aldosterone system [14] as well as the phosphoinositide-3

kinase (PI3K)-Akt pathway contributes further to the development of LVH in these patients' population [15]. LVH also is responsible for the left ventricular dilatation and dysfunction and for the decreased left ventricular ejection fraction.

In addition other factors influence the development of cardiac diseases in CKD patients such as increased levels of homocysteine [16], hyperparathyroidism, hypoalbuminaemia, oxidative stress and inflammation. Anemia and impairment mineral metabolism, stimulate hyperphosphatemia and elevated parathyroid hormones levels leading to vascular calcification by altering the phenotype of vascular smooth muscle cells [14]. Hypovitaminosis D, which is a common disturbance of CKD patients, contributes to myocardial hypertrophy and it has been associated with cardiovascular mortality and sudden cardiac death [17]. A possible explanation is the multifactorial role of vitamin D on heart remodeling such as cardiac cell contraction, proliferation, hypertrophy, differentiation as well as protein and collagen expression [14].

Functional capacity limitations in CKD patients

CKD patients are characterized by very low levels of functional capacity which is responsible for the exercise intolerance and early fatigue that these patients experienced. Consequently, due to the reduced levels of aerobic capacity ESRD have to deal with many difficulties in performing the everyday living activities. Several factors are responsible for the low functional ability found in CKD patients. For example, VO_2peak in ESRD patients is decreased by ≈50% compared to healthy age-matched values and therefore the activities of these patients are limited to those intensities require low level of aerobic capacity [18]. Limitations in oxygen delivery during exercise training due to cardiac dysfunction and complications in blood circulation are considered as the major causes for the reduced VO_2peak that CKD patients present.

Painter [19], suggested that many factors interact and are responsible for the low levels of aerobic capacity seen in CKD patients, such as decreased cardiac output which is attributed to the low heart rate, low arterial oxygen content induced from anemia and abnormal muscle function which is attributed to uremic myopathy and neuropathy. Additionally, malnutrition, impaired energy metabolism, secondary hyperathyreoidism and inactivity enhance the symptoms of uremic myopathy.

Changes induced by uremic myopathy in skeletal muscles are responsible for the muscle wasting and the preliminary fatigue in CKD patients. According to studies decreased fiber size, especially atrophy and loss of IIα and IIx fibers, reduced capillary density and peripheral activation [20] and a significant reduction in the mean diameter of both fiber types have been found in CKD patients [21]. Moreover, disturbances in mitochondrial morphology found in CKD patients possibly explain the increased fatigability [22].

Central or peripheral uremic neuropathy resulted in cardiac autonomic nervous system (ANS) dysfunction, which is a common feature in patients receiving hemodialysis therapy. A reduction in both sympathetic (SNS) and parasympathetic nervous system (PNS) occurs in uremic dysautonomia and especially parasympathetic failure during hemodialysis is a common complication in uremic patients [23]. Spectral analysis of heart rate variability (HRV) is the most commonly noninvasive method used for the assessment of ANS activity and autonomic dysfunction and is usually expressed with depressed HRV in CKD patients. In addition, HRV is considered to be an independent predictor of mortality in hemodialysis patients [24]. Decreased HRV due to dysfunction of the cardiac ANS is a known complication of hemodialysis patients and is associated with an increased risk of ventricular arrhythmias

and sudden death. Furthermore, it has been reported that a sympatho-vagal imbalance in the cardiovascular system which is expressed with reduction in the indices of SDNN, LF and LF/HF ratio is related with sudden cardiac death [25]. Many studies have supported the notion that hemodialysis therapy itself induces changes in HRV of uremic patients [23, 26-29]. Specifically, it has been observed decreased sympathetic activity during hemodialysis [26] in contradiction to the results of some other authors demonstrating a shift in sympathovagal balance towards sympathetic activation during the hemodialysis process [27, 28].

Exercise training can ameliorate or delay the progress of all these consequences of CKD. Since the early ’80 many different modalities of exercise training programs have been applied in CKD patients such as home-based, habitual, center-based and intradialytic. All these studies have documented that exercise training is possible in CKD patients, due to the hemodynamic changes inducing beneficial responses by improving functional capacity and overall health related quality of life.

Hemodynamics changes during exercise training

During exercise in healthy subjects, the induced hemodynamic changes activate many beneficial mechanisms, which in turn cause beneficial adaptations with renoprotective and cardio-protective effects. Furthermore, in healthy subjects during exercise and especially during the first minutes, a rapid increase in heart rate, blood pressure and stroke volume take place. Accordingly an elevation n cardiac output occurs as an adaptive response to the increased muscle metabolic demands for oxygen. Additionally, it has been observed that in response to exercise, hematocrit and blood viscosity are increased, which in turn induce beneficial cardio-protective effects by promoting the nitric oxide (NO) production [30]. Moreover, the increase in blood viscosity during exercise seems to contribute to the circulatory resistance reduction [30]. Also, during exercise training, the sympathetic nervous system activity is crucial for the blood flow and the blood pressure regulation [31]. Animal studies [32, 33] have revealed that exercise has beneficial effects on coronary microcirculation because during submaximal exercise training a slightly or a continued increase of α-adrenergic and β-adrenergic tone occurs and accordingly an increased receptor responsiveness to adrenergic stimulation is adopted. Consequently, a reduction in the circulating catecholamine levels is observed due to increased adrenergic sensitivity to stimulation. Both coronary and peripheral resistance vessels benefit as their constriction is greater and probably the myocardial oxygen extraction could be enhanced even after exercise [34].

Patients with CKD are characterized by a decreased cardiac response during exercise due to cardiac and other abnormalities such as anemia, arteriovenous fistoula, hypertension, etc., which affect cardiac pre-load and after-load (figure 2). Blomqvist [35], who described the cardiovascular adaptations to physical exercise proposed that stroke volume could be elevated during exercise by increasing the cardiac dimensions or by enhancing the performance characteristics of the heart. Cardiac functional and structural abnormalities met in CKD patients, due to uremic cardiomyopathy, probably are responsible for the decreased cardiac response during exercise, observed in these patients. Moreover, increased levels of endothelin 1, which is a vasoconstriction protein, have been observed in CKD patients [36] and likely increase the peripheral resistance in these patients.

Also, impaired cardiac autonomic control is reflected in the increased levels of resting heart rate in CKD patients. However, during exercise heart rate response is decreased and only a small amount of CKD patients can reach the predicted heart rate [37]. The decreased

heart rate response during exercise is attributed to impaired cardiac autonomic nervous system and myocyte dysfunction, which characterize CKD patients [38]. Moreover, anemic dialyzed patients present higher cardiac output and stroke volume and as a consequence an increased prevalence of left ventricular hypertrophy and left ventricular dilatation are observed [39]. Treatment of anemia with erythropoietin in CKD patients seems to have a beneficial impact on hemodynamics as it has been found that patients after treatment presented a tendency to decrease cardiac output and left ventricular mass and as a result exercise tolerance improved [39].

However, varied cardiac adaptations occur during exercise training in different positions. For example a study by Poliner et al [40] who examined the cardiac responses to exercise in upright and supine positions supported that during supine position the Frank-Starling mechanism is activated due to increased left ventricular end-diastolic volume compared with upright or sitting position. Specifically, the increase in left ventricular end-diastolic volume during low-level upright exercise training was doubled compared to exercise training in supine position [40]. Thus, exercise training during hemodialysis therapy where the feet are elevated and fixed on the cycle ergometer probably induce even more beneficial cardiac effects compared to non-dialysis exercise training.

Especially when exercise training is during hemodialysis therapy, the large fluid volume induces changes in cardiovascular response to exercise. Moore et al [41], who described the cardiovascular changes during intradialytic submaximal stationery cycling, found that during the first two hours hemodialysis therapy does not affect the cardiovascular response to exercise. In contrast, in the same study the authors revealed that after 3 hours of hemodialysis therapy hemodynamic changes, which contributed to cardiovascular decompensation, occurred. These findings suggested that after the second hour of hemodialysis therapy exercise training should be precluded [41]. The hemodynamic instability after the third hour of hemodialysis is attributed to the fact that a sympathetic nervous system withdrawal occurs and is responsible for the inappropriate decrease in heart rate and blood pressure presented in hemodialysis patients.

There is limited evidence regarding the beneficial effects of exercise training in kidney function. An animal study by Ito et al [42], who examined the chronic effects of running in Zucker diabetic fatty rats showed that at early stages of diabetic nephropathy, running beneficially induce alterations in kidney oxidative stress status. More precisely, the 8 weeks running on a treadmill increased NOS activity and protein expression of eNOS and nNOS proteins in the renal cortex of the diabetic rats, suggesting that exercise training may provide renoprotective effects and delay the progression of renal failure at the early stages of diabetic nephropathy [42]. In addition, the renoprotective effects of exercise training have been proved in a study by Tucker et al [43], where the authors compare the effects of high intensity interval training with light intensity exercise training or with a sedentary group of rats. The exercise program of running on a treadmill lasted 8 weeks. After completing the training period, the authors found that the group who followed the interval training had elevated mRNA expression of superoxide dismutase (Sod) 1 and catalase (Cat) in the renal tissue [43]. Moreover, the results of the same study revealed that interval exercise training had beneficial effect on inflammation, which was expressed by an up-regulation to *Tnfrsf1b* mRNA expression in kidney tissue [43].

The results of these histopathological studies demonstrated that exercise training through an up-regulation in oxidant and antioxidant status is possible to influence kidney function beneficially. Therefore, the renoprotective effects of exercise training can ameliorate the renal failure progression by reducing oxidative stress and inflammation. However, these

studies have been applied in animal and specifically in animal models of rat and we can only hypothesize that this renoprotective effects could be activated in humans.

On the other hand, the fact that systematic exercise training provides cardio-protection properties against cardiovascular diseases, through adaptations and mechanisms that are activated by the hemodynamic changes during exercise, is well established. This protection could be acute or chronic for example acute protection could be induced immediately after an acute bout of exercise training. Unfortunately this protection lasts only 3 hours while chronic is initiated 24 hours after exercise training and could persist 9 days after completing 5 day exercise training routine [44]. It has been suggested that acute protection occurs by the activation of the antioxidant mechanisms and especially by the enzyme superoxide dismutase, which is found in the mitochondria of the ventricular myocytes [45]. Meanwhile, in chronic protection many beneficial mechanisms have been described that are contributing to cardio-protection [46], such as alterations in oxidant and antioxidant status, in mitochondrial protein expression etc.

In left ventricular dysfunction, which is the most common cardiac abnormality that CKD patients present, cardiac output does not increase in response to exercise. As a consequence an elevation in systemic vascular resistance occurs. In a study by Sowton and Burkart [47], where they estimated the hemodynamic changes during continuous exercise on a bicycle ergometer in cardiac patients, changes were found in: heart rate, blood pressure, cardiac output, stroke volume, arteriovenous oxygen difference, oxygen uptake, total peripheral and pulmonary resistance and in left ventricular work. More precisely, during continuous steady exercise, patients were examined for hemodynamic response at least 30 minutes while no drugs were allowed to be given [47].

Effects of home-based exercise training programs

Home-based exercise training programs have shown to improve functional ability in the CKD patients [48] (table 1) and these results are more profound when home-based exercise training is combined with center-based or intradialytic exercise programs. However, in home-based exercise programs the participation was lower compared the other forms of exercise training programs due to the lack of motivation. Specifically, Nomoyama et al [49] applied for 12 weeks an exercise program, which compared home-based and intradialytic exercise training. The results showed that the participation in the intradialytic exercise program was higher (89%) compared to home-based program (56%) while the differences were attributed to the fact that in intradialytic exercise training program, the patients were more aware of the benefits of exercise because the exercise was taking place during their usual therapy [49]. In order to maximize results in functional capacity, it is suggested that a combination of a home-based exercise program with other types of training is implemented.

Effects of habitual exercise training

Generally, hemodialysis patients are characterized by low physical activity levels and even habitual exercise training programs might improve the functional ability of these patients (table 2). Cupisti et al [50], who evaluated the habitual physical activity levels during a mid-week interdialytic period of 48 hours in 50 ESRD patients, found that patients revealed reduced daily METs value by 14% compared to normal subjects and decreased number of steps/day by 52.4%. In addition these results were correlated with patients' dietary nutrient intake and body composition [50]. These results confirmed that malnutrition and muscle atrophy are important factors which leads to inactivity in CKD patients. However, in another

study by Kosmadakis et al [51], increased exercise tolerance measured with Borg Rating of Perceived Exertion (RPE) after 1 month and 6 months exercise training was found and these beneficial effects did not get lost after 6 months of no training. In the same study [51] 6 months of habitual exercise training weren't enough to induce changes in arterial stiffness biomarkers and baroreflex (BRS) sensitivity. The results of this study [51] indicate that habitual physical activity is not enough to induce beneficial results in the CKD patient's cardiovascular system and systematic exercise training is needed.

In another study by Matsuzawa et al [52] habitual exercise training found to be related with high density lipoprotein cholesterol (HDL-C) levels, which are related with cardiovascular mortality. The authors after examining habitual physical activity levels using accelerometers in 116 CKD patients on hemodialysis, demonstrated that increased physical activity levels were correlated with improved prognosis. Indeed, in 1980 a study by Keys [53] found that in men, low levels of HDL-C were related to coronary artery disease mortality while high levels of HDL-C to other causes of mortality. In a review by Besler et al [54], the authors described the mechanisms of how high HDL-C levels induce cardioprotective effects in the vasculature and indisputably the fact that HDL-C accelerates nitric oxide (NO) synthesis is proved to be a crucial mechanisms, which enhances the atheroprotective effects.

Moreover, a study of Hamasaki et al [55] in heart failure patients found that a correlation existed between physical activity levels and plasma BNP levels, even after an adjustment with age and BMI. B-type natriuretic peptide (BNP) is widely used as a cardiovascular risk biomarker and an increase in serum levels has been related with the degree of left ventricular dysfunction, severity of congestive heart failure symptoms and ultimately poor prognosis [56].

Effects of exercise training on non-dialysis day

Numerous studies in the literature have examined the effects of different modalities of intradialytic exercise training programs in ESRD patients (table 3). Both aerobic and resistance exercise training programs induce favorable effects in aerobic capacity, in muscle strength, and in cardiac function of ESRD patients. Improvements in VO_2peak of between 8% and 48% have been reported in most studies after applying aerobic or combined, (aerobic and resistance) exercise training programs lasting between 3 to 12 months [22, 36, 37, 57-60]. However, in a study by Pechter et al [61] an improvement of 2% in VO_2peak was observed after participants underwent a water-based exercise training program. Even though the intensity of the exercise training program was low in this study leading to low increase in patients' aerobic capacity , the authors claimed that the water-based exercise is superior to land-based exercise due to fact that buoyancy give an advantage to patients to exercise harder [61]. Moreover, in this study in the exercised group a significant reduction in proteinuria was observed and this finding has an important clinical impact because proteinuria has been associated with the rate of renal failure and this reduction might limited the renal decline [62].

Exercise training was usually prescribed for 2-3 times/week, with duration ranging from 30-50 min per session. In most studies the authors reported that the exercise training programs were supervised from qualified health professionals. In none of the studies any serious complications resulted from the participation in the exercise training programs, were reported.

Moreover, exercise training in CKD patients resulted in improvement in their functional capacity [59, 63-65], which means that they were capable to complete their

everyday living activities easier, adopt a healthier way of life and improve overall quality of life. Moreover, the cardiovascular benefits of both resistance and aerobic exercise training were reflected in improvements in lipid profile [57, 66], in echogardiography indices [37], in cardiac autonomic function [58], in arterial stiffness [67], in vessels diameters [68] and size [69] and in blood pressure [68]. The cardiovascular response to exercise training induces changes and accordingly increases heart rate and stroke volume but also reduces the peripheral vascular resistance. These hemodynamics changes induce favorable cardiovascular adaptations with clinical significance. It has been demonstrated that exercise training benefits vascular health by inducing structural modifications such as angiogenesis [70] and vascular remodeling [71].

Effects of intradialytic exercise programs

Intradialytic exercise training with stationery bicycles is the most favorable type of exercise training among ESRD patients. The patients usually cycle for 10-45 min and progressively resistance is applied to the bicycle wheels [72-82]. Also, resistance exercises have been applied in intradialytic exercise training programs without serious complications and induced beneficial effects on patient's muscular strength [83-90] (add Johansen KL et al, JASN, 2006). Usually resistance exercise training includes 1-3 sets of every exercise and 8-15 repetitions with weights of 0.5-2.0 libres (lbs).

The exercises sessions occurred at the hemodialysis centers during the first two hours of the hemodialysis treatment (table 4). According to Moore et al [41] is more safe exercise training programs to be applied during the first 2 hours because cardiac function is more stable. According to authors after 3 hours on hemodialysis cardiac output and mean arterial blood pressure were decreased and these changes were associated with cardiovascular instability [41]. Probably the main reason for this cardiovascular instability is ANS dysfunction seen in CKD and especially impaired baroreflex sensitivity, which characterized CKD patients and is associated with mortality [91].

The findings of all studies that applied intradialytic exercise training programs revealed benefits in aerobic capacity and muscular strength. A study by Wilund et al [77] found that the thickness of the epicardial fat layer was reduced by 11% after a 4 months exercise training program. This finding has an important beneficial clinical effect since epicardial fat is associated with increased levels of inflammation and atherosclerosis [92]. Although, in the same study a significant reduction in oxidative stress biomarker was found, no significant changes in traditional inflammation blood indices such as IL-6 and CRP was observed [77], probably due to the fact that cytokine levels in the blood are not related to the levels of cytokines in the tissue/organ [92]. Inflammation is associated with oxidative stress and these two mechanisms are implicated in the pathogenesis of CVD.

Discussion-Conclusions

All modalities of the exercise training programs induce beneficial effects in CKD patients (figure 3) by playing a cardioprotective role. Systematic exercise training increases functional ability, improves the quality of hemodialysis therapy, and improves the overall health related quality of life. Aerobic type of exercise training is the predominant type of training used in most of the published studies compare to other types of training such as resistance or combined. During exercise training many central and peripheral adaptations

occurs which in turn induce all the aforementioned beneficial effects in the cardiovascular system. Even a short period of exercise training per day lasting no more than 15 min is possible to reduce mortality in otherwise healthy individual by 14% [93] highlighting the important of regular physical activity in the chronic diseases patients.

CKD and hemodialysis therapy are responsible for many complications in CKD patient's cardiovascular health. One of the serious consequences of CKD in the cardiovascular system is impairment in the autonomic cardiovascular control, which is reflected in the depressed HRV. Although, hemodialysis procedure ameliorate clinical outcomes and survival in uremic patients, chronic exposure to hemodialysis seems to induce changes in HRV [94]. In addition autonomic neuropathy induce alterations in HRV and there is evidence that high fluid overload met in hemodialysis patients also impairs ANS activity, leads to hypertension and left ventricular hyperthrophy where enhances cardiac mortality [95]. It has been found that during the ultrafiltration procedure of the hemodialysis therapy an acute decrease in parasympathetic function and a relative hyperactivity of sympathetic nervous system takes place [96]. Moreover, it has been supported that daily hemodialysis induced structural effects on the heart of uremic patients which was associated with alterations in HRV [97]. In particular, ANS dysfunction worsens as the disease progresses [98, 99] and the duration of hemodialysis session increases [100] while age is an important player which contributes in the parasympathetic dysfunction often seen in CKD patients [101].

Moreover, impairment in the ANS function contributes to blood pressure dysregulation in CKD patients by reducing the baroreflex sensitivity leading to blood pressure instability during and after the hemodialysis session. Baroreflex sensitivity is an index of cardiac autonomic control and reflects the interaction between cardiac sympathetic and parasympathetic system [102]. Sympathetic overactivity is responsible for the depressed values in baroreflex sensitivity [102] which are related to arrhythmias [103] and consequently increase mortality in CKD patients. Exercise training has proved to benefit baroreflex sensitivity [51, 104], by improving endothelial function and endoneurial blood flow [105].

In conclusions, systematic exercise training induces a variety of hemodynamics changes that benefit CKD cardiovascular health. Regular exercise training induces beneficial adaptive responses and influences many sensitive physiological biomarkers that are implicated in the development of atherosclerosis. Additionally, exercise training decreases the cardiovascular risk by improving the autonomic nervous system activity, the left ventricular function and by reducing nontraditional risk factors such as the epicardial adipose tissue. It seems that all these central and peripheral adaptations to exercise training significantly contribute to improvements in functional capacity and exercise tolerance among CKD patients and results in the risk reduction of CKD-associated disorders and comorbidities. Exercise training has all the appropriate therapeutic characteristics to serve as a complimentary strategy in CKD patients while health care providers should motivate patients to engage in any type of exercise training programs.

Table 1. Home-based exercise training programs

Authors	Study groups	Exercise intervention			Results
		Duration	Type of exercise	prescription	
Nonoyama 2010 [49]	Home-based & intradialytic exercise group (n= 9)	3 months	➢ Intradialytic ➢ Home-based	20-30 aerobic per session, 6 exercises with exercise bands and 0.5-2.0 lb free weights, 2- 3 times/week at home & intradialytic 20-30 min cycling at 2-4 RPE, flexibility and strengthening exercises of upper & lower extremities with bands of 0.5-2 lb, 1-3 set x 15 repetitions	⬆ 13.3% 2MWT (m) ⬇ 16.2% TUG (s) ⬆10.4% KDQOP physical composite score ⬆ 6% DASI VO_2peak (mi/min/kg)
Mustata 2011 [106]	Exercise group (n= 10) Control group (n= 10)	12 months	➢ Supervised ➢ Home-based	2 times/week aerobic training, 40-60% VO_2peak increased by 5-10% weekly to a maximum of 60 min/ 3 times/week walking started in the 2nd month	⬆ 15.1 % VO_2peak ⬆78.6% Endurance time ⬇5.5% Augmentation index
Baria 2014 [107]	Centre-based (n=10) Home-based (n=8) Control group (n= 10)	3 months	➢ Centre-based exercise ➢ Home-based exercise	30 min aerobic exercise in treadmill at VT, 3 times/day (every 4 weeks the duration increased by 10 min) Aerobic exercise 3 times/day	⬆ 8.6% VO_2peak ⬆50% Sit-to-Stand ⬆ 11.7% 6-MWT ⬇ 6.7% Visceral fat ⬇1.3% Waist circumference ⬇ 2% Total body fat ⬇10.3% Mean blood pressure (mmHg)
Takashi Aoike 2015 [48]	Home-based exercise group (n=14) Control group (n=15)	3 months	Home-based	Aerobic training (walking) 30 min, 3 times/week (every 4 weeks the duration increased by 10 min)	⬆ 8.3% VO_2peak (ml/kg/min) ⬆ 17% VE (L/min) ⬆ 10.1% 6-MWT (m) ⬆21.8% 2-Min Step Test (steps) ⬆8.1% Sit & Reach Test (cm) ⬆28.8% Arm Curl Test (repetitions) ⬆ 39.5% Sit & Stand Test (repetitions) ⬇ 34% Back Scratch Test (cm) ⬇ 10.4% Time up & Go test (s)

2MWT: 2 min walk test; TUG: Time up & go; KDQOL: Kidney Disease Quality of Life questionnaire; STS: Sit-to-Stand Test;6-MWT: 6min walk test; VT: ventilatory threshold

Table 2. Habitual exercise training

Authors	Study groups	Exercise intervention			Results
		Duration	Type of habitual physical activity	Exercise training program	
Cupisti 2011 [50]	Habitual activity group (n= 50 HD patients) Control group (n=33 healthy subjects)	With a wireless multisensory activity monitor physical activity levels were evaluated for a 48 hours period	Walking	no	⬇ 13.3% Daily physical activity levels (METs) ⬇ 37.7% Time spent on activities (min) ⬇ 52.4% Number of steps
Kosmadakis 2012 [51]	Exercise group (n=18 CKD patients stage 4 or 5) Control habitual physical activity group (n=14 CKD patients stage 4 or 5)	6 months, 5 times/week	Every day living activities	30 min walking at RPE 12-14	Arterial stiffness ⬆ 3% Carotid-femoral (m/s) - Carotid-radial ⬆ 6.8% Augmentation index ⬆ 16.1% BRS (ms/mmHg)
Matsuzawa 2013 [52]	Habitual physical activity evaluation (n=116)	An accelerometer pedometer used to evaluate the habitual physical activities for 1 week	Walking-only 1 patient participate in the activity of cycling or swimming	no	HDL-C Levels
Hamasaki 2015 [55]	(n=30 pre-diabetes patients) (n= 30 patients with early untreated type II diabetes)	A triaxial accelerometer used for 1 week	Daily physical activity	no	Physical activity levels BNP

HD: hemodialysized; BRS: Baroreflex sensitivity; BNP: B-type natriuretic peptide;

Table 3. Exercise training in non-dialysis day

Authors	Study groups	Exercise intervention			Outcomes
		Duration	modality	prescription	
Goldberg 1980 [57]		8 months	Aerobic	Bicycle ergometer, walking, jogging 40-75% VO_2peak	⬆ 32.5% Exercise duration (s) ⬆ 16.6% VO_2peak (ml/kg/min) ⬇ 3.7% Fasting glucose levels (mg/dl) ⬆ 30.7% Glucose disappearance rate (%/min) ⬇ 40.6% Fasting plasma insulin (μU/ml) ⬇ 27.9% Triglyceride (mg/dl) ⬇ 29.8% Very-low density lipoprotein triglyceride (mg/dl) ⬆ 21.8% HDL (mg/dl) ⬇ 24.1% Total cholesterol (mg/dl) ⬆ 27.7% Low-density lipoprotein cholesterol (mg/dl)
Kouidi 1998 [22]	Exercised group (n=7 HD patients)	6 months	Aerobic	10 min cycle ergometry or treadmill, 50 min calisthenics & steps, swimming or ball games, 10 min resistances exercises with low-weight, 10 min cool-down, 3 times/week	⬆ 28.8% Exercise time (min) ⬆ 48% VO_2peak (ml/kg/min) ⬆ 55.7% Max left leg isometric force (N) ⬆ 40.2% Max right leg isometric force (N) ⬆ 12.6 Left leg conduction velocity (m/s) ⬆ 12.2% Right leg conduction velocity (m/s) ⬇ 9% Left leg distal time (ms) ⬇ 10.8% Right leg distal time (ms)
Deligiannis (a) 1999 [37]	Exercised group (n=16 HD patients), Home-based exercised group (n=10 HD patients), Control group (n=12 HD patients) Group of healthy subjects (n=15)	6 months		10 min cycle ergometry or treadmill, 50 min calisthenics & steps, swimming or ball games, 10 min resistances exercises with low-weight, 10 min cool-down, 3 times/week	⬆ 42.7% VO_2peak (ml/kg/min) ⬆ 32.5% Exercise time (min) ⬆ 32.5% METs ⬆ 40.6% VE (l/min) ⬆ 5.3% VE/VO_2max ⬆ 3.6% LVIDd (mm) ⬆ 6.1% LVM (g) ⬆ 11.2% LVMI (g/m^2)
Deligiannis (b) 1999 [58]	Exercised group (n=30 HD patients) Control group (n= 30 HD patients), Group C (n=30 nonuremic	6 months	Aerobic	10 min cycle ergometry or treadmill, 50 min calisthenics & steps, swimming or ball games, 10 min resistances exercises with low-weight, 10 min cool-down,	⬆ 41.1% VO_2peak (ml/kg/min) ⬆ 31.2% Exercise time (min) ⬆ 27.2% HRV index ⬆ 18% SDNN (s) ⬇ 5% Sum of beats ⬇ 40% HRV index<25 (no.)

		patients)			3 times/week	⬇ 33.3% Arrhythmias-Lown class>II (no.)
Pechter [61]	2003	Exercise group (n=17 CKD patients) control group (n=9 CKD patients)	3 months	Aerobic water based exercise	10 min warm-up, 10 min cardiovascular exercises, 10 min cool-down, 2 times/week	⬆ 2% Vo_2peak (ml/kg/min) ⬆ 19.8% O_2pulse (ml/beats/min) ⬆ 15% VE (l/min) ⬇ 34.4% LPO (ng/ml) ⬆ 15% GSH (μM) ⬇ 33.3% GSSG/GSH
Leaf [108]	2003	Exercise group (n=5 CKD patients)	6 week	Exercise with heat control& home-based exercise	Isometric hand-grip contractions at 30-40% of MVC, 4 times/week	⬆ 100% Left cephalic vein no tourniquet (cm^2) ⬆ 100% Left cephalic vein with tourniquet (cm^2)
Nindl [109]	2004	Exercised group (n=10)	3 months	Resistance training	2 set of 10-15 repetitions of leg press, leg extension, leg curl, chest press, compound row, lateral raises, biceps curls, triceps extensions, abdominal, 2 times/week	⬆ 6MWT (m) ⬆ STS (s) ⬆ Peak torque of the quadriceps ⬇ 16.5% Total IGF-I (ng/ml) ⬇ 18.7% Ternary IGF-I (ng/ml) ⬇ 22.9% IGF-I/IGFBP-3N(x10) ratio
Mustata [67]	2004	Exercised group (n=11)	3 months	Aerobic	5-10 min warm-up, 40-50 min conditioning exercise (treadmill or bicycle), 5-10 min cool-down, 2 times/week	⬇ 28.2% Arterial stiffness (u) ⬇ 10.9% Pulse pressure (mmHg)
Kuge [110]	2005	Exercised group (n=8 HD patients) Control group (n=7 healthy subjects)	6 weeks	Hand grip exercise training	50-150 repetitive handgrip contractions, at 60% of maximum force 4 times/week	⬆ 24.5% Maximum strength (N) ⬆ 63.1% Maximum endurance (sec)
Clyne 2005		Exercised group (n=7 predialysis patients) Control group (n=5 predialysis patients) Exercise group (n=6 healthy subjects)	3 months	Resistance training	20 repetitions of 60% of 1 RM, 3 times/week	⬆ 40% One repetition maximum (kg) ⬆ 48.6% Muscular endurance (repetitions)
Kopple [111]	2006	Exercise group (n= 10 patients)	9 weeks	Endurance exercise training		⬇ 51% skeletal muscle myostatin mRNA ⬆ 41% mRNA levels for IGF-IR
Manfredini 2009 [63]		Exercise group (n=14 HD patients) Control group (n=8 HD patients)	6 months	Aerobic	Walking 1.5km/h and 0.1 km/h every 10 m, 2 daily indoor/outdoor walking sessions for 10 min each	⬆ 12.6% 6MWT (m) ⬆ 37.8% e-CFUs (colonies/ml)

Kumar [68]	2010	Exercise group (n=23)	1 month	Isometric	Squeezing a tennis ball 30 min/day	⬆ Handgrip strength (kg) ⬇ Systolic blood pressure (mmHg) ⬆ Vessel diameters ⬆ Arterial blood velocity
Takashi Aoike [59]	2012	Exercise group (n=10 CKD patients stage 2-3)	3 months	Aerobic	Treadmill at VT, 3 times/week	⬆19.4% VO_2peak (ml/kg/min) ⬆ 15.1% VE (L/min) ⬆ 9.1% 6MWT (m) ⬆19.7% 2-minutes step test (steps) ⬇ 15.8% TUG (s) ⬇ 11.1% Sit & reach test (cm) ⬆20.3% Arm curl test-right arm (repetitions) ⬆ 15.7% Arm curl test-left arm (repetitions) ⬆ 34.6% STS (repetitions)
Song [66]	2012	Exercise group (= 20 HD patients) Control group (n=20 HD patients)	3 months	Progressive resistance training	20-30 min six routine upper & lower body movements, 3 times/week	⬆ 13% Leg muscle strength (kg) ⬇ 9.2% Total cholesterol (mg/dl) ⬇ 17.6% Triglyceride (mg/dl)
Howden [60]	2013	Exercise group (n=36, CKD patients stage 3-4) Control group (n=36 CKD patients stage 3-4)	12 months	Combined (aerobic & resistance)	Warm-up, 20-30 min treadmill or stationery bike or rowing ergometer & whole-body resistance training, 2-3 times/week	⬆ 11.6% Vo_2peak (ml/kg/min) ⬇ 4.3% E_A (mmHg/ml)
Molsted [112]	2013	Exercise group (n=29 HD patients)	4 months	Resistance	5 min warm-up, five sets of legs presses, leg extensions, leg curls, 30 min, 3 times/week	⬆ 46.4% 1 repetition maximum knee extension (kg) ⬆ 134% 1 repetition maximum leg press (kg)
Kong [69]	2014	Grip exercise group (n=10 HD patients) soft ball exercise group (n=8 HD patients)	1 month	Strength	10 squeezes in grip strength at 10 RM for 3 set, 2 times/weeks, 3 sets of 10 soft ball squeezes 2 times in the morning & in the afternoon	⬆ 33.3%/8.3% Tip pinch (kg) ⬆ 26.6%/ Palmar pinch (kg) ⬆ 32.2%/13.3% Lateral pinch (kg) ⬆ 54.6% Grip strength (kg) ⬆ 3.2%/2% Circumference (cm) ⬆ 27.2%/32.1% Vessel size (mm) ⬆ 92.4%/56.4% Blood flow volume (ml/min)
Headley [36]	2014	Exercise group (n=25 CKD patients) control group (n=21 CKD patients)	4 months	Aerobic	15-55 min continuous aerobic exercise at 50-60%, 3 times/week	⬆ 8.2% Vo_2peak (ml/kg/min) ⬇ 18% ET-1 (fmol/ml) ⬆ 29.5% NO:ET-1 ratio
Molsted [64]	2014	Exercise group (n=23 HD patients)	4 months	Resistance	5 min warm-up, 5 sets of dynamic leg press,	⬆ 24% Left leg muscle power (W/kg) ⬆ 25.1% Right leg muscle power (W/kg)

				extension & curl, 3 times/week	⬆ 21.4 % Chair stand test (repetitions)
Hamada 2015 [65]	Exercise group (n=47 CKD patients)	6 month	Combined	1,5-2 h/ session, resistance training at 3-4METs, Walking, 12-14 RPE 6 times/month	⬆ 30% 30 s Chair stand test ⬆ 8.3% Sit & reach test (cm) ⬆ 29% Single-foot standing test (s) ⬆ 5.4% 6 MWT (m)

VT: ventilatory threshold; LVIDd: left ventricular internal dimension at end-diastole; LVM: left ventricular mass; LVMI: left ventricular mass index; LPO: products of lipid peroxidation; GSSG/GSH: glutathione redox ratio in serum; MVC: maximum voluntary contraction; IGF-I: insulin-like growth factor-I; 6MWT: 6 min walk test; e-CFUs: endothelial colony-forming unit; E_A: arterial elastance; ET-1: endothelin 1; NO: nitric oxide.

Table 4. Intradialytic exercise training

Authors	Study groups	Exercise intervention			Outcomes
		Duration	Modality	Prescription	
Macdonald 2004 [72]	Exercise group (=9)	3 months	Interval training	High intensity interval training on a cycle ergometer 2 min bouts ≈90% VO_2peak followed by 2 min recovery bouts ≈40% VO_2peak, 15 bouts/session, 3 times/week	↑ 24.4% Knee extensor strength ↑ ≈25% 30-s Sit to stand
Storer 2005 [73]	Exercise group (n=12) Non-exercising group (n=12) Healthy group (=12)	10 weeks	Aerobic	20-40 min of cycling at 50% VO_2peak, 3 times/week	↑ 22% Vo_2peak (ml/kg/min) ↑ 144% Endurance time (min) ↑ 197% Constant work rate (kJ) ↑ 16% Maximal voluntary muscle strength ↓ 14.7% Stair-climb time (s) ↑ 21.6% Stair-climb power (w) ↑ 18.6% 10 m walk (cm/s) ↓ 14% Timed up & go (s)
Parsons 2006 [74]	Exercise group (n=13)	5 month	Aerobic	2 bout x 30 min on cycle ergometer or a mini-stepper, 30 min recovery, 3 times/week	↑ 14% 6MWT ↑ 12% spKt/V (Jindal) ↑ 15.4% spKt/V (Daugirdas)
Cheema 2007 [83]	Exercise group (n=24) Control group (n=25)	4 months	Resistance	45 min 2 sets of 8 repetitions of 10 exercises, RPE 15-17, 3 times/week	↑ 15.4% Total strength (kg) ↑ 3.3% 6MWT (m) ↓ 10.2% log CRP
Sakkas 2008 [75]	Exercise group (n=7) Control (n= 7)	4 months	Aerobic	45 min continuous cycling 45-50 rpm, at 65-75% watts, 3 times/week	↓ 28.9% NRSI walk test (s) ↑ 45.3% Total cycling power (w)
Ouzouni 2009 [113]	Exercise group (n=19) Control group (n=14)	10 month	Combined	30 min cycling, 30 min strength and flexibility exercises at 13-14 RPE, 3 times/week	↑ 21.1% Vo_2peak (ml/kg/min) ↑ 23.6% Exercise time (min) ↑ 23% METs ↑ 40.7% VE (L/min)
De Moura Reboredo 2010 [76]	Exercise group (n=11) Control group (n==11)	3 months	Aerobic	10 min warm-up, 35 min aerobic exercise, 3 times	HRV variability Echocardiography
Chen 2010 [84]	Exercise group (n=22) Control group (n=22)	48 sessions	Strength	5 min warm-up, strength exercise for the low body using ankle weights 0.5-20 lbs, 2 set x 8	↑ 38.5% Knee extensor (kg) ↑ 4.5% Whole-body lean mass by DXA (kg) ↑ 4.3% Leg lean mass by DXA (kg)

				repetitions, 6-10 RPE, 2 times/week	⬆ 5.4% whole-body fat mass by DXA (%)
Wilund 2010 [77]	Exercise group (n=8) Control (n=9)	4 month	Aerobic	45 min of cycling at 12-14 RPE 3 time/week	⬆ 17% Shuttle walk test ⬇ 38% TBARS (μmol/L) ⬇ 27% ALP(U/L) ⬇ 11% Epicardial fat thickness (mm)
de Moura Reboredo 2010 [78]	Exercise group (n=14)	3 months	Aerobic	10 min warm-up 30 min cycling at 11-13 RPE 3 times/week	⬆ 9% 6MWT (m) ⬇ 5% Systolic blood pressure (mmHg) ⬇ 3.3% Diastolic blood pressure (mmHg) ⬆ 7.5% Hemoglobin levels (g/dl)
Singh 2011 [85]	Exercise group (n=24) Control group (n=25)	3 months	Resistance	45 min 2 sets x 8 repetitions x 10 exercises RPE 15-17 3 times/week	Interleukin-1β (pg/ml) Interleukin-6(pg/ml) Interleukin-8(pg/ml) Interleukin-10(pg/ml) Interleukin-12(pg/ml) TNF-α (pg/ml)
Dobsak 2011 [79]	Exercise group (n=) Electromyostimulation group (n=11) Control group (n=10)	5 months	➢ Aerobic ➢ Electromyostimulation	Warm-up 5 min, 20 min cycling at 60% of Wpeak, after 5 weeks 2x 20, 3 time/week	⬆ 14.8% CWT ⬆ 16.1% Fmax
Bullani 2011 [87]	Exercise group (n=11)	6 months	Resistance	30-40 min exercises with elastic resistance, 3 sets x 20 repetition, 2 times/week	⬆ 7.5% Tinetti test (score) ⬇ 17.3% TUG (s)
Golebiowski 2012 [80]	Exercise group (n=21)	3 months	Aerobic	~50 min cycling, 3 time/week	⬆ 4% 6MWT velocity ⬆ 7% Extension peak torque at angular velocity of 60^{o}/s ⬆ 4% Extension peak torque at angular velocity of 300^{o}/s ⬆ 13% Flexion peak torque at angular velocity of 180^{o}/s
Orcy 2012 [86]	Combined exercise group (n=12) Resistance exercise group (n=12)	10 weeks	➢ Resistance ➢ Combined	20 min cycling at 13-14 RPE & 10 min of resistance training or 30 min of resistance training with elastic bands, therapeutic balls and dumbbells and ankle of 1or 2 lb, 10-15 repetitions, 3 times/week	⬇ 4.4%/ ⬆9% 6MWT (m)
Ragnarsdottir	Exercise group 3 months	3 month	Aerobic	12-40 min cycling at 11-13 RPE,	⬆ 16.3%/22% 6MWT (m)

2012 [81]	(n=12) Exercise group 6 months (n=9)	6 months		3 times/week	⬇ 16.9%/16.1% TUG ⬇ 17.2%/ 23.4% Timed stand test
Silva 2013 [114]	Exercise group (n=56)	16 months	Combined	10 min cycling at <60-70% HR, strengthening exercises for upper & lower limbs, 3 times/week	⬆ 9.7% 6MWT (m)
Pellizzaro 2013 [88]	Respiratory muscle training group (n=11), Peripheral muscle training group (n=14), control group (n=14)	10 weeks	Resistance	3 set x 15 inspirations at 50% of PI_{max} or strengthen exercises at 50% of 1MR, 3 set x 15 repetitions	⬆ 14.2% /⬆ 6.8% 6MWT (m) ⬆ 21.4%/⬆ 25.9%FVC (l)
Giannaki 2013 [82]	Exercise group (n=12) Control group (n=12)	6 months	Aerobic	45 min cycling at 60-65% VO_2peak, 3 times/week	⬇ 10.5% NSRI (s) ⬇ 20.5% STS-5 (repetitions) ⬆ 22.6% STS-60 (s) ⬇ 20% Sleep Diary ⬇ 57.8% IRLS (score)
Moraes 2013 [89]	Exercise group (n=26) Control group (n=18)	6 months	Resistance	Exercises with elastic bands at 60-70% at 60-70% of 1RM, 3 times/week	⬇ 23% STS-10 (s) ⬆ 10.2% STS-60 (repetitions)
Moraes 2014 [90]	Exercise group (n=37)	6 months	Resistance	Exercises with elastic bands at 60-70% of 1RM, 3 times/week	⬇ 30.4% CRP (pg/ml) ⬇ 18.7% ICAM-I (pg/ml) ⬇ 41.7% VCAM-I (pg/ml) ⬆ 25.4% FFM/IL-6 (ratio) ⬇ 22.5% STS-10 (s) ⬆ 11.2% STS- (repetitions)

spKt/V : a dimensionless value representing fractional urea clearance; Wpeak: peak workload; MR: maximum repetition; NRSI walk test: North Staffordshire royal infirmary walking test; TIIm: time to exercise intolerance; TNF-α: tumor necrosis factor-α; CMT:6-min corridor walking test; Fmax: muscle power; PI_{max}: maximal inspiratory pressure; STS: sit to stand; IRLS: restless leg syndrome severity scale;

Figure 1. Progress of the literature screening

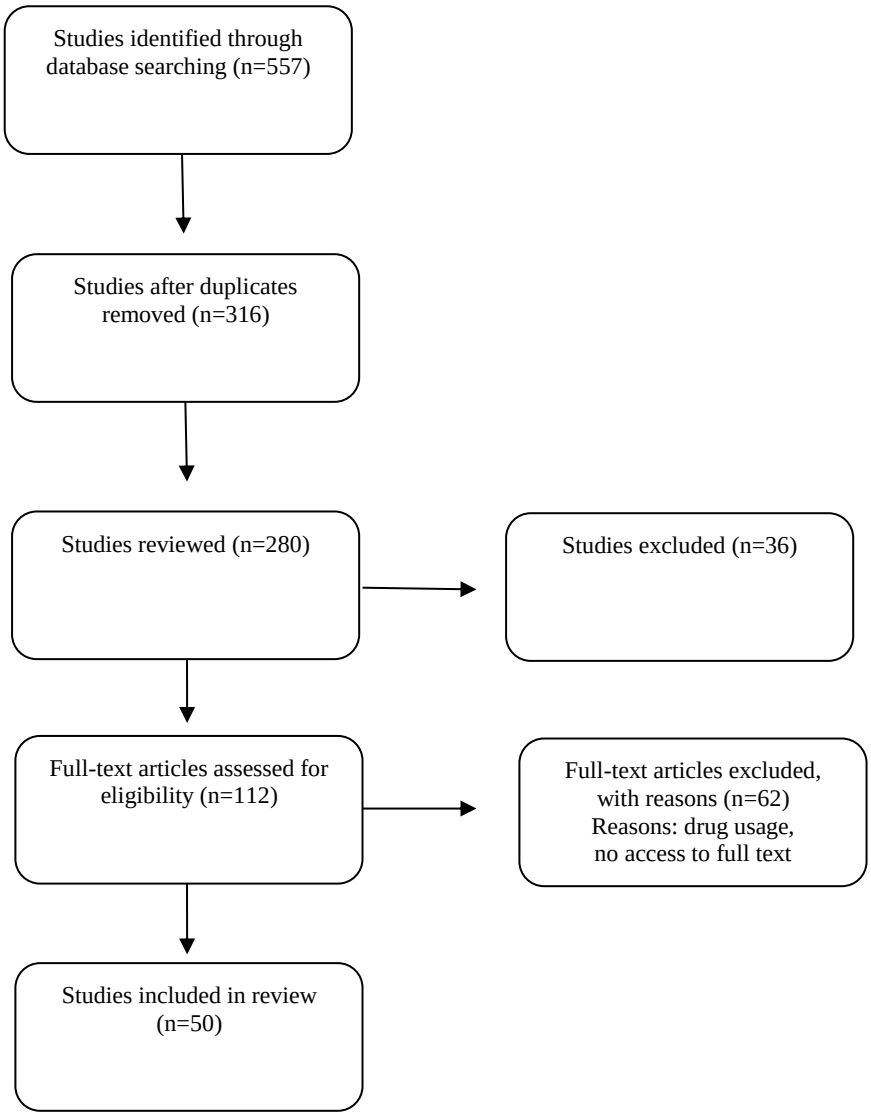


Figure 2. Hemodynamic changes during exercise training in healthy subjects and CKD patients: In healthy subjects during exercise and especially during the first minutes, a rapid increase in heart rate, blood pressure and stroke volume occur and accordingly an elevation in cardiac output takes place as an adaptive response to the increased muscle metabolic demands for oxygen. In contrast, increased levels of resting heart rate characterize patients with CKD, but during exercise heart rate response is decreased and only a small amount of CKD patients can reach the predicted heart rate. Also, they present low levels of blood pressure and higher cardiac output and stroke volume. As a consequence of all these and in combination with other abnormalities caused by uremic cardiomyopathy and myopathy oxygen consumption is decreased, leading to poor levels of functional capacity and exercise intolerance.

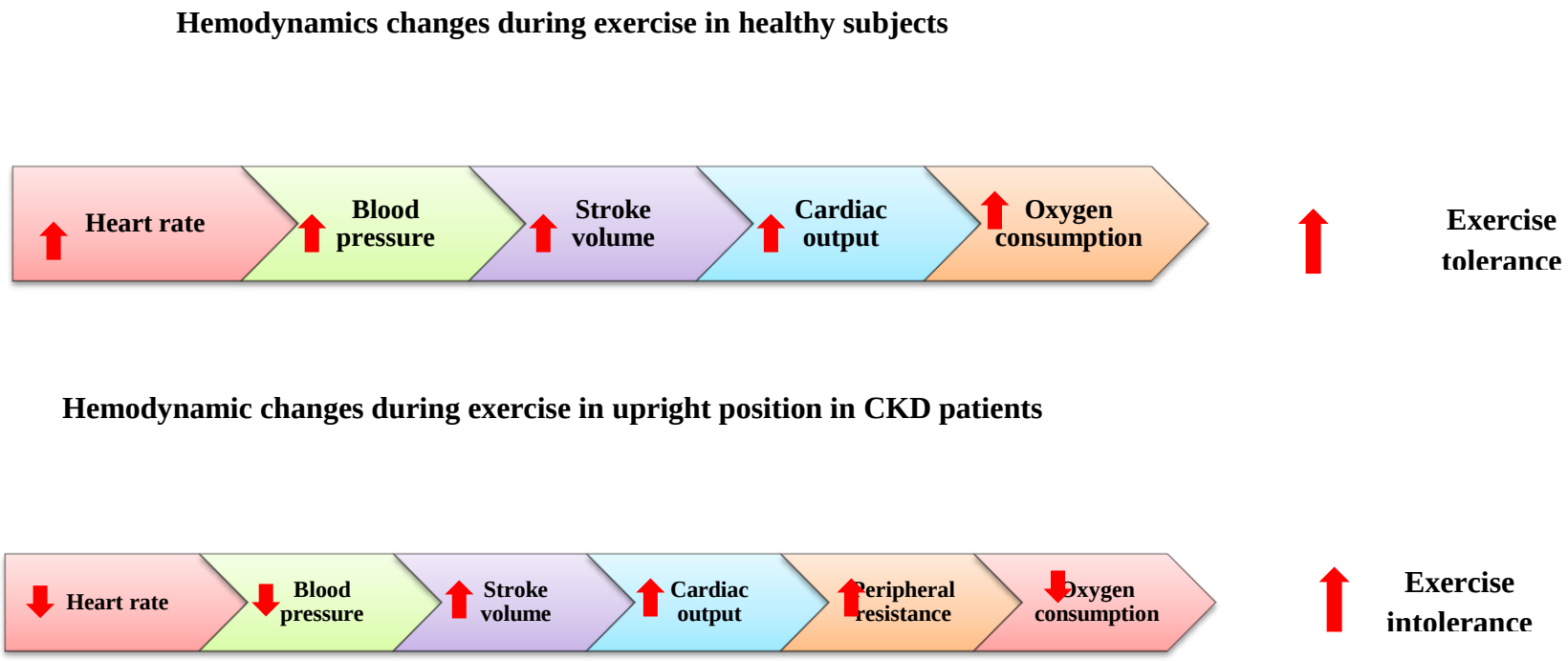
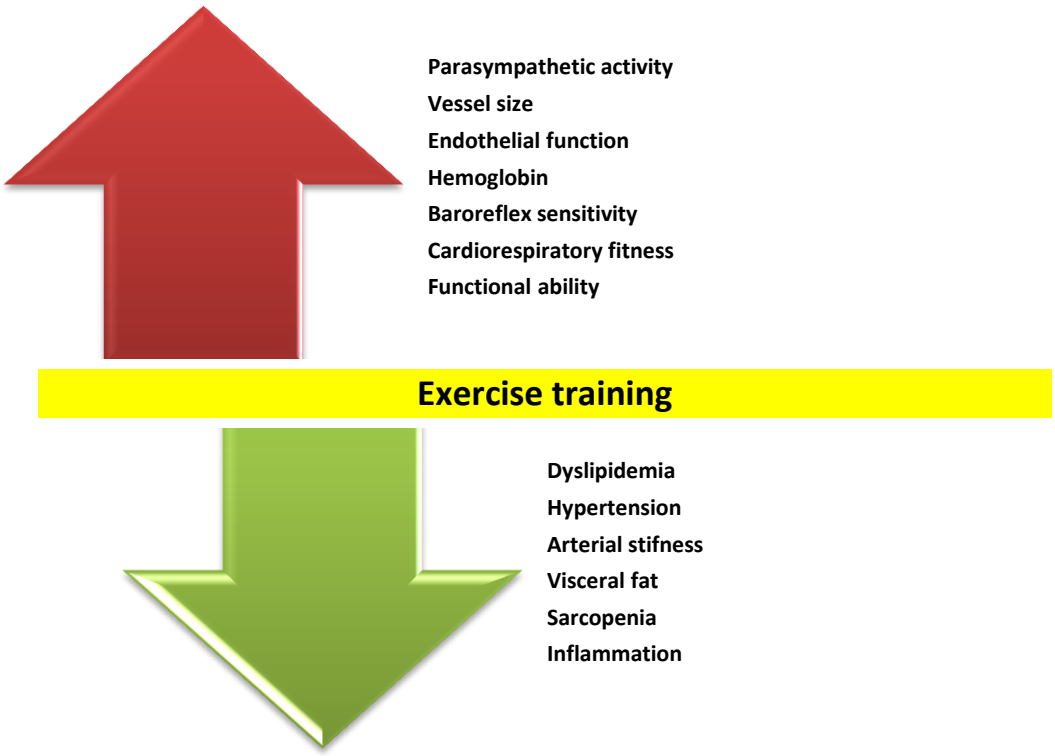


Figure 3. Beneficial effects of exercise training in CKD patients: systemic exercise training induces beneficial adaptations in the Cardiovascular and Autonomic Nervous systems.



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