A Comparison of Aerobic Exercise and Resistance Training in Patients With and Without Chronic Kidney Disease

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The morbidity and mortality associated with chronic kidney disease (CKD) are primarily caused by atherosclerosis and cardiovascular disease, which may be in part caused by inflammation and oxidative stress. Aerobic exercise and resistance training have been proposed as measures to combat obesity, inflammation, endothelial dysfunction, oxidative stress, insulin resistance, and progression of CKD. In non-CKD patients, aerobic exercise reduces inflammation, increases insulin sensitivity, decreases microalbuminuria, facilitates weight loss, decreases leptins, and protects against oxidative injury. In nondialysis CKD, aerobic exercise decreases microalbuminuria, protects from oxidative stress, and may increase the glomerular filtration rate (GFR). Aerobic exercise in hemodialysis patients has been reported to enhance insulin sensitivity, improve lipid profile, increase hemoglobin, increase strength, decrease blood pressure, and improve quality of life. Resistance training, in the general population, decreases C-reactive protein, increases insulin sensitivity, decreases body fat content, increases insulin-like growth factor-1 (IGF-1), and decreases microalbuminuria. In the nondialysis CKD population, resistance training has been reported to reduce inflammation, increase serum albumin, maintain body weight, increase muscle strength, increase IGF-1, and increase GFR. Resistance training in hemodialysis increases muscle strength, increases physical functionality, and improves IGF-1 status. Combined aerobic exercise and resistance training during dialysis improves muscle strength, work output, cardiac fitness, and possibly dialysis adequacy. There is a need for more investigation on the role of exercise in CKD. If the benefits of aerobic exercise and strength training in non-CKD populations can be shown to apply to CKD patients as well, renal rehabilitation will begin to play an important role in the approach to the treatment, prevention, and slowed progression of CKD.

Index Words: Aerobic exercise; Resistance training; Chronic kidney disease; Inflammation; Endothelial dysfunction; Oxidative stress; Obesity; Leptins; Microalbuminuria; Insulin resistance; Progression

There is much interest in the effects of aerobic exercise and resistance (strength) training in chronic disease states. These measures may decrease morbidity and mortality by reducing inflammation, oxidative stress, and endothelial dysfunction. In non–chronic kidney disease (CKD) patients, aerobic exercise and resistance training have been reported to have a beneficial influence on inflammatory cytokines, insulin resistance, obesity, cardiovascular risk factors, microalbuminuria, and anemia related to chronic disease. Whether or not these putative benefits of exercise extend to patients with CKD is unclear. It is possibly because of this uncertainty that renal rehabilitation or even regular home exercise is rarely used in CKD patients. The purpose of this review was to provide a clear and accurate synopsis of the overall benefits of exercise and the benefits of exercise that have been shown specifically in the CKD population.

Effects of Aerobic Exercise and Resistance Training in Non-CKD Patients

Aerobic exercise has long been valued for its benefits of reduction in atherosclerosis. Rauramaa and coworkers[1] showed that in middle-aged white men who were not taking statins aerobic physical exercise attenuated progression of atherosclerosis. Lakka et al[2] showed that good cardiorespiratory fitness (as measured by maximal oxygen uptake in cycle ergometer exercise) is associated with slower progression of early atherosclerosis in middle-aged men. Aerobic exercise also reduces

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coronary heart disease risk and increases peak oxygen consumption.[2,3] In diabetic subjects, aerobic exercise has been shown to lower resting and submaximal heart rate, increase stroke volume and cardiac output, enhance oxygen extraction, lower resting and exercise blood pressure, lower glycosylated hemoglobin, improve glucose tolerance and insulin sensitivity, and cause weight loss.[4,5] Roberts and colleagues[6] reported that an intervention of diet and daily walking resulted in decreased blood pressure, increased urine nitric oxide metabolite excretion, and decreased fasting insulin; they further reported that decreased body mass index (BMI) was not related to the abovementioned variables. Exercise produces a less atherogenic lipid profile (decreased triglycerides, total cholesterol, and high-density lipoprotein [HDL]:total cholesterol ratio) in diabetic patients and in patients with traits of the metabolic syndrome.[7,8] One study of diabetic patients found increased HDL and decreased low-density lipoprotein.[9]

Aerobic exercise, more than strength training, has been shown to decrease insulin resistance. A study in Japan on lifestyle-related diseases (including type 2 diabetes, hypertension, hyperlipidemia, and coronary artery disease) reported that gentle jogging increased insulin action despite no influence on BMI or peak oxygen consumption.[10] Furthermore, they reported that aerobic exercise such as walking was more effective than weightlifting in increasing insulin sensitivity; resistance training alone was not effective. However, the combination of aerobic exercise plus strength training was reported to be superior.[11] Several studies have noted that aerobic exercise in insulin-resistant humans improves insulin sensitivity by enhancing lipid oxidation in muscle, reducing skeletal muscle lipid content and weight loss.[12,13] Finally, it has been stated that insulin sensitivity is directly related to the degree of habitual physical activity and repeated bouts of contractile activity improve glucose tolerance and insulin action in individuals with insulin resistance, obesity, and patients with type 2 diabetes.[14-16] However, patients with diabetes and CKD have not been specifically studied.

Resistance training improves muscular strength and endurance, enhances flexibility, alters body composition (particularly decreases fat-free mass), and decreases risk factors for cardiovascular disease.[16-18] In nondiabetic subjects, resistance training results in improvements in glucose tolerance and insulin sensitivity[19]; similar findings have been shown in diabetic subjects.[20] Resistance training prevents loss of or even increases muscle mass during and after energy restriction.[21-23] Moderate resistance training reduces abdominal obesity.[24] Resistance training in frail elders increases expression of insulin-like growth factor 1 (IGF-1) in skeletal muscle.[25]

Effect of Exercise Type on Cardiovascular Risk Factors in Non-CKD Patients

What are the differential effects of aerobic exercise and resistance training on coronary artery disease risk factors? One study of volunteers with android obesity and at least 1 other risk factor for coronary artery disease showed that resistance training reduced total body fat, whereas only aerobic training raised HDL cholesterol. Neither resistance training nor aerobic exercise affected blood pressure, and both decreased microalbuminuria.[26] A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass, and fat-free mass in obese subjects concluded that weight training as opposed to aerobic exercise resulted in greater increases in fat-free mass.[27] In a study of previously sedentary, moderately obese women, resistance training resulted in significant increases in resting metabolic rate; fat-free mass is an important determinant of resting metabolic rate.[28] Aerobic exercise decreases blood pressure more effectively than strength training.[29]

Aerobic Exercise and Non-Dialysis CKD

Aerobic exercise in nondialysis patients improves symptom scores, sickness impact profiles, and health-related quality of life.[30] Exercise training, via stationary cycling, increases peak oxygen consumption and peak power output and improves maximum aerobic capacity. Four months of exercise training in 16 nondialysis CKD subjects resulted in the following findings: (1) unchanged hemoglobin, lipids, and left ventricular mass and function;

(2) decreased blood pressure (systolic and diastolic); (3) increased peak oxygen consumption; and (4) no effect on declining glomerular filtration rate (GFR).[31] Clyne and coworkers[32] reported that aerobic exercise in nondialysis CKD patients was associated with increased maximum exercise capacity and decreased heart rate but was not associated with improved hemoglobin, GFR, blood pressure, or echographic findings. Eidemak and colleagues[33] studied patients with moderate CKD (GFR range, 10-43 mL/min) and found that aerobic exercise increased maximum work capacity but had no effect on declining GFR. Heiwe and colleagues[34] studied the elderly population (average age, 76 years; average GFR, 18) and showed that aerobic exercise increased muscle strength and functional capacity. Pechter and coworkers[35] found that aquatic exercise in mild to moderate CKD decreased blood pressure, decreased proteinuria, decreased products of lipid peroxidation, and increased glutathione; mean GFR increased from 62.9 to 67.1 mL/min. Physical activity correlated with elevated GFR in an analysis of The Third National Health and Nutrition Examination Survey.[36]

Resistance Training and Non-Dialysis CKD

The nutritional status, protein utilization, and functional capacity in CKD patients is responsive to resistance training. Castaneda and colleagues[37] showed increased total body potassium and type I and II muscle fiber cross-sectional areas, improved leucine oxidation and serum prealbumin, maintenance of body weight, and improved muscle strength in patients with serum creatinine between 1.5 and 5.0 mg/dL.

Aerobic Exercise in Hemodialysis Patients

Intradialytic

Intradialytic aerobic exercise has been shown to be safe in the first 2 hours of dialysis; after 2 hours, cardiac decompensation may preclude exercise.[38] Intradialytic cycling, with normalization of hematocrit, has been shown to improve peak oxygen consumption and quality of life.[39] Storer and colleagues[40] showed that intradialytic cycling increases peak oxygen consumption, power, endurance time, and quadriceps strength and improves fatigability. Macdonald and colleagues[41] reported increased power and increased physical function with intradialytic cycling but were unable to show a change in lean mass or insulin-like growth factor. Dialysis efficacy and physical functioning improve with intradialytic cycle ergometer exercise.[42]

Anderson and co-workers[43] reported that intradialytic exercise bicycle training resulted in decreased blood pressures; however, this effect waned with detraining. Sakkas and colleagues[44] recruited 18 patients to undergo a program of intradialytic aerobic exercise; of 18 patients, 9 completed the study and were biopsied. They found that aerobic exercise corrected fiber atrophy, increased cross-sectional fiber area, and improved capillarization.[44]

Interdialytic

Aerobic exercise on nondialysis days has been shown to be associated with improved quality of life, decreased depression, and decreased anxiety.[45] Regular life-readiness activities, such as household chores and gardening, are also associated with improved physical functioning and improve quality of life.[46] Goldberg et al[47] reported that the benefits of exercise can occur without a change in body weight. In a subsequent study, they again showed that interdialytic aerobic exercise increases maximum aerobic capacity, decreases blood pressure, decreases depression, increases hematocrit/hemoglobin, decreases triglycerides, increases HDL, and increases insulin sensitivity.[48] Shalom and coworkers,[49] in a study of interdialytic aerobic exercise, reported that compliance was very poor, and, although work capacity was increased, there were no improvements in psychological well-being, blood pressure, hematocrit, or left-ventricular ejection fraction.

Molsted and coworkers,[50] in a study of interdialytic aerobic exercise, reported increased aerobic capacity and improved scores on Medical Outcomes Short Form-36 but reported a lack of effect on blood pressure or lipids. They recruited 33 patients for an interdialytic aerobic exercise study in HD patients; 11 patients of the exercise group dropped out, 8 because they did not have time or because they regretted enrolling in the study and 3 because of medical complications. Kouidi and colleagues[51] reported that aerobic exercise on nondialysis days resulted in increased type II fibers, increased muscle fiber area, increased maximal oxygen uptake, and increased exercise time. Mustata and colleagues[52] studied the effect of interdialytic aerobic exercise in hemodialysis patients; they reported that exercise improved arterial stiffness but did not have an impact on insulin resistance. They enrolled 16 patients; 4 patients refused exercise for personal reasons, and 1 patient had sparse participation and was excluded. Overall, participation was 8%.[52] Koufaki and colleagues[53] reported that interdialytic cycling in end-stage renal disease (ESRD) patients resulted in increased VO_2. Of 34 patients, 18 completed the 6-month training. Reasons for dropping out included injury (1), loss of interest (3), noncompliance (2), transportation problems (2), surgery (2), frailty (1), and death (4).[53]

Koufaki and colleagues[54] showed that aerobic exercise is associated with better nutritional status, as evidenced by increased subjective global assessment. Kouidi and coworkers[51] showed that interdialytic aerobic exercise increases muscle fiber cross-sectional area of the vastus lateralis (S). A comparison of 2 equivalent 3-month studies, one on interdialytic aerobic exercise and one on interdialytic resistance training, revealed equal improvements in peak leg strength.[55,56] Myostatin messenger RNA decreases and messenger RNA for insulin-like growth factors increases with interdialytic aerobic exercise.[57]

Resistance Training and ESRD/ Hemodialysis

Resistance training improves exercise capacity. Muscle strength is impaired in ESRD patients.[58,59] Diesel and coworkers[60] showed a stronger correlation between indices of muscular strength and exercise capacity than between variables that reflect oxygen-carrying capacity and exercise tolerance in ESRD patients.

Intradialytic

Resistance training in 1 study increased quadriceps area, muscular strength, and improved physical functioning. There was no increase in lean body mass.[61]

Interdialytic

Interdialytic resistance training increases functional performance, quality of life, and strength. In association with the favorable adaptations of interdialytic resistance training, Nindl and colleagues[62] reported that training was associated with decreased total IGF-1 and stable-free IGF-1. Headley and coworkers,[55] in their interdialytic study of resistance training in HD patients, reported increased peak torque, increased distance on the 6-minute walk, decreased time to complete 10 sit-to-stand-to-sit exercises, and increased maximal walking speed. Ten of 16 patients completed the study. Four dropped out because of unrelated medical reasons, 1 because of a transplant, and 1 because of a lack of motivation. They reported 87.7% attendance to their resistance training sessions; absences were because of illness, nonspecific reasons (forgot), travel, and injury.[55]

Combined Aerobic Exercise and Strength Training in CKD

Intradialytic

Oh-Park and coworkers[63] showed that combined aerobic exercise and strength training, performed during dialysis, has been shown to be safe and to improve muscle strength, mental and physical function, and cardiac fitness, as evidenced by improvement on stress tests and walk tests; 18 of 22 patients completed the study. DePaul and colleagues[64] showed that 12 weeks of isotonic quadriceps and hamstrings exercise and training on a cycle ergometer in hemodialysis patients receiving erythropoietin resulted in improvements in work output and strength; however, there were no changes in quality of life or symptoms. In the study by DePaul and coworkers, 20 patients were recruited; at 12 weeks, there were 5 dropouts, of which 1 stopped dialysis, 1 refused the ergometer test, 2 had medical reasons, and 1 was unable to schedule the exercise sessions. At 5 months, 5 more patients had dropped out for unstated reasons.[64] Van Vilsteren and colleagues[65] found that a combination of strength training before dialysis and aerobic exercise during dialysis in 96 patients resulted in increased Kt/V, increase muscle strength, and increased reaction times. Eighty-eight percent of the participants completed the program; reasons for not participating included unstable health, lack of transport, and lack of motivation.[65]

Intradialytic Versus Interdialytic Exercise in Patients With ESRD on HD

Although interdialytic exercise has been reported to be superior to intradialytic exercise, patients generally have greater difficulty in complying with the interdialytic prescription, and intradialytic exercise prescription usually has fewer dropouts. One study compared 3 kinds of rehabilitation: (1) aerobic exercise and strength training on nondialysis days, (2) aerobic exercise on dialysis days, and (3) unsupervised moderate exercise program at home; the study also included controls. They found that group A was most effective as evidenced by increased peak oxygen consumption, anaerobic threshold, and exercise time. However, group A had a higher dropout rate.[66] Kouidi and colleagues[67] studied intradialytic versus interdialytic aerobic exercise. They reported that interdialytic aerobic exercise is associated with increased exercise time, increased peak VO_2, a perception of improved health, and increased numbers of employed patients; however, interdialytic exercise had a greater dropout rate.[67] Painter and coworkers[68,69] compared independent exercise versus in-center cycling; they reported that both were effective at improving quality of life, although the effect was most pronounced with those whose initial functioning capacity was low.

Adverse Role of Inflammation

Low-grade chronic inflammation, characterized by high serum levels of CRP and interleukin (IL)-6, leads to protein-energy malnutrition and decreased survival.[70-72] A correlation between nutritional indices and acute-phase reactant protein levels has been documented.[73,74] Patients with high serum IL-6 lost body weight by more than 4% over 3 years; serum albumin and creatinine were also low.[75] IL-6 promotes cancer cachexia.[76] It has been reported that there is an association between acute-phase reactant proteins and cardiovascular disease. In the Physicians Health Study, a single CRP measurement was shown to have high predictive power for future myocardial infarction in apparently healthy men.[77]

How Does Exercise Affect Inflammation?

Aerobic exercise has been shown to decrease inflammation, not only in patients with chronic illness such as coronary artery disease but also in healthy subjects. Leisure-time physical activity in healthy subjects has been associated with increased serum albumin and decreased inflammatory markers such as plasma fibrinogen, leukocytosis, and CRP.[78-80] The association between physical activity and serum albumin has been disputed, however.[81] Other associations with physical activity in healthy subjects include decreases in plasma viscosity, platelet count, factors VIII and IX, vonWillebrand factor, and tissue plasminogen activator.[82] One study claimed that the inverse relation between physical activity and CRP did not hold for women.[83] Decreased atherogenic IL-6 and increased atheroprotective IL-10 have been associated with physical activity in healthy subjects; however, this study failed to show a relationship between physical activity and CRP.[84] Nine months of marathon training has been shown to decrease CRP.[85] In healthy subjects, it has also been shown that the association between physical activity and inflammatory markers may be mediated by the effects of physical activity on BMI (reduction) and leptins (downregulation).[86] In a study on the effect of physical activity on mononuclear cells in patients at risk of developing ischemic heart disease (as evidenced by serum complement levels or CRP levels), it was shown that mononuclear cell production of atherogenic cytokines decreased by 58% and atheroprotective cytokines increased by 36%; CRP decreased by 35%.[87]

In an analysis of what kind of exercise is best suited for reduction of inflammation, it has been postulated that physical activity that does not cause muscular microinjury is best; indeed, 1 study of athletes showed that swimming reduced CRP far more than cycling, soccer, running, or controls.[88] However, another study of healthy subjects found that jogging and aerobic dancing were less likely to be associated with elevated inflammatory markers after adjustment for confounding factors such as age, race, sex, BMI, smoking, and health status.[89] The inverse correlation between physical activity and inflammation has also found validity with formal cardiac rehabilitation, and this correlation is still seen in the presence of potential confounders as statin use or weight loss.[90,91] Wannamethee and coworkers[82] reported that physical activity in the elderly (aged 40-59 years) was inversely associated with fibrinogen, CRP, D-dimer, and white blood cell count; in addition, there was a dose-response relationship between physical activity and the inflammatory and procoagulant variables. However, weight loss per se (achieved through diet and without increased physical activity) in obese postmenopausal women was associated with significantly reduced CRP.[92]

One must mention 2 studies that do not conform with the rest of the literature. One study of healthy men and women showed that CRP was associated with BMI but not with physical activity.[93] Another randomized, controlled study, in which 140 middle-aged men were randomly selected from the population, failed to show a relationship between aerobic exercise and atherosclerosis.[95] However, it should be noted that a weekly expenditure of 1,500 kcal or more is required to attenuate atherosclerosis[95]; self-exercise, as in this study, may not achieve such energy expenditure.[94]

Inflammation in Nondialysis CKD

Stenvinkel and colleagues[70] in a study of nondialysis patients with a mean GFR of 7 mL/min showed that 44% of nondialysis CKD patients suffer from malnutrition and 32% of such patients have an active acute phase response, as evidence by increased levels of CRP. Barzilay and coworkers,[95] in a cross-sectional analysis, showed that in nondialysis CKD, microalbuminuria is associated with age, elevated systolic blood pressure, and markers of systemic inflammation, including CRP.

Inflammation in Hemodialysis Patients

CKD and uremia are strongly associated with elevated inflammatory markers; in uremia, this association has been termed the Malnutrition-Inflammation Complex Syndrome.[96-100] In 1 study of 845 hemodialysis patients, 35% had elevated CRP. The study reported a strong inverse relationship between both serum albumin and creatinine and the odds of death; no such relationship was found for CRP.[101] However, many other studies in hemodialysis patients have clearly shown that CRP was as strong a predictor of morbidity/mortality as hypoalbuminemia.[71,72,75,102,103] In hemodialysis patients, CRP is associated with an increased risk of hospitalization.[103] Also, it has been reported that among hypoalbuminemic patients, the degree of hypoalbuminemia correlated with elevation of CRP, alpha$_2$-macroglobulin, ferritin, and serum amyloid A.[72,104-106] It is of note that analbuminemic rats have a normal life span and normal renal function so it is probably the cause of hypoalbuminemia and not hypoalbuminemia itself that leads to higher mortality.[107]

Aerobic Exercise and Inflammation in CKD

There is a paucity of studies that have looked at the effects of aerobic exercise on inflammation in ESRD. This may be because it has been viewed that one must reverse the catabolism of CKD, and this is only effectively achieved with resistance training. However, in dialysis patients, aerobic exercise training can achieve favorable improvements in muscle atrophy and fiber hypertrophy.[108] The aerobic exercise capacity of people on hemodialysis is half the expected value for healthy individuals; dialysis patients report limitation in tasks such as walking several blocks or climbing stairs. One study, albeit in the general population, notes that one must expend 1,500 kcal/wk to attenuate atherosclerosis/inflammation.[94] Uremic myopathy limits aerobic capacity in hemodialysis patients.[109] However, experts in renal rehabilitation recommend that a good rehabilitation program will combine both aerobic training and strength training. For some people with orthopedic compromise, non–weight-bearing activities may be used, and, for people with severe deconditioning, resistive training should be initiated before aerobic exercise.[110-112] A cross-sectional study by Hung and colleagues[113] reported elevated cytokines, including CRP, in the dialysis population but failed to ascertain a correlation between physical activity and cytokines, performance, or functionality.

Resistance Training and Inflammation in Nondialysis CKD

Castaneda and coworkers[114] documented declines in serum CRP and IL-6 in patients with moderately severe CKD who were adherent to a low-protein diet who underwent a 12-week regimen of resistance training. They again showed improved nutritional and functional parameters, including an increase in serum transferrin, muscle hypertrophy, increased muscle strength, and maintenance of body weight.

Effect of Exercise on Microalbuminuria and Progression of CKD

Diabetic patients with CKD and microalbuminuria or overt proteinuria typically develop progressive kidney failure. Therefore, there is much interest in the effects of exercise on microalbuminuria/proteinuria and progression of kidney disease. Because exercise is associated with a decrease in inflammation, the relationship between inflammation and progression of kidney disease is first considered. In a cross-sectional analysis of coronary heart disease data from different years of follow-up, it was concluded that there is a significant relation between inflammation and microalbuminuria. Because of the cross-sectional nature of the study, causality could not be established, but the authors speculated that inflammation probably precedes microalbuminuria.[96] One study of type 2 diabetes established that markers of endothelial dysfunction and inflammation were strongly associated with increases in urinary albumin excretion and were thus involved in the pathogenesis of microalbuminuria. Interestingly, the study also suggested that endothelial dysfunction causes an increase in inflammatory activity, potentially creating a vicious cycle of inflammatory activity and endothelial dysfunction.[115] It has been shown that cytokines and inflammatory markers mediate glomerular and kidney damage and are, hence, involved in the pathogenesis of microalbuminuria and kidney failure.[116]

In view of the evidence linking inflammation, microalbuminuria, and progression of CKD, one would suspect that exercise would also decrease microalbuminuria and slow down the rate of progression of kidney failure. Studies in rats have shown a beneficial effect of exercise on the rate of progression of CKD,[117] but these findings could not be reproduced in humans (median GFR, 25 mL/min/1.73 m^2).[33] However, the human studies failed to note an improvement in blood pressure or plasma lipids, and the improvement in aerobic performance was small. Furthermore, the aerobic exercise group was instructed to train at home.[33] One study of mild to moderate renal failure subjects noted enhanced GFR and diminished proteinuria with aquatic exercise.[35]

Inflammation, Obesity, Leptins, and CKD

Inflammation is also related to obesity. Macrophages invade fat in response to an unknown signal and form giant cells; hence, adipose tissue is the site of active inflammation, characterized by elevated cytokines and leptins. Chronic inflammation and acute infection are associated with anorexia and cachexia, probably through the actions of cytokines and leptins on the hypothalamus. Fasting/starvation leads to declining leptin levels, which, in turn, leads to increased appetite, decreased energy expenditure, diminished thyroid hormone production, inhibition of the reproductive axis, and apoptosis in the thymus. However, despite elevated cytokines and leptins, appetite is not decreased in obesity/metabolic syndrome. This may be because of hypothalamic resistance and concurrent activation of the peripheral immune system (immune cells have leptin receptors). Thus, a vicious cycle of inflammation in adipose tissue leading to

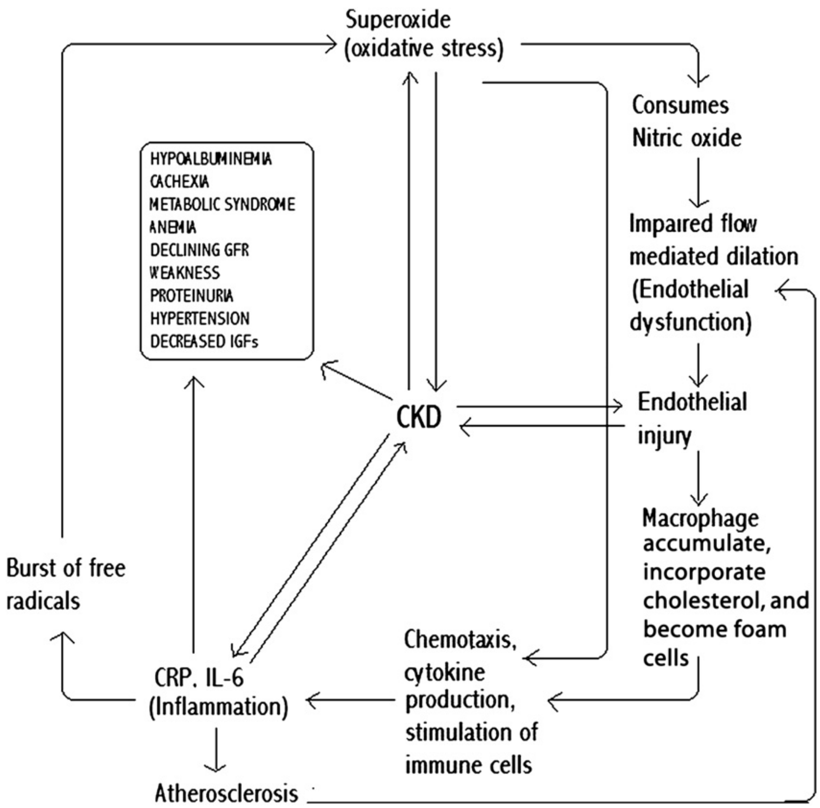

Figure 1. CKD is associated with oxidative stress, endothelial dysfunction, and inflammation. Oxidative stress consumes nitric oxide, which leads to impaired flow-mediated dilation (FMD) of blood vessels (endothelial dysfunction). This subjects the endothelium to injury and is followed by accumulation of microphages, which incorporate cholesterol and become foam cells; production of cytokines; acceleration of inflammation; worsening of blood vessel rigidity because of atherosclerosis; and further impairment of FMD and susceptibility to oxidative stress. CKD, chronic kidney disease; GFR, glomerular filtration rate; CRP, C-reactive protein; IL-6, interleukin 6; IGF-1, insulin-like growth factor.

leptin production coupled with hypothalamic resistance and activation of the inflammatory process may lead to further leptin production.

Similarly, adipose tissue secretes IL-6, which is associated with insulin resistance, inflammation, and the hepatic acute-phase response. IL-6 causes decreased food intake and increased energy expenditure; deletion of IL-6 in mice leads to obesity. Thus, obesity leads to IL-6 production and concurrently induces central nervous system IL-6 resistance, which exacerbates obesity and further increases IL-6 levels.

It is suggested that macrophage invasion of fat and inflammation-related gene expression precedes the development of insulin-resistance. It may be hypothesized that inflammation may also precede chronic kidney disease, which, in turn, worsens inflammation and leads to a vicious cycle.[118] Research regarding the effects of aerobic exercise and strength training on leptins in the population of the obese diabetic with CKD is of particular interest. Aerobic exercise in the general population has been shown to decrease BMI and leptins.[86]

Oxidative Stress

Most cardiovascular risk factors such as smoking, hypercholesterolemia, hypertension, diabetes mellitus, and renal failure are associated with endothelial dysfunction and oxidative stress. CKD is an important cause of oxidative stress, as evidenced by the observation that oxidative stress parameters normalize after kidney transplantation with complete recovery of kidney function.[119] Putative mechanisms whereby CKD increases oxidative stress and cardiovascular disease are depicted in Figure 1. One of the major mechanisms leading to endothelial dysfunction is increased oxidative stress. Oxidative stress causes nitric oxide breakdown; consequently, endothelial cells lose their ability to protect the vessel wall and become atherosclerosis promoters. One study showed that flow-mediated dilation (FMD) was lower in nondialysis CKD after 5 minutes of ischemia when compared with controls and was even lower in hemodialysis patients. Vitamin C–enhanced FMD in hemodialysis patients but not in nondialysis CKD

Table 1. The Effects of Aerobic Exercise on Non-CKD, Non-dialysis CKD, and Hemodialysis Patients

Variable	Aerobic Exercise in Non-CKD	Aerobic Exercise in Non-dialysis CKD	Aerobic Exercise in Hemodialysis	
			Intradialytic	Interdialytic
C-reactive protein	↓[78-82,85-89] No change[1,83,84,93]	?	?	No change[113]
IL-6	↓[1,80,84]	?	?	?
Albumin	↑[78] No change[81]	?	?	No change[53]
HbA1c	↓[4]	?	?	?
Insulin sensitivity	↑[4-6,10-16]	?	?	↑[48] No change[52]
Lipid profile	Improved[7-9,26,111]	No change[31,33]	?	Improved[48] No change[50]
Hemoglobin	No change[82]	No change[31,33]	?	↑[48] No change[49]
Weight	↓[4-6,80,86,126]	?	?	No change[47]
Muscle strength	?	↑[34]	↑[40,44]	↑[51,56]
Leptins	↓[86]	?	?	?
IGF-1	?	?	No Change[41]	↑[57]
Microalbuminuria	↓[26]	↓[33,35]	?	?
Resistance to oxidative stress	↑[6,123-131]	↑[35]	?	?
Blood pressure	↓[4,6,11,29,126] No change[26]	↓[31,35] No change[32,33]	↓[43]	↓[48] No change[49,50]
GFR	?	↑[35] No change[31-33]	?	?

CKD, chronic kidney disease; IL-6, interleukin-6; HbA1c, glycosylated hemoglobin; IGF-1, insulin-like growth factor-1; GFR, glomerular filtration rate.

Table 2. The Effects of Resistance Training on Non-CKD, Non-dialysis CKD, and Hemodialysis Patients

Variable	Resistance Training in Other Groups	Resistance Training in Non-dialysis CKD	Resistance Training in Hemodialysis	
			Intradialytic	Interdialytic
C-reactive protein	↓[89]	↓[114]	?	?
IL-6	?	↓[114]	?	?
Albumin	?	↑[37,114]	?	?
HbA1c	↓[17]	?	?	?
Insulin sensitivity	↑[4,10,11,15-17,19,20]	?	?	?
Lipid profile	Improved[17-20]	?	?	?
Hemoglobin	?	?	?	?
Weight	↑ Muscle ↓ Fat[4,18,23-27]	Maintained[37,114]	?	?
Muscle strength	↑[4,17,18,20,25]	↑[37,114]	↑[61]	↑[55]
Leptins	?	?	?	?
IGF-1	↑[25]	↑[37]	?	↓ Total IGF-1 Stable free IGF-1[62]
Microalbuminuria	↓[26]	?	?	?
Resistance to oxidative stress	?	?	?	?
Blood pressure	↓[17,20,29] No change[26]	?	?	?
GFR	?	↑[37]	?	?

CKD, chronic kidney disease; IL-6, interleukin-6; HbA1c, glycosylated hemoglobin; IGF-1, insulin-like growth factor-1; GFR, glomerular filtration rate.

patients.[120] Asymmetric dimethyl-L-arginine accumulates and inhibits nitric oxide synthase leading to endothelial dysfunction and increased cardiovascular risk.[121,122]

Exercise and Oxidative Stress

Does exercise training affect oxidative stress? Although strenuous exercise acutely increases oxidative stress, most studies have shown increased resistance to oxidative stress with chronic exercise.[123,124] Plasma-reduced glutathione content has been shown to increase with training distance in long-distance runners during a training season and after 20 weeks of physical training in previously sedentary men.[125] It has been reported that endurance exercise in combination with vitamin E reduces oxidative stress (reduced lipid hydroperoxide), improves aerobic fitness, and reduces blood pressure and weight in older adults recruited from a retirement community.[126] Many studies have documented reduced malondialdehyde with chronic endurance exercise.[127-131]

Much less is known about the effects of exercise on oxidative stress in CKD patients. Aquatic exercise diminishes proteinuria, enhances GFR, decreases products of lipid peroxidation, and increases reduced glutathione in subjects with mild to moderate kidney failure.[35]

Summary

Tables 1 and 2 summarize our current knowledge of the effects of exercise in patients with and without CKD. Further study should focus on unexplored variables in patients with CKD.

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