Effects of Diet and Exercise on Metabolic Parameters and Health in Moderate to Advanced Kidney Disease

Lale A. Ertuglu 1,2 and Talat Alp Ikizler 1,2,*

1 Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN 37232, USA; lale.ertuglu@vumc.org
2 Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, TN 37232, USA
* Correspondence: alp.ikizler@vanderbilt.edu; Tel.: +1-(615)-343-2220; Fax: +1-(615)-343-7156

Abstract: Metabolic derangements such as obesity, dyslipidemia, chronic inflammation, and oxidative stress are commonly seen in patients with chronic kidney disease (CKD) and are implicated in the exaggerated cardiovascular disease (CVD) risk observed in this patient population. Lifestyle interventions including healthy dietary patterns and exercise training have been proven effective in modifying these CVD risk factors in the general population. The efficacy and safety of these interventions in CKD patients remain elusive. This review article aims to provide a summary of the current evidence on the effects of different types of dietary and exercise interventions on metabolic biomarkers associated with cardiovascular disease in patients with moderate to advanced CKD.

Keywords: chronic kidney disease; diet; exercise; metabolic health

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1]. Patients with CKD are unproportionally affected not only by the traditional CV risk factors such as obesity and hyperlipidemia but also multiple nontraditional risk factors including, but not limited to chronic inflammation and exaggerated oxidative stress.

Dyslipidemia, characterized by predominant hypertriglyceridemia, high levels of low-density lipoprotein-cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C), is evident from the early stages of kidney disease [2]. Serum inflammatory markers have a dose-dependent relationship with the severity of CKD in predialysis stages [3,4]. In the Chronic Renal Insufficiency Cohort (CRIC) study, the prevalence of patients with an inflammation score above 1 was 39% among patients with stage 1 or 2 CKD and increased strikingly with decreasing estimated glomerular filtration rate (eGFR), reaching 63% and 69% among patients with stage 4 and stage 5 CKD, respectively [5]. The pro-oxidant milieu in CKD is triggered by the combined effects of uremic toxins, inflammatory cytokines, and dialysis-associated factors including blood–dialyzer interaction, peritoneal fluid, and dialysis catheters [6,7]. The oxidative burden in CKD is evident in consistently high concentrations of oxidative stress biomarkers such as oxidized low-density lipoprotein (LDL), total homocysteine, F2-isoprostane, and plasma protein thiol oxidation as well as deficiencies of endogenous antioxidants including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), and reduced glutathione (GSH) [4,8–10]. Like inflammatory markers, oxidative stress markers strongly correlate with CVD risk and mortality in patients with CKD [6,11,12].

Strong evidence supports the concept that healthy dietary habits and regular physical activity significantly diminish cardiovascular risk in the general population [11]. Dietary interventions with exercise training have profound positive effects on body weight and fat mass and its distribution, serum lipids, markers of inflammation, and oxidative stress in...
various chronic disease states [12–14]. In this manuscript, we aim to provide a comprehensive review of the effects of diet and exercise on a number of metabolic markers that are known to be associated with clinical outcomes in patients with CKD.

2. Diet

Strong adherence to Western dietary patterns has been associated with hyperlipidemia, obesity, and inflammation and is a potentially modifiable risk factor for the development of CVD [15–17]. In clinical practice, dietary advice for moderate to advanced CKD mostly focuses on its protein and electrolyte content, while the relationship between other dietary components and their effect on the exaggerated cardiovascular risk in CKD is usually omitted. In the following section, we will discuss caloric intake, dietary patterns, and dietary fiber as they relate to metabolic profile in patients with CKD (Figure 1).

Figure 1. Various dietary interventions, including total caloric restriction [4,18], modified Mediterranean diet [19], very low-protein vegan diet [20,21], and high fiber intake [22] have been associated with decreased inflammation and oxidative stress in patients with CKD.

2.1. Total Caloric Intake

Obesity is highly prevalent among the CKD population, with prevalence rates over 45% and 37% in moderate and advanced CKD, respectively [23] and is primarily caused by an imbalance between calories consumed and calories expended [24]. Exaggerated oxidative stress and inflammation are driven by increased adiposity in many settings, and body mass index (BMI) is strongly associated with biomarkers of these metabolic abnormalities in the general population [25–28] as well as in patients with CKD [4,29]. Thus, total caloric intake is indirectly related with these biomarkers through its effect on BMI and body fat. In a study of 184 patients with stages 3–4 CKD, Ramos et al. investigated the relationship of body composition with markers of inflammation and oxidative stress. Adjusted analysis revealed that increasing BMI and body fat percentage significantly associated with higher serum CRP and oxidative stress markers, such as higher plasma F2-isoprostane and lower protein thiol levels. Furthermore, interaction analysis indicated potential effect modification by CKD status on the effect of BMI and CRP [4], suggesting that increased adiposity may intensify the oxidative stress and inflammatory burden of CKD.
Studies in non-CKD populations indicate that weight loss with caloric restriction is an effective strategy to improve hyperlipidemia [30] and reduce markers of inflammation [31] and oxidative damage [32], suggesting that interventions targeting weight loss in obese patients with CKD may be an efficient strategy to target metabolic derangements [23]. In a study including 111 patients with moderate to severe CKD, Ikizler et al. showed that 4-month dietary calorie restriction by 10–15% induced favorable changes in metabolic risk profile. Specifically, participants were randomized into four intervention arms: caloric restriction and aerobic exercise, calorie restriction alone, aerobic exercise alone, or usual care. Calorie restriction, both alone and combined with exercise, led to significant decreases in body weight and body fat percentage as well as in serum IL-6 and F₂-isoprostane concentrations [18]. Furthermore, dietary restriction significantly increased plasma adiponectin levels [33], a potential inverse predictor of CVD in the general population and in patients with mild to moderate CKD. During the study, 70% of participants consumed the assigned calorie intake or less and all participants except one remained within 20% of their assigned calorie intake, showing that dietary calorie restriction is a feasible and safe lifestyle intervention for this patient population [18]. However, caution should be exerted when low-energy diets are prescribed to patients with advanced CKD, who are more predisposed to adverse events [34] and might suffer from protein energy wasting [35].

2.2. Dietary Patterns

2.2.1. Mediterranean Diet

Mediterranean diet (MD), which traditionally consists of high amounts of olive oil, fruits, vegetables, legumes, fish, and dairy products with low amounts of meat, is known to decrease both traditional and nontraditional risk factors for CVD [36–38]. Per the ATTICA and PREDIMED studies, adherence to an MD effectively reduces inflammatory and coagulation markers, including CRP, IL-6, homocysteine, and fibrinogen, in healthy adults [39] and decreases the CVD incidence by approximately 30% in individuals at high cardiovascular risk [40]. Adherence to MD and other healthy dietary patterns also appears to improve outcomes in CKD patients [41,42]. Analysis of the National Institutes of Health-American Association of Retired Persons Diet and Health Study cohort has revealed that strong adherence to healthy dietary patterns, assessed with Alternate Healthy Eating Index (AHEI), Healthy Eating Index (HEI), Mediterranean Diet, and Dietary Approaches to Stop Hypertension (DASH) scores, was associated with reduced risk of dialysis or death due to a renal cause [42], a finding corroborated by other studies [43,44]. Nevertheless, an analysis of the DIET-HD cohort did not reveal an association of Mediterranean or DASH diet scores with cardiovascular or all-cause mortality in prevalent patients on maintenance hemodialysis (MHD) [45]. Likewise, the potential benefits of MD and other healthy dietary patterns such as DASH in combatting dysmetabolism of kidney disease remain unclear. In a cross-sectional study including 99 patients with non-dialysis-dependent CKD, Bowden et al. showed that higher adherence to several components of MD was associated with lower LDL cholesterol [46]. In another longitudinal study of 50 patients with CKD and diabetes, Picard et al. found no association between annual MD score and cardiometabolic risk factors, including serum lipid and CRP levels. It should be noted that adherence to MD was notably low in both observational studies, limiting the implications of the study results [46,47].

Mekki et al. [19] investigated the effects of 3 months of a modified MD in a clinical trial including 40 patients with stage 2 CKD and dyslipidemia. While all patients received nutritional advice based on the NKF K/DOQI (National Kidney Foundation—Kidney Disease Outcomes Quality Initiative) guidelines, the dietary recommendation was adapted to MD in the intervention group. The adapted MD predominantly consisted of olive oil, nuts, whole grains, fish, and low-potassium fruits and vegetables. After 3 months of initiating the diet, the intervention group had significantly lower triglycerides and LDL-C and an elevated Apo-I/Apo B ratio compared to the control group. Levels of CRP and thiobarbituric acid-reactive substances (TBARS), a marker of lipid peroxidation, also
decreased by 40% versus 21% in the intervention group compared to the control group, respectively. Analysis of the food intake composition among patients on MD revealed that higher MUFA intake correlated with lower triglyceride levels, whereas cooked vegetables, fruits, and fish correlated with lower CRP and TBARS concentrations [19].

2.2.2. Vegan Diet

While quantitative restriction of protein intake is the main dietary recommendation in CKD, the differences between distinct dietary protein sources have rarely been studied. Plant-based vegetarian or vegan diets are known for their lipid-lowering and anti-oxidant properties, owing to their favorable fat composition and high contents of antioxidants, including vitamins A and C and α-tocopherol [22,48]. In studies of non-CKD populations, plant-based diets were consistently associated with lower blood lipids [49–51], inflammatory biomarkers [52–54], oxidative stress [50,55], as well as decreased risk of CVD [56,57] and mortality [58]. While it can be speculated that plant-based diets may benefit CKD patients in a similar fashion, the vegetarian diet has been scarcely studied in the CKD population due to concerns over their potassium and phosphorus content. An observational study in MHD patients reported significantly lower BMI and serum concentrations of CRP and urea in vegetarian patients; however, only 19 out of 318 patients were vegetarian [59]. Bergesio and colleagues compared the cardiovascular risk factors in patients with end-stage renal disease (ESRD) on a very low-protein (0.3 g/kg/day) vegan diet supplemented with essential amino acids and ketoacids with those on a conventional low-protein (0.6 g/kg/day) diet in 60 patients over 6 months. While BMI did not differ between the groups, patients on a vegan-supplemented diet had better lipoprotein profiles with lower LDL and higher HDL cholesterol levels and higher apoA1/apoB ratios compared to patients on a conventional low-protein diet [20]. Oxidized LDL (OxLDL), TBARS, total homocysteine and CRP levels were also significantly lower in the vegan-supplemented group, implying that a vegetarian diet ameliorated the oxidative stress and chronic inflammation in advanced CKD patients. Furthermore, there were positive correlations between CRP and urea, and between lipids and OxLDL in the control group but not in the vegan-supplemented group, interpreted by the authors as that patients on a vegan-supplemented diet were less susceptible to oxidation and inflammation. Interestingly, patients on a vegan-supplemented diet did not have higher levels of vitamins A and E, but had higher folic acid and vitamin B12 levels related to regular supplementation [20]. Furthermore, in a trial of 207 patients with advanced CKD, Garneata et al. showed that 15 months of a supplemented vegetarian very low-protein diet substantially decreased serum CRP levels compared to the low-protein group, whose CRP levels significantly increased over the study period [21]. It should be noted that patients on a vegan-supplemented diet had lower overall protein intake and had significantly lower urea levels [20,21]. Therefore, the benefits of a vegan-supplemented diet in this population could partially be explained by a decreased burden of uremic toxins [20]. Indeed, healthy vegetarians have decreased excretion of uremic solutes associated with lower protein and higher dietary fiber intake [60]. The lower protein and energy contents of vegetarian diets often raise concern over the nutritional status of patients with advanced CKD, who suffer from protein energy wasting. Moreover, diets rich in vegetables and fruits are traditionally regarded unsuitable for the stage 3–5 CKD patients due to their high potassium and phosphorus content. The safety of long-term supplemented vegetarian very low-protein diet was also evaluated in the clinical trial by Garneata et al. [21], including 207 patients with stage 4–5 CKD. Over 15 months, the occurrence of adverse events, compliance to the prescribed diet, withdrawal number, as well as parameters of nutritional status including Subjective Global Assessment (SGA), body measurements, and serum albumin were closely assessed. Patients had good compliance and no adverse event or change in nutritional status was recorded. Compared to a low-protein diet, the intervention group had substantial decrease in serum phosphate levels, while serum potassium levels did not change [21].
Phosphorus from plant-based proteins has low bioavailability in the human digestive tract compared with animal proteins. In fact, a vegetarian-based protein diet has been associated with reduction in serum phosphorus levels compared to a meat-based protein diet in CKD patients [61]. Furthermore, plant-based potassium sources may concurrently promote intracellular potassium distribution through alkalinizing effects and insulin release and increase fecal potassium elimination through increased fecal bulk, induced by their high dietary fiber content. Thus, the high potassium intake in these diets may naturally be counterbalanced [62]. Contrary to the widely accepted recommendation of dietary potassium restriction for patients with chronic kidney disease, increasing fruit and vegetable consumption were not found to lead to hyperkalemia in patients up to stage 4 CKD [63,64]. In a study including 8043 HD patients from Europe and South America, Bernier-Jean et al. examined the association between mortality, hyperkalemia, and potassium intake over the preceding year. Strikingly, higher dietary potassium intake did not associate with higher serum potassium concentrations, the prevalence of hyperkalemia, or mortality [65]. Overall, reports to date suggest that a supplemented vegetarian diet with low or very low protein does not adversely affect nutritional or electrolyte status in patients with advanced CKD and may even defer the onset of uremic symptoms [66–69].

2.3. Dietary Fiber

Rich in both MD and vegetarian diets, dietary fiber has long been established to provide various health benefits in the general population and in patients with high cardiovascular risk [70]. Dietary fibers are plant carbohydrates that are not digestible in human intestines and are present richly in whole grains, fruits, vegetables, and legumes. Owing to their non-digestible nature, dietary fibers decrease the absorption of glucose and cholesterol from the intestinal lumen, while promoting gut microbial diversity and production of short-chain fatty acids (SCFAs) [71]. In the non-CKD population, high dietary fiber intake consistently associates with lower BMI and inflammatory markers, and better lipid profiles [70,72]. Despite their well-acknowledged health benefits, patients with CKD usually have low dietary fiber intake due to restrictions on fruits and vegetables. According to a study of 102 HD patients, MHD patients had an average daily fiber intake of 12 g/day, which was significantly less than healthy controls and less than half of the daily recommendation of 30 g/day for the general population [73].

Nevertheless, evidence points out that dietary fiber intake may be important to modulate cardiovascular risk factors in CKD. In a cohort of 157 patients with stage 3–4 CKD, Lu et al. reported that patients with high fiber intake had significantly lower levels of CRP, IL-6, indoxyl sulfate, and serum cholesterol without a difference in protein nutritional status. Furthermore, over the median follow-up period of 15 months, the relative risk of CVD in the higher fiber intake group was 0.54 [74]. Similarly, analysis of the NHANES III cohort consisting of 14,543 participants revealed that each 10-g/day increase in total fiber intake decreased the odds of elevated CRP levels by 38% and 11% in those with and without kidney disease, respectively. During the follow-up period of 8.4 years, total intake of dietary fiber was also inversely related with mortality, but only in patients with CKD [75]. This discrepancy between patients with and without CKD can be potentially explained by the effects of dietary fibers on gut-derived uremic toxins as well as the low baseline fiber intake and high inflammatory milieu in patients with CKD.

Dietary fibers significantly influence the production of uremic toxins by bacterial fermentation in the gut. Indoxyl sulfate and p-cresyl sulfate are some of the main uremic byproducts of protein fermentation by the gut bacteria that have strong cardioirenal toxicities and proinflammatory properties. Dietary fiber supplementation may shift the gut bacterial metabolism from proteolytic to a saccharolytic fermentation pattern [76], thus limiting the formation of indoles and phenols in CKD [77,78] and inducing the production of anti-inflammatory SCFAs [79]. Among patients with non-dialysis-dependent stage 3–5 CKD, 4-week supplementation of pea hull and inulin, providing 23 g/day of added fiber, has been reported to decrease total plasma p-cresol significantly [78]. Similar re-
sults have also been observed in MHD patients [80]. In a study including 56 MHD patients, increasing dietary fiber for 6 weeks decreased the free plasma levels of indoxyl sulfate and p-cresol sulfate levels by 29% and 28%, respectively [81].

A major concern over the use of fiber supplementation in patients with kidney disease is the risk of suppressed appetite and total energy intake [82]. However, long-term follow-up of patients with moderate to advanced CKD did not find a difference in energy intake or protein nutritional status between high and low fiber consumers [74]. Nevertheless, fiber-rich foods, especially fruits and vegetables, also have a substantial potassium content and are restricted in patients with ESRD. For such cases, fiber intake can be increased via supplementation or low-potassium food enriched with fiber, as suggested by current literature.

3. Exercise

Patients with CKD have impaired physical functioning and reduced exercise capacity, which represent one of the strongest predictors of mortality and hospitalization in this patient population [83,84]. Exercise has substantial favorable effects on cardiometabolic risk factors, including obesity, hypertension, dyslipidemia, insulin resistance, and inflammation in non-CKD populations [85–88]. Despite a paucity of large clinical trials, the available literature suggests that exercise training may have similar benefits in the CKD population.

There are three main exercise training modalities: aerobic, resistance, and combined exercise. While aerobic exercise primarily leads to weight loss, reduction in skeletal muscle fat content and enhancement of muscle lipid oxidation [89,90], resistance training preserves fat-free mass and prevents or even reverses muscle wasting [91,92]. Therefore, aerobic or combined exercise, often together with caloric restriction, can be used to achieve weight loss in obese non-dialysis-dependent patients, while resistance training can be utilized to offset muscle wasting and protein catabolism of advanced kidney disease [93]. A strong body of evidence shows that aerobic exercise training is effective against inflammation, oxidative stress, and dyslipidemia in non-CKD populations [94–97]. Resistance training has also been reported to provide similar benefits, albeit modest [98–100]. In patients on MHD, either exercise training can be done supervised during hemodialysis sessions, referred to as intradialytic exercise. Intradialytic exercise is proposed to be an effective exercise regimen for HD patients and has higher compliance rates compared to outpatient exercise programs in this population (Table 1) [101].

Table 1. Effects of exercise interventions in CKD patients.

|                      | Non-Dialysis-Dependent CKD | Dialysis-Dependent CKD | Non-Dialysis-Dependent CKD | Dialysis-Dependent CKD |
|----------------------|-----------------------------|------------------------|-----------------------------|------------------------|
| **Body Weight**      | No change in body weight/composition [30,102–105] Decrease in BMI [106,107] and waist circumference [107,108] | No change in weight [109] Decrease in weight and waist circumference [107] Improved muscle attenuation [102,110] | No change in weight [102,110] Decrease in weight and waist circumference [107] Improved muscle attenuation [102,110] | No change in weight [109,111] or LBM [112,113] Increase in weight [114,115] and LBM [116] Improved muscle attenuation [114] |
| **Lipid Profile**    | Decrease in TGs and LDL-C [117–119] Increase in TGs and LDL-C [120] No change [103] | Decrease in TG [121,122] and LDL-C [122] Increase in HDL-C Increased TG and LDL-C [123] No change [123–125] | Decrease in LDL-C [117] Decrease in CRP and IL-6 [110] | Decrease in TGs and LDL-C [117] Decrease in TBARS [132] |
| **Markers of Inflammation** | No change in CRP [102,104,105,128,129] or IL-6 [120] Decrease in IL-6 [118] | No change in CRP [130–133] or IL-6 [134] Decrease in CRP [109,135] | No change in CRP [130] or IL-6 [136] Decrease in CRP [117,123,127] | No change in CRP [130] or IL-6 [136] Decrease in CRP [117,123,127] |
| **Markers of Oxidative Stress** | Decrease in products of lipid peroxidation [103] and F2-isoprostane [18] | Decrease in TBARS [132] | N/A | N/A |

BMI: Body mass index; CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; IL-6: Interleukin 6; LBM: Lean body mass; LDL-C: Low-density lipoprotein cholesterol; TBARS: Thiobarbituric acid-reactive substances; TC: Total cholesterol; TG: Triglyceride.
3.1. Effects of Exercise on Body Composition

Exercise may improve dysmetabolism in non-dialysis-dependent obese CKD patients through weight control. In a meta-analysis of eight studies, aerobic exercise was found to induce a significant, but clinically minimal impact on BMI, i.e., 0.73 kg/m\(^2\) over an average of 32 weeks. Only two of the individual studies reported a significant change in BMI [106]. The included studies used a variety of training modalities, including aerobic or combined exercise trainings [107], center- and home-based trainings, and exercise with or without dietary modifications [138], which may have led to inconsistent findings. Indeed, Baria et al. found significant decreases in visceral fat and waist circumference and increase in lean body mass (LBM) with center-based but not with home-based aerobic exercise training among 27 obese patients with CKD [108]. Furthermore, some studies might have not achieved the negative energy balance required for weight loss [139] due to insufficient energy expenditure and lack of calorie restriction. Indeed, aerobic exercise combined with caloric restriction, but not exercise alone, was found effective in decreasing body weight and fat percentage among patients with moderate to severe CKD [18].

Exercise training may have beneficial effects on visceral adipose tissue without clinically evident changes in body mass. Among visceral adipose tissue, pericardial fat has a unique role in cardiovascular risk pertaining to its proximity to the adventitia of coronary arteries and myocardium and its role in inflammatory activation [104]. In non-CKD populations, exercise training leads to reduced epicardial fat tissue mass independent from changes in body composition [124,140]. Similar findings have been reported in patients on MHD; 4 months of intradialytic aerobic exercise has been associated with an 11% reduction in epicardial fat mass [132].

In the setting of ESRD, the primary role of exercise training is prevention of muscle loss and protein energy wasting [125]. Resistance exercise promotes protein utilization in muscle tissue and has been mostly associated with improved muscle mass. While several studies have observed significant improvements in muscle mass and endurance training in dialysis-dependent [114,116] and non-dialysis-dependent patients [102], two randomized clinical trials found no significant change in LBM following intradialytic resistance exercise for 12–24 weeks, with or without intradialytic oral nutritional supplementation [112,113]. In a recent randomized clinical trial including 101 HD patients, 12 months of endurance exercise with intradialytic protein supplementation was not associated with a significant improvement in body composition or muscle strength [141]. Similar findings have been reported for intradialytic aerobic and combined exercise trainings in several other studies [109,111,128]. It should be noted that the sample size, different intensities and modalities of exercise used, and patient compliance limit the generalizability of these studies and further clinical trials are underway to provide more evidence [142] (ClinicalTrials.gov (accessed on 24 February 2022). NCT05207527, NCT04525196).

3.2. Exercise and Dysmetabolism of Kidney Disease

Studies in healthy adults have demonstrated a close relationship between exercise and metabolic markers. Among the general population, exercise induces favorable changes in the lipid profiles, and the significance and magnitude of which depends on the duration and intensity of the exercise regimen [143]. Such promising effects have also been observed in the CKD population. In patients with mild to moderate CKD, short-term aerobic training has been found to significantly decrease total cholesterol, LDL cholesterol, and triglyceride levels and increase HDL cholesterol levels [117–119]. Similar changes have been observed after long-term aerobic exercise training [121], resistance exercise [115], and yoga exercise in dialysis patients [122,127], with almost 85% of patients achieving normal LDL cholesterol levels after 4 months of Hatha yoga [122].

On the contrary, several studies reported increased total cholesterol, LDL, and triglyceride levels following aerobic exercise in CKD patients. While Reboredo et al. attributed the finding in dialysis patients to increased appetite [123], Headley et al. found no change
in dietary intake or body weight with exercise in patients with stage 2–4 CKD [120]. Other studies including a meta-analysis of patients with any stage CKD found no change in lipid levels [126,144,145], although the majority of the studies included in the meta-analysis were limited by their sample size [145].

Exercise has a well-characterized relationship with inflammation in the general population. While a single bout of exercise induces an acute inflammatory response, regular physical activity effectively diminishes chronic inflammation [146]. Viana et al. reported similar findings in a small cohort of predialysis CKD patients (n = 15); while a 30-min bout of walking induced acute and marked increase in both pro- and anti-inflammatory cytokines, 6 months of regular walking exercise led to a borderline decrease in IL-6 and a significant reduction in IL-6/IL-10 ratio, implying an anti-inflammatory effect [137]. Furthermore, higher physical activity and aerobic capacity in patients with CKD consistently correlate with lower levels of pro-inflammatory markers [147–149]. These observational studies were corroborated by several clinical trials, showing significant decreases in CRP and IL-6 levels following resistance and aerobic exercise trainings in predialysis [18,110] and dialysis patients [117,123,137,146]. Importantly, the compliance rates were high. For example, 85% of the 111 patients with moderate to severe CKD completed half or more of the assigned exercise sessions within the 4-month aerobic exercise program [18]. However, contrary to these results, numerous pilot studies and randomized clinical trials found no association of aerobic or resistance exercise trainings with serum CRP in dialysis-dependent [130–133] and non-dialysis-dependent patients [102,104,105,129]. Another marker of interest in this context is adiponectin, an adipocytokine with anti-inflammatory effects. In the general population, exercise training leads to increased adiponectin levels [105]. However, the relationship was assessed by one clinical trial in the CKD population, which found no in adiponectin levels following 4 months of aerobic exercise [33]. The presence of such an association in the CKD population remains unclear.

The effects of exercise on oxidative stress are similar to inflammation. Although the release of various reactive species and free radicals create an acute state of oxidative stress during strenuous exercise, routine exercise boosts antioxidant mechanisms and chronic resistance to oxidative stress [8,129]. In fact, the production of ROS during exercise seems to be an important signal for the long-term adaptations to training and upregulation of antioxidant enzymes [150,151]. In the very limited number of available studies investigating the effects of exercise on oxidative stress in CKD, aerobic exercise has been associated with significant reductions in lipid peroxidation, plasma F2-isoprostane, and TBARS and increases in levels of reduced glutathione [30,103,115].

These potential benefits of exercise on the cardiometabolic health raises the most pertinent question of whether exercise training may modify cardiovascular outcome in the CKD population. Nevertheless, like the observations on metabolic markers, evidence on patient outcomes currently remains inconclusive. A 2022 meta-analysis in Cochrane Database including 77 studies and 3846 patients on dialysis could not conclude on the impact of exercise in outcome including mortality and cardiovascular events [152]. The results pointed to the need for long-term studies with adequate follow-up periods to assess such outcomes in this patient population.

4. Conclusions

CKD is characterized by exceptionally high cardiovascular risk. Metabolic markers of CV risk, including body composition, lipid profile, oxidative stress, and chronic inflammation, are important predictors of morbidity and mortality in patients with CKD. Therefore, it is imperative to identify potential strategies to improve metabolic parameters and potentially subsequent cardiovascular outcome in this population. Lifestyle changes, namely dietary modifications and exercise training, have been recognized as major preventive and therapeutic interventions to promote health in both non-dialysis- and dialysis-dependent CKD [153]. Caloric restriction and healthy dietary habits may improve dyslipidemia, inflammation, and oxidative burdens in patients with non-dialysis-dependent CKD. Adher-
ence to healthy dietary patterns may benefit dialysis-dependent patients similarly, without leading to protein energy wasting or electrolyte disturbances. The common features of these healthy dietary patterns are a high intake of vegetables, fruits, and legumes. These foods have a high dietary fiber content, which may have additional health benefits in CKD. The data on the benefits of exercise training on dysmetabolism of CKD are controversial. The lack of a standardized exercise intervention specific for the CKD population, in terms of type, intensity, and duration of the exercise, may be responsible for these inconsistent findings. Furthermore, low compliance rates limit the efficacy of exercise interventions in dialysis patients [94]. Overall, lifestyle modifications may be effective and readily available interventions to improve the metabolic disturbances in patients with CKD (Figure 2). Future large-scale randomized clinical trials are required to provide conclusive evidence on the effectiveness of dietary interventions and exercise training programs in improving markers of cardiovascular risk in CKD patients.

**Figure 2.** Patients with CKD exhibit an elevated cardiovascular risk, partially mediated by hyperlipidemia, chronic inflammatory status, and oxidative stress associated with CKD. Healthy lifestyle modifications including dietary interventions and exercise training attenuate these risk factors and may decreased CV risk in this population.

**Author Contributions:** Conceptualization: T.A.I. and L.A.E.; Investigation: L.A.E. and T.A.I.; Writing–original draft: L.A.E.; Writing–review & editing: L.A.E. and T.A.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work is supported in part by the U.S. Department of Veterans Affairs under Award Number 1101CX000414, Clinical Translational Science Award UL1TR000445 from the National Center for Advancing Translational Sciences, Vanderbilt Diabetes Research and Training Center Grant P30 DK62849, Vanderbilt O’Brien Mouse Kidney Center Grant P30 DK079341, T32 DK007569 and K24 DK62849 from the National Institute of Diabetes and Digestive and Kidney Diseases, and Vanderbilt Diabetes Research and Training Center Grant P30 DK020593, Vanderbilt O’Brien Mouse Kidney Center Grant P30 DK079341, T32 DK007569 and K24 DK62849 from the National Institute of Diabetes and Digestive and Kidney Diseases, and Vanderbilt Center for Kidney Disease.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* 2004, 351, 1296–1305. [CrossRef] [PubMed]

2. Hager, M.R.; Narla, A.D.; Tannock, L.R. Dyslipidemia in patients with chronic kidney disease. *Rev. Endocr. Metab. Disord.* 2017, 18, 29–40. [CrossRef] [PubMed]

3. Romão, J.E., Jr.; Haiashi, A.R.; Elias, R.M.; Luders, C.; Ferraboli, R.; Castro, M.C.; Abensur, H. Positive acute-phase inflammatory markers in different stages of chronic kidney disease. *Am. J. Nephrol.* 2006, 26, 59–66. [CrossRef] [PubMed]
4. Ramos, L.F.; Shintani, A.; Ikizler, T.A.; Himmelfarb, J. Oxidative Stress and Inflammation Are Associated with Adiposity in Moderate to Severe CKD. *J. Am. Soc. Nephrol.* 2008, 19, 593–599. [CrossRef] [PubMed]

5. Gupta, J.; MITRA, N.; Kanetsky, P.A.; Devaney, J.; Wing, M.R.; Reilly, M.; Shah, V.O.; Balakrishnan, V.S.; Guzman, N.J.; Girndt, M.; et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin. J. Am. Soc. Nephrol.* 2012, 7, 1938–1946. [CrossRef]

6. Liakopoulos, V.; Roumeliotis, S.; Gorny, X.; Dounoussi, E.; Mertens, P.R. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. *Oxid. Med. Cell. Longev.* 2017, 2017, 3081856. [CrossRef]

7. Vaziri, N.D. Roles of oxidative stress and antioxidant therapy in chronic kidney disease and hypertension. *Curr. Opin. Nephrol. Hypertens.* 2004, 13, 93–99. [CrossRef]

8. Gomes, E.C.; Silva, A.N.; de Oliveira, M.R. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. *Oxid. Med. Cell. Longev.* 2012, 2012, 756132. [CrossRef]

9. Öberg, B.P.; McMenamin, E.; Lucas, F.L.; McMonagle, E.; Morrow, J.; Ikizler, T.A.; Himmelfarb, J. Increased prevalence of oxidative stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int.* 2004, 65, 1009–1016. [CrossRef]

10. Garcia-Bello, J.A.; Gómez-Díaz, R.A.; Contreras-Rodriguez, A.; Talavera, J.O.; Mondragón-Gonzalez, R.; Sanchez-Barbosa, L.; Diaz-Flores, M.; Valladares-Salgado, A.; Gallardo, J.M.; Aguilar-Kitsu, A.; et al. Carotid intima media thickness, oxidative stress, and inflammation in children with chronic kidney disease. *Pediatr. Nephrol.* 2014, 29, 273–281. [CrossRef]

11. Lloyd-Jones, D.M.; Hong, Y.; Labarthe, D.; Mozaffarian, D.; Appel, L.J.; Van Horn, L.; Greenlund, K.; Daniels, S.; Nichol, G.; Tomaselli, G.F.; et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association’s strategic Impact Goal through 2020 and beyond. *Circulation* 2010, 121, 586–613. [CrossRef] [PubMed]

12. Hwang, W.J.; Kang, S.J. Interventions to Reduce the Risk of Cardiovascular Disease among Workers: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* 2020, 17, 2267. [CrossRef] [PubMed]

13. Kraus, W.E.; Houmard, J.A.; Duscha, B.D.; Knetzger, K.J.; Wharton, M.B.; McCartney, J.S.; Bales, C.W.; Henes, S.; Samsa, G.P.; Otvos, J.D.; et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N. Engl. J. Med.* 2002, 347, 1483–1492. [CrossRef]

14. Zheng, G.; Qiu, P.; Xia, R.; Lin, H.; Ye, B.; Tao, J.; Chen, L. Effect of Aerobic Exercise on Inflammatory Markers in Healthy Middle-Aged and Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front. Aging Neurosci.* 2019, 11, 98. [CrossRef]

15. Cena, H.; Calder, P.C. Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. *Nutrients* 2020, 12, 334. [CrossRef]

16. Zarraga, I.G.; Schwarz, E.R. Impact of dietary patterns and interventions on cardiovascular health. *Circulation* 2006, 114, 961–973. [CrossRef] [PubMed]

17. Heidemann, C.; Schulze, M.B.; Franco, O.H.; van Dam, R.M.; Mantzoros, C.S.; Hu, F.B. Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation* 2008, 118, 230–237. [CrossRef]

18. Ikizler, T.A.; Robinson-Cohen, C.; Ellis, C.; Headley, S.A.E.; Tuttle, K.; Wood, R.J.; Evans, E.E.; Milch, C.M.; Gomes, E.C.; Silva, A.N.; de Oliveira, M.R. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. *Curr. Opin. Nephrol. Hypertens.* 2004, 13, 93–99. [CrossRef]

19. Mekki, K.; Bouzidi-bekada, N.; Kaddous, A.; Bouchenak, M. Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. *Food. Nut.* 2010, 110–115. [CrossRef]

20. Bergesio, F.; Monzani, G.; Guasparini, A.; Citiu, R.; Gallucci, M.; Cristofalo, C.; Castrignano, E.; Cupisti, A.; Barsotti, G.; Marcucci, R.; et al. Cardioprotective and renal risk factors in severe chronic renal failure: The role of dietary treatment. *Clin. Nephrol.* 2016, 84, 103–112. [CrossRef]

21. Garneata, L.; Stancu, A.; Dragomir, D.; Stefan, G.; Mircescu, G. Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression. *J. Am. Soc. Nephrol.* 2016, 27, 2164–2176. [CrossRef] [PubMed]

22. Carlsen, M.H.; Halvorsen, B.L.; Holte, K.; Bohn, S.K.; Dragland, S.; Sampson, L.; Willey, C.; Senoo, H.; Umezono, Y.; Sanada, C.; et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr. J.* 2010, 9, 3. [CrossRef] [PubMed]

23. Evangelista, L.S.; Cho, W.-K.; Kim, Y. Obesity and chronic kidney disease: A population-based study among South Koreans. *PLoS ONE* 2018, 13, e0193559. [CrossRef] [PubMed]

24. WHO. WHO Obesity and Overweight. 2022. Available online: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 17 January 2022).

25. Keaney, J.F., Jr.; Larson, M.G.; Vasan, R.S.; Wilson, P.W.; Lipinska, I.; Corey, D.; Massaro, J.M.; Sutherland, P.; Vita, J.A.; Benjamin, E.J. Obesity and systemic oxidative stress: Clinical correlates of oxidative stress in the Framingham Study. *Arterioscler. Thromb. Vasc. Biol.* 2003, 23, 434–439. [CrossRef]

26. Timpson, N.J.; Nordestgaard, B.G.; Harbord, R.M.; Zacho, J.; Frayling, T.M.; Tybjaerg-Hansen, A.; Smith, G.D. C-reactive protein levels and body mass index: Elucidating direction of causation through reciprocal Mendelian randomization. *Int. J. Obes.* 2011, 35, 300–308. [CrossRef]

27. Cohen, E.; Margalit, I.; Shochat, T.; Goldberg, E.; Krause, I. Markers of Chronic Inflammation in Overweight and Obese Individuals and the Role of Gender: A Cross-Sectional Study of a Large Cohort. *J. Inflamm. Res.* 2021, 14, 567–573. [CrossRef]
28. Choi, J.; Joseph, L.; Pilote, L. Obesity and C-reactive protein in various populations: A systematic review and meta-analysis. Obes. Rev. 2013, 14, 232–244. [CrossRef]

29. Wing, M.R.; Yang, W.; Teal, V.; Navaneethan, S.; Tao, K.; Ojo, A.; Guzman, N.N.; Reilly, M.; Wolman, M.; Rosas, S.E.; et al. Race modifies the association between adiposity and inflammation in patients with chronic kidney disease: Findings from the chronic renal insufficiency cohort study. Obesity 2014, 22, 1359–1366. [CrossRef]

30. Kraus, W.E.; Bhapkar, M.; Huffman, K.M.; Pieper, C.F.; Krupa Das, S.; Redman, L.M.; Villareal, D.T.; Rochon, J.; Roberts, S.B.; Ravussin, E.; et al. 2 years of calorie restriction and cardiometabolic risk (CALERIE): Exploratory outcomes of a multicentre, phase 2, randomised controlled trial. Lancet Diabetes Endocrinol. 2019, 7, 673–683. [CrossRef]

31. Harvie, M.N.; Pegington, M.; Mattson, M.P.; Frystyk, J.; Dillon, B.; Evans, G.; Cuzzick, J.; Jebb, S.A.; Martin, B.; Cutler, R.G.; et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: A randomized trial in young overweight women. Int. J. Obes. 2011, 35, 714–727. [CrossRef]

32. Dandona, P.; Mohanty, P.; Ghanim, H.; Aljada, A.; Browne, R.; Hamouda, W.; Prabhala, A.; Afzal, A.; Garg, R. The suppressive effect of dietary restriction and weight loss in the obese on the generation of reactive oxygen species by leukocytes, lipid peroxidation, and protein carbonylation. J. Clin. Endocrinol. Metab. 2001, 86, 355–362.

33. Aydemir, N.; Pike, M.M.; Alsouqi, A.; Headley, S.A.E.; Tuttle, K.; Evans, E.E.; Milch, C.M.; Moody, K.A.; Germain, M.; Lipworth, L.; et al. Effects of diet and exercise on adipocytokine levels in patients with moderate to severe chronic kidney disease. Nutr. Metab. Cardiovasc. Dis. 2020, 30, 1375–1381. [CrossRef]

34. Lambert, K.; Beer, J.; Dumont, R.; Hewitt, K.; Manley, K.; Meade, A.; Salamon, K.; Campbell, K. Weight management strategies for those with chronic kidney disease: A consensus report from the Asia Pacific Society of Nephrology and Australia and New Zealand Society of Nephrology 2016 renal dietitians meeting. Nephrology 2018, 23, 912–920. [CrossRef]

35. Ikizler, T.A. Optimal nutrition in hemodialysis patients. Adv. Chronic. Kidney Dis. 2013, 20, 181–189. [CrossRef]

36. Soltani, S.; Jayedi, A.; Shab-Bidar, S.; Becerra-Tomás, N.; Salas-Salvadó, J. Adherence to the Mediterranean Diet in Relation to All-Cause Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. Adv. Nutr. 2019, 10, 1029–1039. [CrossRef]

37. Martinez-González, M.A.; Gea, A.; Ruiz-Canela, M. The Mediterranean Diet and Cardiovascular Health. Circ. Res. 2019, 124, 779–798. [CrossRef]

38. Steckhan, N.; Hohmann, C.-D.; Kessler, C.; Dobos, G.; Michalsen, A.; Cramer, H. Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: A systematic review and meta-analysis. Nutrition 2016, 32, 338–348. [CrossRef]

39. Chrysohou, C.; Panagiotakos, D.B.; Pitsavos, C.; Das, U.N.; Stefanadis, C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J. Am. Coll. Cardiol. 2004, 44, 152–158. [CrossRef]

40. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutierrez, V.; Fiol, M.; Lapetra, J.; et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N. Engl. J. Med. 2013, 368, 1279–1290. [CrossRef]

41. Huang, X.; Jiménez-Moleón, J.J.; Lindholm, B.; Cederholm, T.; Arnlöv, J.; Risérus, U.; Sjögren, P.; Carrero, J.J. Mediterranean diet, kidney function, and mortality in men with CKD. Clin. J. Am. Soc. Nephrol. 2013, 8, 1548–1555. [CrossRef]

42. Smyth, A.; Griffin, M.; Yusuf, S.; Mann, J.F.; Reddan, D.; Canavan, M.; Newell, J.; O’Donnell, M. Diet and Major Renal Outcomes: A Prospective Cohort Study. The NIH-AARP Diet and Health Study. The NIH-AARP Diet and Health Study. J. Ren. Nutr. 2016, 26, 288–298. [CrossRef] [PubMed]

43. Lin, J.; Fung, T.T.; Hu, F.B.; Curhan, G.C. Association of Dietary Patterns With Albuminuria and Kidney Function Decline in Older White Women: A Subgroup Analysis From the Nurses’ Health Study. Am. J. Kidney Dis. 2011, 57, 245–254. [CrossRef] [PubMed]

44. Banerjee, T.; Crews, D.C.; Tuot, D.S.; Pavkov, M.E.; Burrows, N.R.; Stack, A.G.; Saran, R.; Bragg-Gresham, J.; Powe, N.R. Poor adherence to a DASH dietary pattern is associated with higher risk of ESRD among adults with moderate chronic kidney disease and hypertension. Kidney Int. 2019, 95, 1433–1442. [CrossRef]

45. Saglimbene, V.M.; Wong, G.; Craig, J.C.; Ruospo, M.; Palmer, S.C.; Campbell, K.; Garcia-Larsen, V.; Natale, P.; Teixeira-Pinto, A.; Carrero, J.J.; et al. The Association of Mediterranean and DASH Diets with Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study. J. Am. Soc. Nephrol. 2018, 29, 1741–1751. [CrossRef] [PubMed]

46. Bowden, K.; Gray, N.A.; Swanepeol, E.; Wright, H.H. A Mediterranean lifestyle is associated with favourable cardiometabolic markers in people with non-diabetes dependent chronic kidney disease. J. Nutr. Sci. 2021, 10, e42. [CrossRef]

47. Picard, K.; Senior, P.A.; Adam-Perez, S.; Jindal, K.; Richard, C.; Mager, D.R. Low Mediterranean Diet scores are associated with reduced kidney function and health related quality of life but not other markers of cardiovascular risk in adults with diabetes and chronic kidney disease. Nutr. Metab. Cardiovasc. Dis. 2021, 31, 1445–1453. [CrossRef]

48. Pronczuk, A.; Kipervarg, Y.; Hayes, K.C. Vegetarians have higher plasma alpha-tocopherol relative to cholesterol than do nonvegetarians. J. Am. Coll. Nutr. 1992, 11, 50–55. [CrossRef]

49. Wang, F.; Zheng, J.; Yang, B.; Jiang, J.; Fu, Y.; Li, D. Effects of Vegetarian Diets on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J. Am. Heart Assoc. 2015, 4, e002408. [CrossRef]

50. Kim, M.K.; Cho, S.W.; Park, Y.K. Long-term vegetarians have low oxidative stress, body fat, and cholesterol levels. Nutr. Res. Pract. 2012, 6, 155–161. [CrossRef]
76. Shen, Q.; Zhao, L.; Tuohy, K.M. High-level dietary fibre up-regulates colonic fermentation and relative abundance of saccharolytic bacteria within the human faecal microbiota in vitro. *Eur. J. Nutr.* 2012, 51, 693–705. [CrossRef]

77. Rossi, M.; Johnson, D.W.; Xu, H.; Carrero, J.J.; Pascoe, E.; French, C.; Campbell, K.L. Dietary protein-fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients. *Nutr. Metab. Cardiovasc. Dis.* 2015, 25, 860–865. [CrossRef]

78. Salmean, Y.A.; Segal, M.S.; Palii, S.P.; Dahl, W.J. Fiber supplementation lowers plasma p-cresol in chronic kidney disease patients. *J. Ren. Nutr.* 2015, 25, 316–320. [CrossRef]

79. Camerotto, C.; Cupisti, A.; D’Alessandro, C.; Muzio, F.; Gallieni, M. Dietary Fiber and Gut Microbiota in Renal Diets. *Nutrients* 2019, 11, 2149. [CrossRef]

80. Meijers, B.K.; De Preter, V.; Verbeke, K.; Vanrenterghem, Y.; Evenepoel, P. p-Cresyl sulfate serum concentrations in haemodialysis patients are reduced by the prebiotic oligofructose-enriched inulin. *Nephrol. Dial. Transplant.* 2010, 25, 219–224. [CrossRef]

81. Sirich, T.L.; Plummer, N.S.; Gardner, C.D.; Hostetter, T.H.; Meyer, T.W. Effect of increasing dietary fiber on plasma levels of colon-derived metabolites in hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* 2014, 9, 1603–1610. [CrossRef]

82. Pasman, W.J.; Saris, W.H.; Wauters, M.A.; Westerterp-Plantenga, M.S. Effect of one week of fibre supplementation on hunger and satiety ratings and energy intake. *Appetite* 1997, 29, 77–87. [CrossRef]

83. Desmeules, S.; Lévesque, R.; Jaussent, I.; Leray-Moragues, H.; Chalabi, L.; Canaud, B. Creatinine index and lean body mass are excellent predictors of long-term survival in haemodiafiltration patients. *Nephrol. Dial. Transplant.* 2004, 19, 1182–1189. [CrossRef] [PubMed]

84. Sietsema, K.E.; Amato, A.; Adler, S.G.; Brass, E.P. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int.* 2004, 65, 719–724. [CrossRef] [PubMed]

85. Thorogood, A.; Mottillo, S.; Shimony, A.; Filion, K.B.; Genest, J.; Pilote, L.; Poirier, P.; Schiffrin, E.L.; Eisenberg, M.J. Isolated aerobic exercise and weight loss: A systematic review and meta-analysis of randomized controlled trials. *Am. J. Med.* 2011, 124, 747–755. [CrossRef] [PubMed]

86. Wen, H.; Wang, L. Reducing effect of aerobic exercise on blood pressure of essential hypertensive patients: A meta-analysis. *Medicine* 2017, 96, e6150. [CrossRef] [PubMed]

87. Wood, G.; Taylor, E.; Ng, V.; Murrell, A.; Patil, A.; van der Touw, T.; Sigal, R.; Wolden, M.; Smart, N. Determining the effect size of aerobic exercise training on the standard lipid profile in sedentary adults with three or more metabolic syndrome factors: A systematic review and meta-analysis of randomised controlled trials. *Br. J. Sports Med.* 2021. [CrossRef]

88. Pischon, T.; Hankinson, S.E.; Hotamisligil, G.S.; Rifai, N.; Rimm, E.B. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obes. Res.* 2003, 11, 1055–1064. [CrossRef]

89. Berggren, J.R.; Hulver, M.W.; Dohm, G.L.; Houmard, J.A. Weight loss and exercise: Implications for muscle lipid metabolism and insulin action. *Med. Sci. Sports Exerc.* 2004, 36, 1191–1195. [CrossRef]

90. Shaw, C.S.; Clark, J.; Wagenmakers, A.J. The effect of exercise and nutrition on intramuscular fat metabolism and insulin sensitivity. *Ann. Rev. Nutr.* 2010, 30, 13–34. [CrossRef]

91. Willey, K.A.; Singh, M.A. Battling insulin resistance in elderly obese people with type 2 diabetes: Bring on the heavy weights. *Diabetes Care* 2003, 26, 1580–1588. [CrossRef]

92. Ballor, D.L.; Keesey, R.E. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int. J. Obes.* 1991, 15, 717–726. [PubMed]

93. Willis, L.H.; Slenz, C.A.; Bateman, L.A.; Shields, A.T.; Piner, L.W.; Bales, C.W.; Houmard, J.A.; Kraus, W.E. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J. Appl. Physiol.* 2012, 113, 1831–1837. [CrossRef] [PubMed]

94. Moinuddin, I.; Leehey, D.J. A comparison of aerobic exercise and resistance training in patients with and without chronic kidney disease. *Adv. Chronic. Kidney Dis.* 2008, 15, 83–96. [CrossRef] [PubMed]

95. Roberts, C.K.; Vaziri, N.D.; Barnard, R.J. Effect of diet and exercise intervention on blood pressure, insulin, oxidative stress, and nitric oxide availability. *Circulation* 2002, 106, 2530–2532. [CrossRef]

96. Abramson, J.L.; Vaccarino, V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch. Intern. Med.* 2002, 162, 1286–1292. [CrossRef]

97. Esposito, K.; Pontillo, A.; Di Palo, C.; Giugliano, G.; Masella, M.; Marfella, R.; Giugliano, D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. *JAMA* 2003, 289, 1799–1804. [CrossRef]

98. Soukup, J.T.; Koval, K.E. A review of the effects of resistance training for individuals with diabetes mellitus. *Diabetes Educ.* 1993, 19, 307–312. [CrossRef]

99. Gacita, T.; Karachon, L.; Romero, E.; Parra, P.; Poblete, C.; Russell, J.; Rodrigo, R. Effects of resistance training on oxidative stress-related biomarkers in metabolic diseases: A review. *Sport Sci. Health* 2018, 14, 1–7. [CrossRef]

100. Cerqueira, É.; Marinho, D.A.; Neiva, H.P.; Lourenço, O. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. *Front. Physiol.* 2020, 10, 1550. [CrossRef]
102. Castaneda, C.; Gordon, P.L.; Uhlin, K.L.; Levey, A.S.; Khayyas, J.; Dwyer, J.T.; Fielding, R.A.; Roubenoff, R.; Singh, M.F. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Ann. Intern. Med.* 2001, 135, 965–976. [CrossRef]

103. Pechter, U.; Ots, M.; Mesikepp, S.; Zilmer, K.; Kulissaar, T.; Vihamemm, T.; Zilmer, M.; Maaroos, J. Beneficial effects of water-based exercise in patients with chronic kidney disease. *Int. J. Rehabil. Res.* 2003, 26, 153–156.

104. Mazurek, T.; Zhang, L.; Zalewski, A.; Mannion, J.D.; Diehl, J.T.; Arafat, H.; Sarov-Blat, L.; O’Brien, S.; Keiper, E.A.; Johnson, A.G. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003, 108, 2460–2466. [CrossRef]

105. Yu, N.; Ruan, Y.; Gao, X.; Sun, J. Systematic Review and Meta-Analysis of Randomized, Controlled Trials on the Effect of Exercise on Serum Lipin and Adiponectin in Overweight and Obese Individuals. *Horm. Metab. Res.* 2017, 49, 164–173. [CrossRef]

106. Vanden Wyngaert, K.; Craenenbroeck, A.; Biesen, W.; Dhondt, A.; Tanghe, A.; Ginckel, A.; Celis, B.; Calders, P. The effects of aerobic exercise on eGFR, blood pressure and VO2peak in patients with chronic kidney disease stages 3–4: A systematic review and meta-analysis. *PLoS ONE* 2018, 13, e0203662. [CrossRef]

107. Greenwood, S.A.; Koufaki, P.; Mercer, T.H.; MacLaughlin, H.L.; Rush, R.; Lindup, H.; O’Connor, E.; Jones, C.; Hendry, B.M.; Castaneda-Sceppa, C. Effect of a Caffeine-Free Supplement on Exercise Capacity in Patients with Chronic Kidney Disease. *Clin. J. Am. Soc. Nephrol.* 2016, 11, 2083–2092. [CrossRef]

108. Baria, F.; Kamimura, M.A.; Aoike, D.T.; Ammirati, A.; Leister Rocha, M.; de Mello, M.T.; Cuppari, L. Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients. *Nephrol. Dial. Transplant.* 2014, 29, 857–864. [CrossRef]

109. Afshar, R.; Shegarfy, L.; Shavandi, N.; Sanavi, S. Effects of aerobic exercise and resistance training on lipid profiles and inflammation status in patients on maintenance hemodialysis. *Indian J. Nephrol.* 2010, 20, 185–189.

110. Castaneda, C.; Gordon, P.L.; Parker, R.C.; Uhlin, K.L.; Roubenoff, R.; Levey, A.S. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am. J. Kidney Dis.* 2004, 43, 607–616. [CrossRef]

111. Koufaki, P.; Nash, P.F.; Mercer, T.H. Assessing the efficacy of exercise training in patients with chronic disease. *J. Cardiol.* 2010, 21, 149–159. [CrossRef][PubMed]

112. Johansen, K.L.; Painter, P.L.; Sakkas, G.K.; Gordon, P.; Doyle, J.; Shubert, T. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. *J. Am. Soc. Nephrol.* 2006, 17, 2307–2314. [CrossRef][PubMed]

113. Cheema, B.; Abas, H.; Smith, B.; O’Sullivan, A.; Chan, M.; Patwardhan, A.; Kelly, J.; Gillin, A.; Pang, G.; Lloyd, B.; et al. Progressive Exercise for Anabolism in Kidney Disease (PEAK): A Randomized, Controlled Trial of Resistance Training during Hemodialysis. *J. Am. Soc. Nephrol.* 2007, 18, 1594–1601. [CrossRef]

114. Song, W.J.; Sohn, K.Y. Effects of progressive resistance training on body composition, physical fitness and quality of life of patients on hemodialysis. *J. Korean Acad. Nurs.* 2012, 42, 947–956. [CrossRef][PubMed]

115. Chen, P.-Y.; Huang, Y.-C.; Kao, Y.-H.; Chen, J.-Y. Effects of an Exercise Program on Blood Biochemical Values and Exercise Stage of Chronic Kidney Disease Patients. *J. Nurs. Res.* 2010, 18, 98–107. [CrossRef]

116. Miele, E.M.; Headley, S.A.E.; Germain, M.; Joubert, J.; Herrick, S.; Milch, C.; Evans, E.; Cornelius, A.; Brewer, B.; Taylor, B.; et al. High-density lipoprotein particle pattern and overall lipid responses to a short-term moderate-intensity aerobic exercise training intervention in patients with chronic kidney disease. *Clin. Kidney J.* 2017, 10, 524–531. [CrossRef]

117. Toyama, K.; Sugiyama, S.; Oka, H.; Sumida, H.; Ogawa, H. Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. *J. Cardioi.* 2010, 56, 142–146. [CrossRef]

118. Headley, S.; Germain, M.; Milch, C.; Pescatello, L.; Coughlin, M.A.; Nindl, B.C.; Cornelius, A.; Sullivan, S.; Gregory, S.; Wood, R. Exercise Training Improves HR Responses and VO2peak in Predialysis Kidney Patients. *Med. Sci. Sports Exerc.* 2012, 44, 2392–2399. [CrossRef]

119. Goldberg, A.P.; Geltman, E.M.; Gavin, J.R., 3rd; Carney, R.M.; Hagberg, J.M.; Delmez, J.A.; Naumovich, A.; Oldfield, M.H.; Harter, H.R. Exercise training reduces coronary risk and effectively rehabilitates hemodialysis patients. *Nephron* 1986, 42, 311–316. [CrossRef]

120. Gordon, L.; McGrowder, D.A.; Pena, Y.T.; Cabrera, E.; Lawrence-Wright, M. Effect of exercise therapy on lipid parameters in patients with end-stage renal disease on hemodialysis. *J. Lab. Physicians* 2012, 4, 17–23. [CrossRef]

121. Reboreda Mde, M.; Henrique, D.M.; Faria Rde, S.; Chauobah, A.; Bastos, M.G.; de Paula, R.B. Exercise training during hemodialysis reduces blood pressure and increases physical functioning and quality of life. *Artif. Organs* 2010, 34, 586–593. [CrossRef][PubMed]
124. Christensen, R.H.; Wedell-Neergaard, A.-S.; Lehrskov, L.L.; Legaard, G.E.; Dorph, E.; Larsen, M.K.; Lau, N. O.; Fagerlind, S.R.; Seide, S.K.; Nymand, S.; et al. Effect of Aerobic and Resistance Exercise on Cardiac Adipose Tissues: Secondary Analyses From a Randomized Clinical Trial. *JAMA Cardiol.* 2019, 4, 778–787. [CrossRef] [PubMed]

125. Mercer, T.H.; Koufaki, P.; Naish, P.F. Nutritional status, functional capacity and exercise rehabilitation in end-stage renal disease. *Clin. Nephrol. 2004*, 61 (Suppl. S1), S54–S59. [PubMed]

126. Molsted, S.; Eidemak, I.; Sorensen, H.T.; Kristensen, J.H. Five months of physical exercise in hemodialysis patients: Effects on aerobic capacity, physical function and self-rated health. *Neurolon. Clin. Pract. 2004*, 96, C76–C81. [CrossRef]

127. Yurtkuran, M.; Alp, A.; Yurtkuran, M.; Dilek, K. A modified yoga-based exercise program in hemodialysis patients: A randomized controlled study. *Complement. Ther. Med.* 2007, 15, 164–171.

128. van Vlietseren, M.C.; de Greef, M.H.; Huisman, R.M. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: Results of a randomized clinical trial. *Nephrol. Dial. Transplant.* 2005, 20, 141–146. [CrossRef]

129. Evelo, C.T.; Palmen, N.G.; Artur, Y.; Janssen, G.M. Changes in blood glutathione concentrations, and in erythrocyte glutathione reductase and glutathione S-transferase activity after running training and after participation in contests. *Eur. J. Appl. Physiol. Occup. Physiol.* 1992, 64, 354–358.

130. Koppole, J.D.; Wang, H.; Casaburi, R.; Fournier, M.; Lewis, M.I.; Taylor, W.; Storer, T.W. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. *J. Am. Soc. Nephrol.* 2007, 18, 2975–2986. [CrossRef]

131. Toussaint, N.D.; Polkinghome, K.R.; Kerr, P.G. Impact of intradialytic exercise on arterial compliance and B-type natriuretic peptide levels in hemodialysis patients. *Hemodial. Int.* 2008, 12, 254–263.

132. Wilund, K.R.; Tomayko, E.J.; Wu, P.T.; Ryong Chung, H.; Vallurupalli, S.; Lakshminarayanan, B.; Fernhall, B. Intradialytic exercise training reduces oxidative stress and epicardial fat: A pilot study. *Nephrol. Dial. Transplant.* 2010, 25, 2695–2701. [CrossRef] [PubMed]

133. Gołębiewski, T.; Kusztal, M.; Weyde, W.; Dźubiak, W.; Wóżniewski, M.; Madziarska, K.; Krajewska, M.; Letachowicz, K.; Strempaska, B.; Klinger, M. A program of physical rehabilitation during hemodialysis sessions improves the fitness of dialysis patients. *Kidney Blood Press. Res.* 2012, 35, 290–296. [CrossRef] [PubMed]

134. Daniilidis, M.; Koudi, E.; Giagoudaki, F.; Efta, A.; Nikolaides, P.; Vasilaki, A.; Deligiannis, A.; Tourkantonis, A. The immune response in hemodialysis patients following physical training. *Sport Sci. Health* 2004, 1, 11–16. [CrossRef]

135. Zafuska, A.; Zafuska, W.T.; Bednarek-Skublewska, A.; Ksiazek, A. Nutrition and hydration status improve with exercise training using stationary cycling during hemodialysis (HD) in patients with end-stage renal disease (ESRD). *Ann. Univ. Mariae Curie Sklodowska Med.* 2002, 57, 342–346. [PubMed]

136. Cheema, B.S.; Abas, H.; Smith, B.C.; O’Sullivan, A.J.; Chan, M.; Patwardhan, A.; Kelly, J.; Gillin, A.; Pang, G.; Lloyd, B.; et al. Effect of resistance training during hemodialysis on circulating cytokines: A randomized controlled trial. *Eur. J. Appl. Physiol. 2011*, 111, 1437–1445. [CrossRef] [PubMed]

137. Viana, J.L.; Kosmadakis, G.C.; Watson, E.L.; Bevington, A.; Feehally, J.; Bishop, N.C.; Smith, A.C. Evidence for Anti-Inflammatory Effects of Exercise in CKD. *J. Am. Soc. Nephrol.* 2014, 25, 2121–2130. [CrossRef] [PubMed]

138. Leehey, D.J.; Moinuddin, I.; Bast, J.P.; Qureshi, S.; Jelinek, C.S.; Cooper, C.; Edwards, L.C.; Smith, B.M.; Collins, E.G. Aerobic exercise in obese diabetic patients with chronic kidney disease: A randomized and controlled pilot study. *Cardiovasc. Diabetol.* 2009, 8, 62. [CrossRef]

139. Aoike, D.T.; Baria, F.; Kamimura, M.A.; Ammirati, A.; de Mello, M.T.; Cuppari, L. Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. *Int. Urol. Nephrol.* 2015, 47, 359–367. [CrossRef]

140. Colonetti, T.; Grande, A.J.; Amaral, M.C.; Colonetti, L.; Uggiioni, M.L.; da Rosa, M.; Hernandez, A.V.; Tse, G.; Liu, T.; Nerlekar, N.; et al. Effect of exercise on epicardial adipose tissue in adults with chronic kidney disease: A randomized and controlled pilot study. *Cardiovasc. Diabetol.* 2011, 10, 81. [CrossRef]

141. Jeong, J.H.; Biruete, A.; Tomayko, E.J.; Wu, P.T.; Fitschen, P.; Chung, H.R.; Ali, M.; McAuley, E.; Fernhall, B.; Phillips, S.A.; et al. Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients. *Kidney Int.* 2016, 99, 777–786. [CrossRef]

142. Chan, K.N.; Chen, Y.; Lit, Y.; Massaband, P.; Kiratli, J.; Rabkin, R.; Myers, J.N. A randomized controlled trial of exercise to prevent muscle mass and functional loss in elderly hemodialysis patients: Rationale, study design, and baseline sample. *Contemp. Clin. Trials Commun.* 2019, 15, 100365. [CrossRef] [PubMed]

143. Kannan, U.; Vasudevan, K.; Balasubramaniam, K.; Yerrabelli, D.; Shanmugavel, K.; John, N.A. Effect of exercise intensity on lipid profile in sedentary obese adults. *J. Clin. Diagn. Res. 2014*, 8, BC08–BC10. [CrossRef] [PubMed]

144. Liu, Y.-M.; Chung, Y.-C.; Chang, J.-S.; Yeh, M.-L. Effects of Aerobic Exercise During Hemodialysis on Physical Functional Performance and Depression. *Biol. Res. Nurs.* 2015, 17, 214–221. [CrossRef] [PubMed]

145. Heiwe, S.; Jacobson, S.H. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst. Rev.* 2011, Cd003236. [CrossRef] [PubMed]

146. Beavers, K.M.; Brinkley, T.E.; Nicklas, B.J. Effect of exercise training on chronic inflammation. *Clin. Chim. Acta Int. J. Clin. Chem.* 2010, 411, 785–793. [CrossRef] [PubMed]
147. Shiraishi, F.G.; Stringuetta Belik, F.; Oliveira, E.S.V.R.; Martin, L.C.; Hueb, J.C.; Gonçalves Rde, S.; Caramori, J.C.; Barreti, P.; Franco, R.J. Inflammation, diabetes, and chronic kidney disease: Role of aerobic capacity. *Exp. Diabetes Res.* **2012**, 2012, 750286. [CrossRef]

148. Mafra, D.; Deleaval, P.; Teta, D.; Cleaud, C.; Arkouche, W.; Jolivot, A.; Fouque, D. Influence of inflammation on total energy expenditure in hemodialysis patients. *J. Ren. Nutr.* **2011**, 21, 387–393. [CrossRef]

149. Anand, S.; Chertow, G.M.; Johansen, K.L.; Grimes, B.; Kurella Tamura, M.; Dalrymple, L.S.; Kaysen, G.A. Association of self-reported physical activity with laboratory markers of nutrition and inflammation: The Comprehensive Dialysis Study. *J. Ren. Nutr.* **2011**, 21, 429–437. [CrossRef]

150. Gomez-Cabrera, M.C.; Domenech, E.; Viña, J. Moderate exercise is an antioxidant: Upregulation of antioxidant genes by training. *Free Radic. Biol. Med.* **2008**, 44, 126–131. [CrossRef]

151. Wang, F.; Wang, X.; Liu, Y.; Zhang, Z. Effects of Exercise-Induced ROS on the Pathophysiological Functions of Skeletal Muscle. *Oxid. Med. Cell. Longev.* **2021**, 2021, 3846122. [CrossRef]

152. Bernier-Jean, A.; Beruni, N.A.; Bondorno, N.P.; Williams, G.; Teixeira-Pinto, A.; Craig, J.C.; Wong, G. Exercise training for adults undergoing maintenance dialysis. *Cochrane Database Syst. Rev.* **2022**, 1, Cd014653. [PubMed]

153. KDIGO. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Int. Soc. Nephrol.* **2013**, 3, 1–150.