Exercise in Men and Women with Pre-Dialysis Chronic Kidney Disease: A Review

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Abstract
Chronic kidney disease (CKD) is a gradual loss of renal function, and is associated with multiple health consequences. It is well recognized that patients with CKD have poor physical function negatively impacting quality of life and increasing morbidity. This review paper summarizes the effectiveness of exercise on physiological health in adult men and women with predialysis (stages 1 to 3) CKD. The overall objective of this paper is to determine which type of exercise provides the greatest benefit to CKD patients. Three types of exercise interventions are studied in this review; moderate intensity aerobic exercise, resistance training and a combination of aerobic and resistance training. We also briefly discuss the recent data on high intensity interval training in CKD patients. This review focuses on multiple physiological outcomes, including shifts in aerobic capacity (VO2 max), strength, arterial stiffness, oxidative stress, inflammation, blood pressure, and glomerular filtration. The overall findings of the studies analyzed suggest that training either improves or maintains exercise capacity and physical functioning among non-dialysis dependent CKD patients, with no study indicating lowered kidney function as a result of exercise. In addition, several studies suggest that oxidative stress, blood pressure and inflammation all improve in response to exercise. In conclusion, exercise prescription should be considered more often as this review shows strong evidence that moderate-intensity physical activity is safe and associated with improved physiological health in pre-dialysis CKD patients.

Keywords
Physiology — Health Science — High Intensity Interval Training — Kidney Disease

1. Introduction
Chronic kidney disease (CKD) is becoming more prevalent today and is associated with high costs and poor outcomes of treatments, making it a worldwide public health threat (Tonelli and Riella 2014). The high occurrences of CKD are in part due to the rising prevalence of diabetes and obesity, which according to the National Kidney Foundation (NKF), are the two main causes of CKD which are responsible for over 60\% of cases (National Kidney Foundation, 2016). CKD is a progressive disease that is defined according to the level of kidney function and kidney damage. The level of function and failure can be classified into stages, which provides a template for the institution of preventative measures (Hogg et al. 2003). Stage 1 is the least severe stage of CKD, while stage 5 is the most severe stage of the disease. The main determinant of the patient’s classification is their glomerular filtration rate (GFR). GFR is defined as the rate at which the kidneys can filter waste and excess fluid out of the blood, the lower the GFR the more progressed the disease is. There are multiple ways to calculate GFR which results in an estimated GFR measurement. The estimated GFR is a validated method and is a good indicator of kidney function. This review focuses on pre-dialysis patients with a glomerular filtration rate of 30-90 ml/min/1.73m², which correlates to stages 1 to 3, as outlined by the NKF in Table 1. This population was chosen for this review because addressing the issues CKD patients live with should be done before the disease becomes too severe. Additionally, most of the research regarding exercise prescription for individuals affected by CKD has been completed on dialysis patients.

Individuals diagnosed with CKD experience fatigue, weakness, and joint pain due to lack of oxygenated, waste free blood circulating the body. These symptoms can cause difficulty exercising resulting in markedly lower levels of daily physical activity compared to a healthy individual, in turn, increasing the risk of coronary artery disease (Cook et al. 2008). The exercise ability of CKD patients is often measured in tests such as the 6-minute walk test (SMWT) and the sit-to-stand test. The SMWT measures the distance an individual can travel in 6 minutes on a hard, flat surface, in order to analyze the individual’s exercise capacity and tolerance. It has been found that men and women with CKD perform at about half the exercise capacity of “normal” sedentary individuals (Cook et al. 2008). One important treatment consideration is the use of “exercise as medicine” in CKD. Exercise prescriptions are a treatment plan for many chronic diseases, but have only recently been considered for CKD patients. Exercise interventions can prevent the adverse outcomes of CKD, such as cardiovascular complications; it also slows the progression of the disease and improve survival and quality of life (Levey
and Coresh, 2012). Mustata et al found that at the initiation of dialysis, individuals that were sedentary during earlier stages had a 62\% higher risk of dying when compared with non-sedentary patients (Mustata et al. 2010). It was found that VO$_{2\text{peak}}$ was the strongest predictor of survival in CKD patients. VO$_{2\text{peak}}$ is the highest volume of oxygen consumed during an exercise test, which can be improved by exercise training (Howden et al. 2012). Other improvements that have been known to result from exercise interventions include reduced blood pressure and inflammation, improved oxidative stress, and increased muscle strength (Howden et al. 2012).

This review focuses on the impact of three different types of exercise interventions, namely moderate intensity training, resistance training, and a combination of the two on multiple outcomes including: shifts in aerobic capacity (VO$_2$ max), strength, arterial stiffness, oxidative stress, inflammation, blood pressure, and GFR. Furthermore, the new exercise area of high intensity interval training (HIIT) is briefly investigated. This review concludes with an overall exercise recommendations for CKD and future research directions.

### 2. Moderate Intensity Aerobic Training

The most researched exercise prescription pertaining to CKD patients has been aerobic training. This review will focus on four studies that used aerobic exercise to conduct research. They ranged between modes of exercise prescribed including: aquatic exercises (Pechter et al, 2003), treadmill walking (Headley et al. 2014), a combination of elliptical trainer, treadmill walking, and stationary cycling (Mustata et al, 2010), as well as a combination of elliptical trainer, treadmill walking, stationary cycling and given the additional choice of Stairmaster (Headley et al, 2012). Study designs included random controlled trials and non-random trials. Table 2 gives a summary of the studies investigated, including their aerobic intervention and duration.

#### 2.1 Aerobic Capacity

*wk: week, mo:months* Research has shown that aerobic capacity, as measured by peak oxygen consumption, was the strongest predictor of mortality (Howden et al. 2012). Therefore, improving aerobic capacity in stage 1-3 CKD patients may lead to higher survival rates, a very important possible consequence of this type of exercise intervention (Bronas et al. 2009). Mustata et al found an increase in both the exercise group’s mean VO$_{2\text{peak}}$ (+2.4 ml O$_2$/kg/min) and the control group’s mean VO$_{2\text{peak}}$ (+0.7 ml O$_2$/kg/min) after 12 months of aerobic intervention (Mustata et al. 2010). The more significant increase in the intervention group shows promising health improvements with the use of exercise. Pechter and colleagues also found that mean peak oxygen consumption at maximum load was improved, but not significantly when compared to the control group, where the experimental group improved 0.4ml/kg/min and the control group improved 0.3ml/kg/min after the 12 week intervention (Pechter et al 2003). This increase in VO$_{2\text{peak}}$ means there was more oxygen effectively carried throughout the blood which can have a beneficial effect on strength and endurance leading to mobility independence.

#### 2.2 Arterial Stiffness

Arterial stiffness is caused by a reduction in arterial compliance that occurs due to arterial damage and is a known symptom in CKD patients due to their dysregulation of phosphorus-calcium balance (Bronas et al. 2009). High arterial stiffness can lead to cardiovascular risks such as stroke or myocardial infarction (Sarnak et al. 2003). Mustata and colleagues found that one year of aerobic training improves arterial stiffness in predialysis patients with the exercise group’s mean augmentation index dropping 1.5\%, while the control group’s mean only dropped 0.5\% (P=0.003) (Mustata et al. 2010). Mustata’s research team used augmentation indexes, but in future studies pulse wave velocity should be used as the measure of oxidative stress as it gives a more accurate measurement of arterial stiffness (Howden et al. 2012). In contrast to Mustata’s findings, Headley et al found that the 16-week exercise program did not influence the arterial stiffness for either the control or exercise group (Headley et al. 2014). This could be due to the lower intensity or shorter intervention period as Headley aimed for a 50-60\% VO$_{2\text{peak}}$ compared to Mustata et al, who completed the intervention up to 70\% VO$_{2\text{peak}}$. Arterial stiffness can alter the pressure-volume relationship within the myocardium which causes an increase in systolic blood pressure (Bronas et al. 2009). If blood pressure can be reduced to 175/75 mmHg it has been shown to improve CKD outcomes by slowing the deterioration of renal function (Howden et al. 2012). Blood pressure changes in response to aerobic exercise were recorded in one of the studies investi-
Table 2. Summary of investigated studies for moderate intensity aerobic training interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Patients, (Control/ Intervention)</th>
<th>Exercise Intervention apparatus</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Mustata et al. 2010</td>
<td>Random Control Trial</td>
<td>10/10</td>
<td>Supervised treadmill, stationary cycle, elliptical trainer 5-60min, 3x wk.</td>
<td>4 wk supervised, 11 mo home based 16 wk</td>
</tr>
<tr>
<td>Headley et al. 2014</td>
<td>Randomized Control Trial with Parallel-group design</td>
<td>21/25</td>
<td>5 minute warm up, 30 minutes treadmill walking (50-60% VO2max), 5 minute cool down</td>
<td>16 wk</td>
</tr>
<tr>
<td>Headley et al. 2012</td>
<td>Random Control Trial</td>
<td>11/10</td>
<td>Choice of treadmill, cycle ergometers, elliptical machines and the Stairmaster. Up to 55 min, 3x wk</td>
<td>48 wk</td>
</tr>
<tr>
<td>Pechter et al. 2003</td>
<td>Non-random Trial</td>
<td>9/17</td>
<td>Aerobic aquatic exercises. 30 min, 2x wk</td>
<td>12 wk</td>
</tr>
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</table>

gated in this review. Pechter et al found a reduction in resting blood pressure from 147/87 to 139/85 mmHg in the exercise group, whereas the control group only went from 148/90 to 147/87 mmHg (Pechter et al. 2003).

2.3 Oxidative Stress
Oxidative stress is a measure by the amount of reactive oxygen species (ROS) in the body produced during normal aerobic processes (BioTek, 2016). They can react and modify other oxygen-rich molecules such as DNA or proteins. CKD patients often have an imbalance in these species resulting in high oxidative stress leading to cardiovascular diseases such as heart failure (Bronas et al. 2009). Only one of the studies investigated reported on the effects of oxidative stress from aerobic exercise. Pechter et al found a significant improvement in anti-oxidative levels in response to 12 weeks of aquatic training intervention, compared to sedentary control groups. To investigate this, they measured products of lipid peroxidation; total glutathione, its oxidized and reduced forms, glutathione redox in serum, and isoprostanes in urine, finding positive results in all products (Pechter et al. 2003). However, this was a pilot study; therefore, it is difficult to generalize this finding.

2.4 Glomular Filtration Rate
Recording the GFR over a 3-month period gives the best estimate of kidney function (National Kidney Foundation, 2016). As the kidneys deteriorate, the GFR value decreases. Pechter et al used the Cockcroft-Gault formula to find that the GFR in the aquatic exercise group improved from 62.9 to 67.1ml/min, whereas the control group’s mean GFR declined from 69.8 to 66.3ml/min (Pechter et al. 2003). Headley et al used two different methods: an estimation method using creatinine levels (eGFR) and a direct method by analyzing creatinine clearance (CrCl). They found a slight increase in both the training group’s mean eGFR (33.2 to 34.2 ml/min per 1.73m²) and the usual care group’s mean GFR (48.5 to 53.5ml/min per 1.73m²) (Headley et al. 2012).

3. Resistance Training
Resistance training is known to improve skeletal muscle mass and strength which can benefit an individual’s endurance and mobility independence (Howden et al. 2012). Three studies were used in this review to analyze the health benefits associated with resistance training for pre-dialysis CKD patients. The three published manuscripts were based on one randomized controlled trial, which prescribed 3 sets of 8 repetitions 3 times a week, for 12 weeks, of the following exercises: chest and leg press, latissimus pull down, knee extension, knee flexion, and stretching. Table 3 gives a summary of the studies investigated, including the resistance training intervention and duration.

3.1 Muscle Wasting
Patients with CKD often experience muscle wasting. Resistance training has been shown to slow this loss of muscle mass by significantly increasing the total body potassium and type I and II skeletal muscle fiber size (Castaneda et al. 2001). This improvement was observed in the study by Balakrishnan et al, where the phenotypic changes in the skeletal muscle fiber cross-sectional area were estimated to be positively correlated to the changes in median mtDNA copy number (Balakrishnan et al.2010). They found the distribution of mtDNA copy number significantly improved after 12 weeks of resistance training. Changes before and after the 12 weeks were significant in the intervention group (p=0.22, 13125 to 14099 mtDNA copies), but were not significant in the control group (p=0.04,
14762 to 12094 mtDNA copies). The increased mtDNA copy number in the resistance training group is similar to that seen in a healthy muscle (Balakrishnan et al. 2010). This finding is important as muscle wasting in CKD patients has been shown to be associated with mitochondrial biogenesis dysfunction. Mitochondrial biogenesis is critical for the maintenance of skeletal muscle function and structural integrity (Balakrishnan et al. 2010). This countermeasure for muscle wasting also results in a lowered oxidative stress and enhanced mitochondrial function, showing that muscle integrity and accretion may be restored. A future direction for this study could investigate the effects of increased mtDNA copy number on insulin resistance, since it is linked to protein wasting and is a major predictor of cardiovascular risk in CKD patients (Balakrishnan et al. 2010).

### 3.2 Strength
The evidence of increased muscle fiber size seen in Castaneda et al also correlates to increased strength. Castaneda et al reported significant improvements in whole body muscle strength (+86kg) in the experimental group compared to a decrease (-35kg) in the control group (Castaneda et al. 2004). This increased strength would help improve mobility independence as well as aid in preventing injuries.

### 3.3 Inflammation
The majority of CKD patients have evidence of low-grade chronic inflammation such as high levels of serum C-reactive protein (CRP), pentraxin-3, and interleukin-6 (IL-6). The levels of these inflammatory biomarkers can be a predictor in survival. Castaneda et al found a direct correlation between changes in CRP levels and IL-6 levels, which is expected as IL-6 stimulates the production of CRP. In the resistance training group, the mean CRP level dropped 1.7mg/L and the IL-6 dropped 4.2pg/mL, compared to the control group, which had a change in CRP level of +1.5mg/L and a change of +2.3pg/mL in IL-6 levels (Castaneda et al. 2004). Another important correlation made was between the serum IL-6 levels and the phenotypic size of type I (r= -0.58) and II (r= -0.68) muscle fibers. The training group had a mean increase of 934um² for type I muscle fiber area compared to the control group which had a decrease of 618um². For type II, the training group had a mean muscle fiber area increase of 811um², whereas the control group had a decrease of 558um². Overall Castaneda et al found a reduction in systemic inflammation through declines in CRP and IL-6 levels, which is associated with reversed muscle wasting, reduced cardiovascular atherosclerotic disease, and survival (Castaneda et al. 2004).

### 3.4 Glomerular Filtration Rate
GFR was only reported in one of the studies investigated in this review. Castaneda et al found that after the 12-week resistance training, the mean GFR value increased a small but significant amount of 1.18 mL/min per 1.73m², whereas the control group’s mean GFR dropped 1.62mL/min per 1.73m² (Castaneda et al. 2001).

### 4. Combined Resistance and Aerobic Exercise Training
As discussed in the review thus far, there are health benefits associated with both anaerobic and aerobic training, but a combination of these has been reported as the most effective in achieving the best health outcomes in pre-dialysis CKD (Howden et al. 2012). Three studies were used in this review to assess the health benefits associated with combined aerobic and resistance training exercise for pre-dialysis, stage 1-3 CKD patients. Two used a randomized controlled trial design, while the other was non-randomized trial. Table 4 gives an overview of the studies investigated, including the intervention and duration.

### 4.1 Physical Capacity
All studies reported an increase in patient’s physical capacity and functional ability. Rossi et al found that after the intervention there was a +19\% increase in distance travelled (+210ft) during the 6-minute walk test and a +29\% improvement in the sit to stand test. This is compared to the usual care group who had a mean decrease in the distance traveled in 6 minutes by 10ft and only a +0.7\% increase during the sit to stand test (Rossi et al. 2014). These positive results were also found by Cook et al who reported a +45\% improvement in the 6-minute walking test and a +30\% improvement during the sit to stand test, after 12 months of combined exercise. The improvement in physical capacity is likely to lead to increased independence, as Cook et al found that some patients could

<table>
<thead>
<tr>
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<th>Exercise Intervention apparatus</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Castaneda et al. 2001</td>
<td>Random Controlled Trial</td>
<td>12/14</td>
<td>chest and leg press, latisimus pull down, knee extension, knee flexion and stretching 80% 1-RM, 3x wk</td>
<td>12wk</td>
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<tr>
<td>Castaneda et al. 2004</td>
<td>Random Controlled Trial</td>
<td>12/14</td>
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<td><strong>&quot;</strong></td>
<td>12wk</td>
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complete daily living activities, and some patients were even able to return to sports (Cook et al. 2008). Howden et al found that 12 months of combined training was successful in improving VO$_{2peak}$ with evidence from an 11\% increase in the exercise group compared to a 1\% decrease in the control group (Howden et al. 2013). The increase in VO$_{2peak}$ resulted in 10 individuals from the intervention group meeting their age-predicted exercise capacity, which was significantly more than the controls.

4.2 Glomerular Filtration Rate
eGFR was analyzed in two of the studies. Cook et al found a significant reduction in the exercise group (44.8 to 35.5ml/min), as well as a non-significant reduction in the control group (38.8 to 33.6ml/min) (Cook et al. 2008). As stated earlier, the lower the GFR level the greater the kidney damage. This decline may be due to only sampling a subgroup of the intervention patients (12/32 patients). Interestingly, a reduction in eGFR is also reported by Howden et al, where the exercise group’s eGFR declined 1.4ml/min per 1.73m$^2$, whereas the control group had a mean increase of 0.5ml/min per 1.73m$^2$ (Howden et al. 2013). These results may be concerning as they appear to suggest that exercise results in a decline in kidney function. One explanation for this finding is that both studies used an intervention duration of 1 year. As such, a decline in kidney function may be expected as exercise isn’t a cure for CKD, rather it is just a way of slowing down the progression of some of the symptoms associated with it. As well, the reduction in eGFR from these studies was also not very large; a decrease in a few ml/min does not significantly change kidney function and the change may be due to regular fluctuation.

4.3 Arterial Stiffness
Pulse wave velocity, as mentioned earlier, is an accurate measure of arterial stiffness which was recorded in Howden et al. There was a significant (P=0.85) increase in both the intervention group (9.2m/s to 9.6m/s) and the control group (9.8m/s to 9.9m/s). A pulse wave velocity measurement larger than 10 m/s is found to be an independent marker of end-stage organ damage. The negative finding is inconsistent with their reported mean max blood pressure, which decreased in the lifestyle intervention group (178.4/81.6 mmHg to 174.4/79.6mmHg) but increased in the control group (191.9/86.3 mmHg to 204.1/78.9 mmHg) (Howden et al. 2013). These findings are supported by the Cochrane review, which is an internationally accepted standard aimed at investigating the effects of intervention for prevention, treatment and rehabilitation. They reported that combination exercise training reduced systolic and diastolic blood pressure by 4-7 mmHg in CKD patients (Bronas et al. 2012). This reduction in blood pressure can reduce the stress on the heart and decrease the risk of coronary heart disease, stroke and mortality for CKD patients.

5. High Intensity Interval Training
The effects of high intensity interval training (HIIT) is a new exercise type that has become of interest to many researchers due to the improved cardiovascular and metabolic outcomes. The exercise is also less time consuming and has been reported as safe for high-risk populations, such as CKD patients (Tucker et al. 2015). HIIT has not been investigated in CKD patients yet, though an animal model of CKD was recently investigated (Tucker et al. 2015). 8 week old rats that expressed early stage CKD symptoms through performing a unilateral nephrectomy were randomly assigned into one of three groups; sedentary (SED, n=12), light intensity aerobic activity (LIT, n=13), or high intensity interval aerobic activity (HIIT, n=14) (Tucker et al. 2015). Table 5 indicates the exercise intervention and duration that each rat group was assigned.

### 5.1 mRNA Gene Expression
This study was the first to look at changes in mRNA expression at specific genes after an exercise intervention. The most interesting finding was a down-regulation of $Agt$-mRNA, expressed as normal to GAPDH (Norm. to GAPDH), expression...
The studies examined in this review have limitations such as low participation rate matched with high dropout rates, and some do not include exclusion criteria, limiting the ability to generalize findings (Mustata et al. 2010, Cook et al. 2008, Headley et al. 2012). More research needs to be done in all areas of exercise prescription, especially for patients classified as pre-dialysis. I believe this is because there has been little research in the pre-dialysis population compared to the dialysis population. Slowing the progression of the disease should be a priority for researchers, rather than addressing the issues once it has progressed to dialysis stages.

In my opinion, the most promising study based on health benefits analyzed in this review was completed by Pechter et al., who implemented the 12 week water aerobics intervention. The results of this study found that water aerobics increased peak oxygen consumption, improved anti-oxidative levels, and significantly increased GFR levels, which may be associated with the aerobics training in combination with slight resistance from the water. Aside from the physiological benefits, another benefit that the water aerobics has for CKD patients is reduced stress on joints, which may help with joint pain that a lot of CKD patients suffer from (Pechter et al. 2003). Unfortunately, Pechter et al was a pilot study so it is difficult to make overall conclusions about the intervention. This is an area for future research as it displayed a variety of positive effects even in the short amount of exercise intervention time.

It should be noted that there may be underlying issues with pure resistance training, such as muscle soreness, muscle strains and pulls or muscle tearing (Rossi et al. 2014). Although the studies reviewed here found that RT was generally safe, future research should evaluate the safety concerns associated with these training prescriptions, especially for unsupervised exercise, such as Cook et al. and Mustata et al.

In addition to researching safety of resistance training, protein diet analysis in conjunction with resistance training should be completed to see the overall effect on health and strength.

Another possible area for future research is expanding on HIIT interventions. Future work would also benefit from examining whether the positive HIIT-related effects, seen in Tuckers study, are apparent in different related disease models. The promising results from Tucker and colleague’s animal model shows that there is a possibility of the health benefits transferring to humans suffering from stages 1 to 3 CKD. There is no current research for pre-dialysis patients completing a HIIT training program.

### 7. Conclusion/Future Recommendations

The 2011 Cochrane Review recommended including regular exercise in the treatment regime for CKD patients, as most studies, including the ones in this review, showed positive health benefits (Bronsas et al. 2012). Out of the studies reviewed here, the most positive health benefits were associated with aerobic exercise, which resulted in increased aerobic capacity, reduced arterial stiffness, reduced blood pressure, and improved oxidative stress (Pechter et al, 2003, Headley et al. 2012, Headley et al. 2014 and Mustata et al. 2010).

Resistance training is an important aspect of exercise training for CKD patients, as most patients terminate exercise treatments because of skeletal muscle fatigue (Painter et al., 2009). The increased phenotypic type I and II muscle fibers and increased strength will assist in counteracting the mus-
There are also promising results that anaerobic resistance training may reverse the catabolic state of CKD through the decreased levels of chronic inflammation biomarkers (Howden et al, 2012).

Despite a combination of moderate aerobic intensity exercise and resistance training being the current preferred method, there is little evidence from the studies reviewed here that this is the best intervention modality (Howden et al. 2012). This is especially true when analyzing the significant reduction in eGFR levels for patients that completed combination exercise for 12 months in Cook et al and Howden et al. Estimated GFR is a validated method in determining kidney function that has been accepted by the NKF, but the reduction in eGFR levels could be due to analyzing only a portion of the population or because of the long duration of the study as mentioned earlier. There were also negative results seen in the combined exercise group with increased pulse wave velocity measurements, making participants closer to a significant marker of end-stage organ failure. On the other hand, all the combined exercise studies did show a significant improvement in patient’s physical capacity, giving them the improved VO$_2$peak and strength that are needed to complete daily living activities.

Overall, exercise has a beneficial effect on reversing the symptoms commonly seen in CKD patients, as well as slowing the deterioration of the kidneys and reducing the risk of complications such as stroke or myocardial infarction. A summary of the findings can be found in Figure 1. In addition to prescribing exercise to CKD patients, realistic and achievable goals should be set as to not get discouraged. Specialized exercise interventions that are modified to the patient’s abilities and condition should be considered in CKD treatment.

8. References


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