Exercise and the patient with chronic kidney disease

For patients with chronic kidney disease, the importance of regular physical activity should not be overlooked. The case is put forward that physical activity promotion and exercise prescription should become an integral part of the care of these patients, especially those requiring haemodialysis.

It is well established that being physically active through all stages of life is important for good health. There is also a large body of evidence that increased physical activity can have health benefits for a number of chronic medical conditions, both in prevention and management. Indeed, if exercise was considered to be a pill, prescribed by a physician, it would be hailed as the wondrous 'poly-pill'.

Increasingly a number of centres are using exercise as a therapeutic option as part of the multidisciplinary approach to chronic disease management, although this is mainly in the form of cardiac and pulmonary rehabilitation programmes. Patients with chronic kidney disease have high levels of physical inactivity and a number of comorbidities that exercise can greatly benefit. Physical activity promotion and the use of exercise as a therapeutic modality for renal patients in the UK remains, at best, infrequent and non-uniform despite an increasing amount of reported clinical benefits, evidenced by review articles on exercise in chronic kidney disease patients (Beekley, 2007; Johansen, 2007; Cheema, 2008; Brenner, 2009; Bohm et al, 2010; Kosmadakis et al, 2010; Koufaki and Kouidi, 2010; Painter, 2010).

Why exercise?

The benefits of exercise in the chronic kidney disease population have been researched for over 30 years, with evidence now for the primary and secondary prevention of chronic kidney disease and tertiary prevention of end-stage renal disease through restoration of physical function and reduction of disease-related complications (Kosmadakis et al, 2010). As the incidence of patients with chronic kidney disease reaching end-stage renal disease in the UK is increasing, added to the current shortage of organ donors, a considerable strain is placed on renal units to provide life-maintaining dialysis. The financial considerations of this cannot be under-estimated. Haemodialysis is estimated to cost around £35 000–60 000 per patient per year, leading to more than 3% of the NHS budget being spent on end-stage renal disease services alone (Baboolal et al, 2008). Therefore there are clear pressures to help curtail the number of patients with chronic kidney disease reaching end-stage renal disease and improve the efficiency of haemodialysis. Exercise could help.

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In the management of these patients, attempts are made to optimize sugar and blood pressure control to reverse, arrest or delay progression of renal impairment. In the general population individuals who undergo regular physical activity have improved diabetic control, improved blood pressure control in hypertensives and overall improved health-related quality of life as a result of enhanced psychological wellbeing and improved physical functioning (Johansen, 2007). This is significant as many patients with chronic kidney disease are hypertensive and/or diabetic. Further the level of physical inactivity in chronic kidney disease patients is high which, in itself, is an independent risk factor for cardiovascular disease, by far the most common cause of mortality in end-stage renal disease patients (Byrne and Murphy, 2010).

Central to the reduced physical capacity and difficulty experienced with many activities of daily living is the marked muscle wasting and poor physical conditioning that many chronic kidney disease patients have, especially those with end-stage renal disease. Building muscle strength through resistance exercise leads to an improvement in daily function (Wang et al, 2009; Koufaki and Kouidi, 2010).

Aerobic exercise

A number of parameters are commonly used to predict survival status in the end-stage renal disease population. These include nutritional status, serum levels of albumin, pre-albumin, inflammatory markers such as C-reactive protein and measures of cardiac dysfunction, notably left ventricular hypertrophy and pulse pressure (Sietsema et al, 2004). Peak oxygen uptake (VO_2max) is the capacity of the body to maximally deliver, uptake and use oxygen during incremental exercise. Delivery and uptake of oxygen is determined by cardiac function and haemoglobin concentration. Use of oxygen is related to skeletal muscle mass and function, which is dependent on nutritional status. A measurement of VO_2max would therefore encompass a number of important prognostic variables and act as a strong predictor of outcome in the chronic kidney disease population (Sietsema et al, 2004). In the general population predicted VO_2max equates to overall survival and is of clinical prognostic significance in a number of medical conditions (Diamond, 2007). Patients with chronic kidney disease have reduced VO_2max when compared to age- and sex-matched controls (Johansen, 2007; Cheema, 2008). As a result of improvements in VO_2max that occur from cardiovascular training it has been hypothesized that if patients with chronic kidney disease were able to increase their VO_2max a survival benefit may be found.

Studies have shown an improvement in VO_2max can be achieved in patients with chronic kidney disease and the physiological response is similar to other patient groups (Johansen, 2007; Kosmadakis et al, 2010). Most studies have been of between 3 and 6 months' duration and involved 30 minutes of moderate, with progression to vigorous exercise, on 3 or more days a week, either during dialysis (intradialytic exercise) or on the day after. However, the improvement seen is modest; on average it equates to about 17% of predicted VO_2max and predicted age-adjusted VO_2max levels are not attained (Johansen, 2007). This may be because moderate intensity of exercise was prescribed. When more vigorous exercise intensity has been used, a greater improvement has been seen (Johansen, 2007), although the patients enrolled have often been the healthiest end-stage renal disease individuals, of small number and considered not to be a true reflection of the end-stage renal disease population. Equating survival benefit and VO_2max improvement in this cohort is therefore difficult but the greatest physiological changes appear to be in those who were least active beforehand (Johansen, 2007; Kosmadakis et al, 2010).

Of great interest is the reported improvement in a number of intrinsically relevant physiological parameters and psychological wellbeing measured alongside the recorded VO_2max improvements (Kosmadakis et al, 2010). These include favourable lipid metabolism, blood pressure control with reduced use of hypertensives and reduced risks of arrhythmias (Cheema, 2008, Kosmadakis et al, 2010). In addition, high levels of inflammation are are considered to be an independent risk factor for cardiovascular disease. Studies have shown aerobic exercise can lead to reduced levels of inflammation, especially reduced circulating levels of interleukin-6 (Cheema, 2008). Studies also report significant reduction in anxiety and depression levels and improvements in self-reported physical functioning (Kosmadakis et al, 2010).

Resistance exercise

Generalized muscle atrophy with subsequent loss of strength, coupled with reduced cardiorespiratory capacity, can make the performance of a number of activities of daily living profoundly tiresome and difficult. This may ultimately lead to loss of independence and reliance on family members and carers, especially in the elderly population. Resistance exercise improves physical performance through improved muscle strength in the elderly and in many patients with chronic conditions.

Patients with end-stage renal disease are weaker than healthy age-matched sedentary controls as a result of widespread structural and biochemical changes that occur in skeletal muscle in chronic kidney disease (Adams and Vaziri, 2006; Chan et al, 2007; Cheema et al, 2007; Wang et al, 2009; Kosmadakis et al, 2010; Painter, 2010). In the catabolic state, skeletal muscle atrophy is a common occurrence. This is perpetuated by pre-existing sedentary levels of activity, malnutrition and the diseased kidney with protein losing nephropathy, as well as the direct effects of uraemic myopathy. Peripheral neuropathy may lead to reduced or even total loss of motor unit recruitment. Muscle fibres can switch type but mitochondria and myofilaments are abnormal leading to inefficient muscle contraction. Attempts at muscle repair are made but the ubiquitin-proteosome system is energy dependent and disordered, resulting in dysfunctional atrophied muscle (Cheema et al, 2007). There is also thought to be an underlying inflammatory basis with elevated levels of the pro-inflammatory cytokines C-reactive protein and interleukin-6 in patients with chronic kidney disease (Chan et al, 2007; Cheema et al, 2007).

Resistance exercise is relatively under-studied compared to aerobic exercise which is perhaps surprising considering the favourable outcomes that are reported (Johansen, 2007; Kosmadakis et al, 2010; Painter, 2010). Designated muscle strengthening studies have shown that muscle hypertrophy can be achieved in patients with chronic kidney disease with resulting improvements in a variety of physical performance outcomes. Commonly 12-week programmes have been used with supervised weight-machine-based exercise sessions, performed three–four times per week (Cheema et al, 2007; Kosmadakis et al, 2010; Painter, 2010).

Many patients have been on low-protein diets but have still achieved improved muscle power. This reported anabolic effect may be the result of increased levels of insulin-like growth factors 1 and 2 seen in chronic kidney disease patients undergoing resistance exercise (Cheema et al, 2007). Of further, added significance is that levels of C-reactive protein and interleukin-6 are reduced after a 12-week resistance-based programme (Adams and Vaziri, 2006; Cheema et al, 2007). Other outcome measures concentrating on quality of life have also shown improvements with this mode of exercise (Johansen, 2007; Painter, 2010).

Combined aerobic and resistance exercise

As has been reported in patients with chronic kidney disease undergoing aerobic exercise alone, predicted VO_2max levels are not obtained and improvements of

VO_2max have been modest. As Beekley (2007) comments this may be because the limiting factor to VO_2max is not the cardiorespiratory system but skeletal muscle dysfunction. Combined aerobic and resistance-based exercise programmes lead to greater improvements in VO_2max (40–50%) which may mean that this is more efficacious for patients with chronic kidney disease then aerobic or resistance-based programmes alone (Johansen, 2007; Kosmadakis et al, 2010; Painter, 2010). In addition marked improvements in muscle size have been reported in this combined programme (Johansen, 2007; Kosmadakis et al, 2010; Painter, 2010). When quality of life has been measured, similar beneficial changes are also seen.

Intradialytic exercise

Patient compliance can be a problem with therapeutic interventions, especially medications with commonly occurring unpleasant side effects. Exercises, whether rehabilitative following an injury or advised for general health, are often not adhered to in the unsupervised home environment and ensuring compliance is a major problem with exercise programme interventional studies. Dialysis, however, is maintaining life and patients who are dependent on this are left with little choice as to attend for their allotted session or risk becoming very unwell or, ultimately, dying. The frequency and duration of a dialysis session varies but commonly patients require three or four sessions per week for 3–4 hours. While receiving the dialysis, patients typically lie in bed or sit in a chair and their sedentary lifestyle is continued. Intradialytic exercise (dialysis during exercise) is of particular interest as the regularity of the sessions and direct supervision mean that compliance levels following an exercise prescription are likely to be relatively high as no extra visits are required. The usual enforced periods of physical inactivity during dialysis now provides an opportune moment to regularly exercise (Brenner, 2009). Modes of exercise that are available include cycle ergometers and hand-held ergometers as well as foot pumps (Cheema, 2008).

Intradialytic exercise programmes continue to be the most studied regimen in chronic kidney disease patients, largely because of the practical benefits mentioned (Cheema and Singh, 2005; Brenner, 2009; Kosmadakis et al, 2010; Painter, 2010). Another hugely potential benefit is improved dialysis efficiency (Cheema, 2008). Intradialytic exercise, through increased blood flow to muscles, significantly enhances the removal of urea, potassium and creatinine by reducing the postdialysis rebound of these solutes (Cheema, 2008).

Safety

The risk of cardiac events during exercise testing in patients with chronic kidney disease has not been specifically addressed (Johansen, 2007; Kosmadakis et al, 2010; Painter, 2010). No cardiac events (death or myocardial infarction) have been reported in any study of exercise testing in patients with chronic kidney disease and although the patients may be highly selected in some studies, the risk appears to be low (Kosmadakis et al, 2010; Painter, 2010). Exercising end-stage renal disease patients may be higher risk when compared with the general population because of the high prevalence of risk factors and already established cardiac disease, although their risk is not considered to be significantly greater than the risk in patients who are required to undergo diagnostic testing for cardiovascular disease (Johansen, 2007).

Whether a patient with chronic kidney disease patient requires any further investigations before undertaking an exercise programme depends on the intensity of the proposed exercise testing. Studies that have used only moderate intensity levels exercise have relied on history, examination and electrocardiography and have not documented any adverse events (Johansen, 2007). Before vigorous activity, patients with symptoms suggestive of cardiac disease or known, established cardiac disease should undergo exercise testing. For most patients, exercise of at least a low intensity should be possible (Brenner, 2009; Kosmadakis et al, 2010; Painter, 2010).

Volume status is also considered important in the end-stage renal disease population and frequent dry weight assessment should be used, together with close monitoring of blood pressure. Patients may tolerate exercise best either during dialysis or on the day after (Johansen, 2007).

Musculoskeletal injuries can occur in any individual undergoing physical activity but hyperparathyroidism and renal bone disease may place the end-stage renal disease population at higher risk. No study has been designed to specifically address the risk of exercise in patients with chronic kidney disease (Johansen, 2007; Kosmadakis et al, 2010; Painter, 2010). There have been a few reports of tendon rupture and fracture but the number of adverse outcomes is still extremely low (Johansen, 2007; Painter, 2010). Further, the improved muscle strength and regular exercise may lead to a reduced risk of falls and improved bone health. Risks can be minimized by designated time for warm-up and gradually build up of exercise intensity, with avoidance of high-impact activity (Johansen, 2007; Painter, 2010).

Discussion

Despite the ever-enlarging pool of evidence of the potential benefits of physical activity in the chronic kidney disease population, renal centres are not routinely assessing patients' levels of activity or counselling them to increase activity (Johansen et al, 2003; Kosmadakis et al, 2010; Koufaki and Kouidi, 2010; Painter, 2010). This goes against the Kidney Disease Outcomes Quality Initiative (National Kidney Foundation, 2005) which states that 'all dialysis patients should be counselled and regularly encouraged by nephrology and dialysis staff to increase their levels of physical activity'. Reasons why this statement is not being adhered to are likely to be multifactorial. These include time and financial pressures and lack of perceived awareness and training in exercise prescription by nephrology staff (Johansen et al, 2003). There may also be underlying anxiety to advocate exercise because of fears of adverse events, especially in the end-stage renal disease population (Koufaki and Kouidi, 2010). However, the very low levels of adverse outcomes from both aerobic and resistance exercise are encouraging (Cheema et al, 2005; Beekley, 2007).

A lack of robust, randomized trials and methodological flaws in pre-existing studies have been cited as reasons why exercise programmes are not more commonly used by nephrologists (Cueto-Manzano et al, 2010). Although some studies have been uncontrolled, with the patient cohort highly selected and of small number, randomized, controlled studies continue to be carried out and published in leading nephrology and medical journals. If exercise could be considered to be a pill, the outcomes that are demonstrated would certainly make more of a major impact. As Johansen (2007) states:

> **'although there is no doubt that larger studies of the effects of exercise interventions on survival are needed, there is now more compelling evidence to support the benefits of exercise in the dialysis population than there is to support several other commonly used therapies, such as "statins"'.**

Within the UK it appears that the benefits of exercise in patients with chronic kidney disease have been overlooked with the vast majority of research on this topic being US or European based (Kosmadakis et al, 2010). The National Institute for Health and Clinical Excellence (2008) gives exercise a very brief mention in that regular exercise should be encouraged as part of lifestyle advice and currently there is no recommendation that exercise prescription should be implemented (Kosmadakis et al, 2010). However, with a large number of renal units with a multidisciplinary team approach to patients care, the UK should be well placed to conduct research in this field (Cueto-Manzano et al, 2010; Kosmadakis et al, 2010).

Implementation of an exercise service should not be difficult and comparisons could be drawn to the services that are more routinely available in cardiac and respiratory departments (Byrne and Murphy, 2010). In the outpatient setting physical activity level could also be easily added as a measurable parameter, with the vast majority of patients being in the sedentary or low levels. A simple alert could be placed to remind the clinician to record the patient's physical activity level and promote the benefits of regular physical activity (Koufaki and Kouidi, 2010; Kosmadakis et al, 2010; Painter, 2010). The number of times that patients are undergoing 30 minutes of moderate intensity physical activity per week could be recorded. This would help the nephrology team to meet the UK Renal Association (2010) guidelines for the management of cardiovascular disease in chronic kidney disease.

Currently, renal units may report that lifestyle advice is provided but, in terms of physical activity, that entails little more than a statement of 'you need to exercise more'. More detailed physical activity advice is not offered, usually as a result of a lack of training in exercise prescription (Kosmadakis et al, 2010). In addition, barriers to increasing physical activity levels in those not meeting the target of 30 minutes of moderate intensity exercise at least three or more times per week are not addressed. Such barriers may actually be easily overcome by reassurance only. Patients who are symptomatic of or who have established cardiac disease may require stress testing before exercise, but the cardiac disease is unlikely to be so severe that exercise is contraindicated. In contrast, many of the risk factors for cardiovascular disease could be addressed as a result of exercise; this should be highlighted to the patient (Byrne and Murphy, 2010).

For early stage chronic kidney disease regular physical activity exercise should be promoted, if not just for help in the management of the commonly associated hypertension and diabetes. Exercise may also be of added benefit to the increasing numbers of elderly patients who are referred to renal services, chiefly in terms of improved physical functioning (Bohm et al, 2010; Kosmadakis et al, 2010; Koufaki and Kouidi, 2010).

Ideally increased physical activity would be assessed, monitored and promoted. Additionally an exercise service should be in place to prescribe tailored programmes dependent on patient choice and stage of chronic kidney disease, at least for patients who are interested. In the interim nephrologists should begin to encourage more physical activity (Bohm et al, 2010; Kosmadakis et al, 2010). Although there is no clear consensus on a set exercise prescription a general rule of advocating an activity that the patient chooses, of low intensity and on a regular basis, would be a good start (Bohm et al, 2010). For patients not wishing to initially embark on an exercise programme, the notion that some physical activity is better than none should at least be used by staff and encouraged to the patient. Patient associations arrange organized walks and a list of local services, including parks and swimming pools, could be advertised in waiting rooms.

Offering a service for the younger, more active haemodialysis patients could easily be made available, especially intradialytic exercise (Bohm et al, 2010). This can have a number of benefits for both the patients and clinicians. Patients would appreciate both the break in the monotony and sedentary nature of the dialysis session and also generally feeling better (Takhreem, 2008). For the clinicians there would be a good platform for multi-centre research and the potential for improved dialysis efficiency could have wider implications including less dialysis time and happier, healthier patients. Further, combination with resistance-based exercises is likely to lead to added benefits with improved muscle strength and physical functioning and represents the current best standard, in terms of outcome measures, for end-stage renal disease patients wishing to embark on an exercise programme (Bohm et al, 2010; Kosmadakis et al, 2010). The full cooperation of dialysis staff would be required but the training involved is short and the benefits ascertained should make this easily achieved. Space may be at a premium in many dialysis centres in the UK but cycle ergometers could be placed instead of a bed or chair and foot pumps are designed to fit at the end of a chair.

Conclusions

In a time when the funding of services is reviewed and cost-effective practice is of paramount importance, exercise programmes provide a relatively cheap therapeutic option, with a myriad of potential benefits, and should form part of the multidisciplinary approach to patients with renal disease. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The importance of encouraging regular physical activity in patients with chronic kidney disease cannot be underestimated.
- Exercise as a therapeutic option can have a number of significant health benefits of great relevance to the patient with chronic kidney disease.
- Dialysis sessions provide an ideal opportunity to provide an exercise service.