Exercise-induced biochemical modifications in muscle in chronic kidney disease (CKD):

Occult acidosis as a potential factor limiting the anabolic effect of exercise

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It is well documented that CKD patients have poor physical functioning (reduced ability to perform everyday activities), low exercise capacity, and significant muscle wasting - a field that has recently been reviewed[1]. These problems arise from a number of factors[1] including inactivity, inflammation, anaemia, reduced muscle function and increased muscle protein catabolism[2]. There is growing evidence that exercise can provide benefits to patients with advanced CKD[1] such as improved exercise capacity, a reduction in cardiac risk factors, improved insulin sensitivity and glucose disposal, increased quality of life and reduced depression. However, even though there is some evidence that the serious problem of muscle protein catabolism can be slowed by both strength and endurance exercise training in dialysis patients[2], a number of studies have been unable to detect a net increase in lean body mass in response to such exercise. For example in a study[3] involving an 18 week exercise programme of aerobic or resistance training, alone or in combination, no significant change in body composition was observed. This implies that metabolic abnormalities in muscle during CKD may be limiting the anabolic effectiveness of exercise.

Skeletal muscle abnormalities in CKD patients

CKD patients exhibit severe muscular atrophy that appears to affect type II fibres more than type I[4]. Many abnormalities are present at the ultrastructural level, for example   swollen mitochondria, disappearance of the cristae and reduced matrix density[4]. Electron microscopy has shown Z-band degeneration, myofilament loss and accumulation of intracellular glycogen. Fibre splitting, internalized nuclei and moth-eaten fibres have also been observed by light microscopy. Furthermore, this atrophy has also been seen in non-locomotor muscles, demonstrating that these changes are unlikely to be caused purely by disuse, and are probably a consequence of some aspect of uraemia. As well as the abnormalities in mitochondrial structure described above, these patients also exhibit defective intramuscular energy

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metabolism[5]. Following a bout of exercise, the rate of resynthesis of phosphocreatinine (PCr) is reduced, the inorganic phosphate/ PCr ratio is elevated, and an abnormally low intramuscular pH is observed[5], indicating that the ability of the myocytes to restore their pH homeostasis is impaired.

In addition to this intracellular pH defect, systemic metabolic acidosis is reported in the majority of CKD patients when their GFR declines to less than 20-25% of normal i.e. CKD Stage 4 onwards. The degree of acidosis usually correlates with the severity of the renal failure and is the result of a reduced ability to excrete ammonia and titratable acids in the face of a reduced reabsorption and synthesis of bicarbonate. Metabolic acidosis is a well-established cause of increased protein catabolism and muscle wasting[6]. The reason for the failure of exercise in CKD to increase muscle mass is unknown, but exercise in CKD patients could potentially result in a transient worsening of the pre-existing metabolic acidosis through exercise-induced lactic acid generation, especially in view of the low lactate threshold expected in previously sedentary deconditioned patients with CKD. Such acidosis could potentially off-set any anabolic effects gained from the exercise in at least two ways. Firstly acidosis blunts anabolic signals through effectors such as mTOR and PKB/Akt[6], signals which are vital mediators of the hypertrophic effects of exercise on protein synthesis. It is well documented that myocyte growth is regulated by mTOR, at least partly through the PI3-K/PKB signalling pathway and this is probably the pathway that is stimulated in response to resistance exercise *in vivo* resulting in muscle hypertrophy[7]. Secondly, possibly through direct inhibitory effects of low pH on active amino acid transporters in skeletal muscle cells[6], acidosis in CKD significantly depletes intramuscular pools of free amino acids, thus reducing capacity for protein synthesis, and impairing amino acid-dependent anabolic signalling through mTOR.

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Occult acidosis.

At first sight, judging from conventional measures of acid-base status (such as venous bicarbonate concentration or arterial blood pH) there is little direct evidence that exercise in CKD induces significant acidification of the blood. However, direct measurements of tissue interstitial fluid pH in animal models of systemic metabolic acidosis suggest that blood measurements may fail to detect an occult component of acidosis which is confined to the interstitial fluid in the tissues. In rats with normal renal function which were subjected to a level of dietary acid loading which failed to alter blood pH, significant acidification of the tissue interstitial fluid was observed even in the renal cortex, in spite of the animals' normal capacity for renal acid excretion[8]. It should also be noted that previous reports of beneficial effects of alkali therapy in peritoneal dialysis patients, for example the study by Stein and co-workers[9], occurred without substantial increases in arterial blood pH, presumably reflecting functional effects confined to the tissue interstitial fluid. While some[10] but not all studies using micro-dialysis probes in healthy humans have found acidification of skeletal muscle interstitial fluid following muscle contraction in the absence of imposed systemic acidosis; it has also been shown that the fall in the pH of dog muscle interstitial fluid is particularly large during muscle contraction when this is superimposed on a background of pre-existing systemic metabolic acidosis[11], the acidification effects of the systemic acidosis and of the lactic acid generated being more than additive. Such interstitial acidification, resulting in a thermodynamically less favourable pH gradient for extrusion of intracellular protons by the cells, following exercise-induced lactic acid generation, may explain the abnormally prolonged and severe intramuscular acidification observed in patients with advanced CKD following exercise[5], an observation that has been confirmed by several other laboratories. In healthy individuals it has also been demonstrated that metabolic acidosis induced by NH_4Cl

administration, or through diet manipulation, reduces exercise capacity in high intensity exercise[12]. Intramuscular acidification during exercise was also formerly considered to be a major factor in the development of fatigue, but more recently this has been questioned[13].

Treatment to control muscle acidification

The lactic acid response to exercise in CKD may decline spontaneously following a period of exercise training: Kouidi and co-workers[4] showed that 6 months of a mixed exercise training programme resulted in lower blood lactate concentrations by the end of the programme, and attributed this to a block in glycolysis, resulting in an increase in muscle glycogen levels. However, it is also likely that this reduced lactate response arises from a training effect on aerobic metabolism.

It has also been shown in healthy subjects that alkali ingestion significantly suppresses the acidification of muscle interstitial fluid that accompanies one-legged knee-extensor exercise[10]. This was found to be acting selectively on exercise-induced acidification, because alkali had no effect on interstitial pH at rest. However, even though oral sodium bicarbonate is a widely used treatment for uraemic metabolic acidosis – intended to control basal levels of acidosis in the non-exercising state, routine administration of additional sodium bicarbonate to prevent exercise-induced exacerbation of acidosis carries the theoretical risk of sodium and water retention, resulting in worsening of hypertension. Reducing the titratable (non-volatile) acid load which gives rise to the underlying uraemic metabolic acidosis when renal acid excretion fails in CKD is, in principle, a feasible alternative treatment which would avoid the undesirable sodium loading associated with alkali therapy.

The dominant contributor to the daily titratable acid load of around 40-70mEq of H^+ in humans is catabolism of the sulphur amino acids L-cysteine and L-methionine derived from dietary protein (Figure 1). These are irreversibly metabolised, primarily by the liver, to sulphuric acid or to the alternative non-acidic end product taurine[14] (Figure 1). Skeletal muscle also has the ability to convert cysteine to taurine and sulphuric acid (accounting for up to 10% of the whole body sulphuric acid production). While dietary protein restriction (hence reducing sulphur intake) could reduce this sulphur flux, investigation of novel metabolic manoeuvres to suppress this flux or to divert it from sulphuric acid to taurine would be a worthwhile future research objective. In addition to acid, it is important to note that this metabolic pathway to sulphuric acid also generates significant concentrations of the toxic intermediate sulphite (SO_3^{2-}) from sulphurous acid (H_2SO_3) owing to the relatively low activity of the enzyme sulphite oxidase encountered in human tissues (Figure 1). Sulphite accumulates in patients with advanced CKD, attaining concentrations of approximately 5 micromoles per litre[15] - concentrations which are known to induce oxidative stress and hence inflammation which is a further important contributor to cachexia. Therefore, in future, therapeutic reduction of endogenous production of sulphuric acid in CKD patients might generate additional benefits beyond improvements in acid-base balance, which would be of value to the patients both in the resting and exercising state.

Figure legend

Figure 1. Simplified schematic diagram showing the metabolic pathways for catabolism of sulphur amino acids in mammalian tissues.

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Dietary Protein

⇩

L-Methionine (L-Met)   Glutathione (GT)

⇩

L-Cysteine (L-Cys)

Cysteine Dioxygenase
(CDO)

⇩

L-Cysteinesulphinate (L-CSA)

Aspartate (CSA) Transaminase   Cysteinesulphinate
                                       Decarboxylase
⇕   (CSAD)

β-sulphinylpyruvate

⇩   Hypotaurine

Pyruvate + H_2SO_3 ⟺ $2H^+$ + SO_3^{2-}

⇩ Sulphite Oxidase   ⇩

Sulphuric Acid   Taurine
H_2SO_4 ⟺ $2H^+$ + SO_4^{2-}