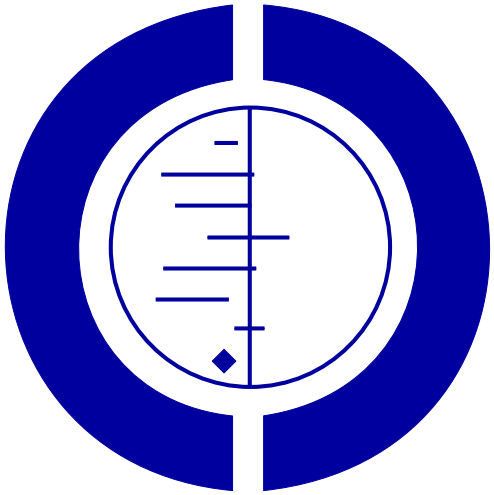
Pharmacological and nutritional treatment for McArdle's disease (Glycogen Storage Disease type V) (Review)

Quinlivan R, Beynon RJ



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2005, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Pharmacological and nutritional treatment for McArdle's disease (Glycogen Storage Disease type V) (Review)

Quinlivan R, Beynon RJ

This Review should be cited as:
Quinlivan R, Beynon RJ. Pharmacological and nutritional treatment for McArdle's disease (Glycogen Storage Disease type V). *The Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003458.pub2. DOI: 10.1002/14651858.CD003458.pub2.

This version first published online: 19 July 2004 in Issue 3, 2004.
Date of most recent substantive amendment: 01 March 2004

ABSTRACT

Background
McArdle's disease (Glycogen Storage Disease type V) is caused by the absence of the glycolytic enzyme, muscle phosphorylase. Patients present with exercise-induced pain, cramps, fatigue, myoglobinuria and acute renal failure, which can ensue if the myoglobinuria is severe.

Objectives
To systematically review the evidence from randomised controlled trials of pharmacological or nutritional treatments in improving exercise performance and quality of life in McArdle's disease.

Search strategy
We searched the Cochrane Neuromuscular Disease Group register (searched December 2001 and updated in December 2003), MEDLINE (January 1966 to December 2003) and EMBASE (January 1980 to December 2003) using the search term 'McArdle's disease and it's synonym 'Glycogen Storage Disease type V'.

Selection criteria
We included randomised controlled trials (including crossover studies) and quasi-randomised trials. Open trials and individual patient studies with no patient or observer blinding were included in the discussion but not the review. Types of interventions included any pharmacological agent or micronutrient or macronutrient supplementation. Primary outcome measures included any objective assessment of exercise endurance (for example VO2 max, walking speed, muscle force/power and improvement in fatiguability). Secondary outcome measures included metabolic changes (such as reduced plasma creatine kinase activity and a reduction in the frequency of myoglobinuria); subjective measures (including quality of life scores and indices of disability); and serious adverse events.

Data collection and analysis
Two reviewers checked the titles and abstracts identified by the search, independently assessed methodological quality of the full text of potentially relevant studies and extracted data onto a specially designed form.

Main results
We reviewed 20 trials. Ten trials fulfilled the criteria for inclusion and ten trials were included in the discussion. The largest treatment trial included 19 cases, the other trials included fewer than 12 cases. As there were only single trials for a given intervention we were unable to undertake a meta-analysis.

Authors' conclusions
It is not yet possible to recommend any specific treatment for McArdle's disease. Low dose creatine supplementation was shown to demonstrate a statistically significant benefit, albeit modest, in ischaemic exercise in a small number of patients. Ingestion of oral sucrose immediately prior to exercise reduces perceived ratings of exertion and heart rate and improves exercise tolerance. This treatment will not influence sustained or unexpected exercise and may cause significant weight gain. Because of the rarity of McArdle's disease, there is a need to develop multicentre collaboration and standardised assessment protocols for future treatment trials.

SYNOPSIS

Low-dose creatine supplementation and oral ingestion of sucrose prior to exercise have been shown to benefit a small number of patients with McArdle's disease. Further research is needed.

McArdle's Disease (also known as glycogen storage disease type V) is a metabolic muscle disorder, caused by the absence of an enzyme called muscle phosphorylase. This absence causes an inability to utilise glycogen stores (or 'fuel') which results in pain and fatigue on starting exercise. If exercise continues, severe muscle damage may develop and in some cases, acute renal failure. Low dose creatine supplementation has been shown to have a modest benefit in improving exercise tolerance in a small number of people with McArdle's disease. Oral ingestion of sucrose prior to exercise reduces ratings of perceived exertion and heart rate but this treatment is not practical for day-to-day living. Further research is needed.

BACKGROUND

McArdle's disease (glycogen storage disease type V) is a disorder of muscle metabolism caused by the absence of the glycolytic enzyme, muscle phosphorylase. The first case was described by McArdle (McArdle 1951). His patient presented with exercise induced myalgia and failed to produce a rise in blood lactate during ischaemic forearm exercise. In 1959 muscle phosphorylase was discovered and subsequently its deficiency confirmed in McArdle's disease (Mommaerts 1959; Schmidt 1959). There is no detectable muscle glycogen phosphorylase activity in the majority of affected individuals. However in a small number, the levels of this enzyme are reduced (20% to 30% of normal values) but not absent (Beynon 1995).

The inheritance of McArdle's disease is autosomal recessive and heterozygotes are usually asymptomatic. The muscle phosphorylase gene is located at 11q13 and spans 20 exons (Bartram 1993). The most common mutation in Northern European and North American patients is the nonsense mutation at R50X (usually referred to as R49X for historical reasons) (Kubisch 1998). There are at least 20 other rare mutations. The preferred method of diagnosis is by muscle histochemistry following muscle biopsy.

The consequence of muscle phosphorylase deficiency is the inability to mobilise muscle glycogen stores during anaerobic metabolism. To exacerbate the situation in McArdle's disease, oxidative phosphorylation is also impaired because of an abnormally low substrate flux through the tricarboxylic acid cycle. This is most likely the result of virtual absence of pyruvate from glycolysis. This reduces the rate of acetyl-Co enzyme A formation, which in turn affects the tricarboxylic acid cycle. Acetyl-Co enzyme A can be generated from the breakdown of fatty acids, but without training, most individuals will have limited capacity for fatty acid oxidation during exercise (De Stefano 1996; Ruff 1998). The effect of this decline in oxidative phosphorylation is a decrease in oxygen consumption in affected individuals to 35% to 40% of that seen in normal muscle. Two other physiological effects may exacerbate the symptoms. Firstly a reduction in the blood flow of contracting muscle may lead to partial ischaemia (Libonati 1998). Secondly, a disproportionate increase in heart rate and ventilation rate occurs in affected individuals compared with normal controls (Vissing 1998).

Most patients present in the second or third decade, although symptoms are often reported retrospectively from childhood. The main complaints are exercise induced myalgia and fatigue. With severe sustained exercise through pain, a muscle contracture will occur and myoglobinuria (excretion of myoglobin, a muscle protein, in the urine causing dark discolouration), with or without acute renal failure, may follow due to acute rhabdomyolysis (breakdown of the muscles). The majority of patients learn to manage their condition using an exercise pattern which exploits a phenomenon known as a 'second wind'. In McArdle's disease, pain occurs within a few minutes of initiating exercise. However, if at this stage the patient rests until the pain subsides there will be a metabolic shift to fatty acid oxidation enabling exercise to continue. This shift in metabolism occurs more effectively in individuals whose muscles have been conditioned through undertaking regular aerobic exercise.

The diagnosis is suspected by the history and the finding of a raised plasma creatine kinase activity. Patients will fail to produce lactate during an ischaemic exercise test, although this test is not specific for the disorder and could potentially cause acute muscle necrosis and compartment syndrome. The definitive diagnosis is made by muscle histochemistry and the finding of absent functional muscle phosphorylase. In some cases DNA analysis for the common mutations can yield unambiguous diagnosis.

There is considerable heterogeneity in the severity of symptoms, even in individuals who possess the same genetic mutation. The exact reasons are unclear, but might include differences in lifestyle including diet, fitness and aerobic capability or some other interacting metabolic mechanism. Because of the block in glycolytic

metabolism, muscle activity occurring after the first few minutes of exercise is highly dependent on alternative energy sources including amino acids and free fatty acids. Research strategies have focused on increasing the availability of these sustrates through either supplementation or dietary modification. At least 80% of the total body pool of vitamin B6 (pyridoxine) is in skeletal muscle bound to phosphorylase, in McArdle's disease this large pool of vitamin B6 is deficient (Haller 1983). The active form of vitamin B6 is an important co-factor for a number of enzymes involved in amino acid metabolism, thus the extra demands placed on alternative fuel sources in McArdle's disease may make patients more dependent on vitamin B6. Dantrolene sodium is used as a muscle relaxant for spasticity and for the prevention and treatment of malignant hyperthermia, the drug decreases calcium flux from the sarcoplasmic reticulum, impairing the initiation of the excitation-contraction coupling mechanisms. A positive effect of Dantrolene sodium in reducing exertional myalgia was reported in a single McArdle's patient (Bertorini 1982). Creatine supplementation may increase the availability of Adenosine Triphosphate (ATP) from Adenosine Diphosphate (ADP) and has been shown to benefit the exercise capacity of healthy individuals undergoing resistance training (Vandenberghe 1997) and to increase strength in patients with mitochondrial myopathies (Tarnopolsky 1997). In McArdle's disease magnetic resonance spectroscopy studies during exercise have demonstrated a rapid depletion of phosphocreatine with exercise, creatine supplementation, therefore might be beneficial. Upregulation of oxidative metabolism through diet, drugs or exercise might potentially increase the availability of a second wind for example an intravenous infusion of glucose during exercise enables glycolysis which in turn up-regulates oxidative phosphorylation (Haller 2002).

OBJECTIVES

To systematically review the evidence from randomised controlled trials examining the efficacy of pharmacological or nutritional treatments in improving exercise performance and quality of life in McArdle's disease.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included randomised controlled trials (including crossover studies) and quasi-randomised trials. Open trials and single case studies without patient blinding are included in the discussion but not the review.

Types of participants

We included males and females, both adults and older children (aged eight years and above) with a confirmed diagnosis based upon muscle histochemistry and/or unambiguous DNA studies.

Types of intervention

We considered any pharmacological agent or micronutrient or macronutrient supplementation.

Types of outcome measures

The primary outcome measures included: any objective assessment of exercise endurance (for example VO2 max, walking speed, muscle force/power and improvement in fatiguability) measured over a three month period after starting treatment.

Secondary outcome measures after three months of treatment included:
(1) metabolic changes including reduced plasma creatine kinase activity and reduction in the frequency of myoglobinuria;
(2) subjective measures including quality of life scores and indices of disability;
(3) serious adverse events as measured by mortality and morbidity including adverse drug reactions, weight changes, atypical progression of the disease and poor quality of life scores.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Neuromuscular Disease Group search strategy
We used the search strategy of the Cochrane Neuromuscular Disease Group's trials register using the terms: McArdle's disease, Glycogen Storage Disease Type V (GSDV) or Muscle Phosphorylase Deficiency. We adapted this search strategy to examine the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 3, 2003), MEDLINE (January 1966 to December 2003) and EMBASE (January 1980 to December 2003). We searched for randomised controlled trials and quasi-randomised controlled trials. We also searched for open trials, single case studies and anecdotal reports which could be used as part of the discussion. We have included an unpublished study by the authors of this review.

METHODS OF THE REVIEW

Two reviewers checked titles and abstracts identified and both reviewers independently assessed the full text of all potentially relevant studies. Each reviewer assessed the full text independently using pre-agreed data extraction forms. The reviewers decided which trials fitted the inclusion criteria and graded methodological quality, including allocation concealment, observer blinding, patient blinding, explicit diagnostic criteria and explicit outcome

criteria. We aimed to obtain any missing data from the authors if needed.

We did not subdivide the patient cohort into any subcategories. If appropriate data were available from more than one trial with a given intervention, we planned to undertake meta-analysis using the Cochrane Review Manager (RevMan) software to combine differences in relative risks or in means as a weighted mean difference with 95% confidence intervals to provide pooled estimates. If heterogeneity had been identified, meta-analysis would have been repeated excluding studies of lower methodological quality, for example those which have not used allocation concealment. Separate analyses would have been undertaken for each different class of pharmacological or nutritional treatment.

DESCRIPTION OF STUDIES

Twenty studies were assessed and ten studies were included in the review (including one unpublished study undertaken by the authors). The studies reviewed evaluated the following treatments: high dose oral ribose, fat rich diet, glucagon, verapamil, vitamin B6, high protein diet, branched-chain amino acid supplementation, dantrolene sodium, low dose creatine, high dose creatine and oral sucrose. Because of the paucity of studies, we decided to include studies of treatment duration of less than three months. The excluded studies were open studies or single patient studies with no observer or patient blinding (these are summarised in the table entitled characteristics of excluded studies) and will be discussed further in the discussion section of this review.

METHODOLOGICAL QUALITY

The methodological rating for included studies is summarised in the table entitled characteristics of included studies. The majority of studies included only a small number of patients or even single cases. The methodological quality of these studies was assessed and graded according to Cochrane criteria where: A is adequate, B is unclear, C is inadequate and D is not done. These results are summarised in the table entitled methodological quality of included studies. There were no studies using the same treatment to allow any formal meta-analysis to be undertaken, apart from two trials using branched-chain amino acids but with such different regimens as to preclude meta-analysis for that intervention also.

RESULTS

Steele 1996 studied five patients with McArdle's disease (four male and one female, age range 20 to 60 years) in a double-blind randomised crossover controlled study of oral ribose solution (15 g D-ribose made up in 150 ml water taken four times a day for seven days). Baseline measurements were made on no treatment, treatment and placebo. A Borg score for ratings of perceived exertion was used (Borg 1982). Patients underwent a weekly incremental exercise treadmill test with respiratory gas analysis. All five patients completed the trial, although some developed symptoms of hypoglycaemia which included light-headedness and hunger. One patient developed increased bowel frequency after ribose. Many found the drink too sweet and unpleasant to taste, and this may have compromised concealment. The study failed to show any normalisation of metabolic parameters or improved activity, although there was some normalisation of the ventilatory response to exercise.

Day 1985 undertook a single-blind controlled trial of glucagon in one female patient with McArdle's disease. The diagnosis was based upon forearm ischaemic exercise testing and muscle biopsy which demonstrated absent phosphorylase activity. Isometric grip strength was measured in the left hand using a rolled sphygmomanometer cuff inflated to 200 mmHg. The grip strength at maximum effort was recorded at 10 second intervals. The patient was asked to report when the forearm became fatigued or painful, at which point exercise was stopped. Various treatments were assessed and neither the patient nor the investigator was aware of the treatment received. Measurements were performed no more than twice a day with at least six hours between the tests. Three baseline measurements were performed, after subcutaneous injection of saline (placebo), two measurements after 2 mg of subcutaneous glucagon and five measurements after administration of 2 mg depot glucagon. The endurance curves for different treatment modalities were plotted. There was a trend towards improvement with glucagon but this was not statistically significant when compared with placebo.

Lane 1986 undertook a double-blind placebo controlled crossover study of the effect of verapamil on muscle pain. Three patients with McArdle's disease (diagnosed by muscle biopsy) were studied compared with eight patients with an exertional pain syndrome of unknown cause. Patients were randomly assigned to a placebo or treatment group. After six weeks, medication was stopped for two weeks and then the two groups crossed over following the same regimen for another six weeks. The patients were asked to keep a pain and activity diary, at the same time each week the patients undertook specific timed exercise that would normally produce pain and the maximum level of pain graded on a scale of 0 to 10 during or following this task was recorded. None of the McArdle's patients kept satisfactory diaries, two more patients withdrew from the study because of severe headaches and so were not included in the analysis. No significant benefit was observed in any of the McArdle's cases.

Beynon 1998 (unpublished data) undertook a randomised double blind placebo controlled crossover trial of vitamin B6. Ten patients (eight male and two female) with biochemically and genetically proven McArdle's disease were given either placebo or Vitamin B6 in a once daily dose of 50 mg. Ethical approval was obtained and patient data were compared with age and sex matched controls.

Sachets containing either treatment or placebo were made up by the hospital pharmacy department and posted to the subjects, who were randomly assigned to one of two groups. There was a six week wash out phase between treatment or placebo, which was given for ten weeks. Erythrocyte AST activity was measured to assess vitamin B6 status and patients underwent programmed stimulation electromyogram (PSEM) to assess force generation and fatiguability under ischaemic conditions. The investigators were unaware of the phase in the trial for each patient (i.e. placebo or treatment). No significant difference was found between the treatment and placebo.

Kushner 1990 studied three patients and three controls comparing the immediate and long-term effects of oral branched-chain amino acids (BCAAs). The authors did not specify their diagnostic criteria and the age and sex of the subjects were not revealed but the controls were age, sex, height and weight matched. Prior to the two month period of dietary supplementation, the subjects underwent assessment daily for three days either in the fasting state or after immediate administration of 100 g dextrose or 0.3 g /kg BCAAs, respectively Subjects were then assessed prior to, and after one and two months of BCAA dietary supplementation. Two types of muscle function were measured: maximal concentric strength and muscle endurance (absolute work performed to fatigue).Urine 3-methylhistidine/ creatine ratio was measured. The study failed to demonstrate any immediate or long-term benefit from oral branched-chain amino acid supplementation.

MacLean 1998 performed a single-blind controlled trial of BCAAs (leucine, isoleucine and valine) compared with a control non-calorific drink. The six patients (three males and three females) were unaware of treatment or placebo, but the investigators were not blinded to treatment. The patients were exercised for 20 minutes on a cycle ergometer at maximal intensity without experiencing pain or exhaustion. Work intensity converted to Watts and heart rate were measured. Levels of branched chain amino acids were measured in the bloodstream to assess for compliance. Despite increased availability of branched chain amino acids in the bloodstream, exercise capacity was lower in five of the six patients. The authors concluded that functional activity was worse with high dose branched-chain amino acids compared with fasting conditions.

Poels 1990 studied the effect of dantrolene sodium on the second wind phenomenon. Five patients (two women and three men aged 21 to 41 years), in whom muscle phosphorylase protein was shown to be absent on sodium dodecyl sulphate-gel electrophoresis, were included in a randomised double-blind placebo controlled crossover trial. Dantrolene was built up over three days to 150 mg, given in three divided doses of 50 mg. Treatment was given for six weeks with a four week washout period, followed by crossover to either placebo or treatment. Dose dependent side-effects were noted which included: tiredness, somnolence, dizziness and muscle weakness resulting in four of the five patients reducing the dose. At the end of both treatment phases patients were tested on a bicycle ergometer at 30% VO2 max during 2 hours and after a 12 hour fast. Surface EMG was recorded during exercise. Patients were asked to use the Borg scale to rate their maximum perceived effort. Statistical analysis showed no significant symptomatic benefit with dantrolene.

Vorgerd 2000 undertook a randomised double-blind placebo controlled crossover study of creatine supplementation in nine enzymatically and genetically proven McArdle's disease patients (six men and three women). Placebo was compared with creatine, initially at 150 mg/kg/day for five days followed by 60 mg/kg/day taken in three divided doses with meals. Each phase lasted five weeks followed by a four week washout period and then crossover. Patients were asked to keep a symptom record of exercise intolerance using a fatigue severity scale devised by the authors. On the final day of treatment, clinical measures and laboratory tests were performed including 31-phosphorous magnetic resonance spectroscopy (31P-MRS), two sets of three minute static plantar flexion exercise under natural perfusion and ischaemic conditions (arterial occlusion). A substantial rise in plasma creatine was noted and the treatment was well tolerated. Five of the nine patients noted some subjective improvement when taking creatine compared with placebo, an increased tolerance of workload and depletion of phosphocreatine which increased significantly during ischaemic exercise as seen on 31P-MRS was demonstrated, although an overall increase in muscle phosphocreatine was not seen. A subsequent study undertaken by the same group (Vorgerd 2002) compared 60 mg/kg creatine with 150 mg/kg creatine given daily. Nineteen patients were studied in a double-blind placebo controlled trial. The outcome measures were the same as those used for the lower dose creatine trial. Treatment with high dose creatine significantly worsened the clinical symptoms of exercise-induced myalgia, the authors suggested that one possible explanation for this is that an insufficient adaptation to improved electromechanical efficacy leads to overuse of the muscle contractility in exercise and thus a worsening of symptoms. Although no changes were seen on phosphorous 31P-MRS.

Vissing 2003 undertook a single-blind randomised cross over study of oral sucrose (75 g in a drink) compared with placebo (a drink with artificial sweetener) taken 30 to 40 minutes before fixed intensity exercise on a cycle ergometer for 15 minutes. Twelve subjects (7 men and 5 women) aged 22 to 57 years, known to have McArdle's disease were asked to exercise at a fixed intesity on a bicycle ergometer for 15 minutes and had to rate perceived exertion at one minute intervals (using the Borg scale), heart rate and workload were assessed. Blood samples were taken to measure glucose, lactate, pyruvate, ammonia, insulin, and free fatty acids. The mean plasma glucose rose significantly, the mean maximum heart rate dropped by 34 +/- 3 beats per minute and the level of perceived exertion dropped when sucrose was ingested compared with placebo. The authors concluded that oral ingestion of sucrose can markedly improve exercise tolerance in McArdle's disease. When used regularly, however, sucrose ingestion may result in weight gain and would be of no benefit for unaccustomed

exercise. Oral sucrose would be contraindicated in diabetics.

Results Summary

There are few good quality controlled treatment trials for McArdle's disease. Those trials which do exist have included only small numbers of patients (a maximum of 19 cases in only one study, Vorgerd 2000). Meta-analysis was not appropriate because there are virtually no replicated studies, irrespective of methodological quality. There is a lack of evidence to show benefit from supplementation with branched chain amino acids, depot glucagon, dantrolene sodium, verapamil, vitamin B6, high dose oral ribose or high dose creatine. Low dose creatine conferred a modest benefit on ischaemic exercise testing in five out of nine patients, although high dose creatine worsened symptoms. Oral ingestion of sucrose taken 30 minutes before exercise improved exercise tolerance in twelve patients undertaking planned exercise.

DISCUSSION

McArdle's disease is a rare metabolic muscle disease and the rarity of the condition is the reason for the methodological difficulties seen in many of the studies. The largest randomised controlled trial reviewed included 19 cases, the remaining studies included no more than 12 cases. Ten studies which were excluded from the review, however, merit further description.

Treatment with a high protein diet has been recommended for patients with McArdle's disease, but there are no published randomised controlled trials to support its use. Two studies have looked at the effect of a high protein diet. Slonim 1985 studied a single affected male aged 50 years. The patient suffered cramps on exertion and had significant upper limb muscle wasting and weakness and was confirmed to have McArdle's disease following a muscle biopsy, which showed absent muscle phosphorylase on muscle histochemistry. The patient was initially studied during cycle ergometer exercise, serum lactate and alanine levels taken serially were compared with an age and sex matched control. The subject (but not control) was then studied on four separate occasions following a 10 hour fast after which either glucose or protein (broiled beef) were given orally, or saline or fructose were administered intravenously. The patient was exercised carefully through a second wind phase and then exercised to exhaustion. The patient exercised for a longer period of time following protein ingestion compared with the other nutritional interventions. A high protein diet and daily exercise (which included tennis) were recommended for three years. The subject was then re-tested following protein or glucose administration and after a mixed meal of his choice, comparison with a control for strength measurement was made after a mixed diet only. The authors reported anecdotal improvements in the patient's exercise ability and an improvement in strength in the upper limbs. There was no concealment of allocation and the patient's performance may have improved through practice. Furthermore, it is possible that the improvement in strength and endurance noted over the three year period was a consequence of the exercise programme which included one hour of aerobic exercise daily.

Jensen 1990 studied the effect of a high protein diet for six weeks on a male patient with McArdle's disease, confirmed by muscle biopsy. Bicycle ergometry was performed two hours after meals of the patient's normal diet (15% protein, 42% fat and 43% carbohydrate) and after six weeks on an isocaloric high-protein diet (28% protein, 29% fat and 43% carbohydrate). Maximal muscle strength was measured by a stepwise increase in workload by 10W: 2 minutes work followed by 10 minutes rest. Endurance at submaximal muscle strength was measured after 15 minutes rest. Treadmill exercise combined with 31P-MRS was then studied two hours after a meal on the usual diet, following an intravenous glucose (20% solution) infusion, after an intravenous infusion of amino acids (0.3g/kg body weight/hr) and after six weeks of high protein diet. Six age matched normal controls were also examined with phosphorous-31 nuclear magnetic resonance (31-PNMR) to study adenosine triphosphate (ATP), phosphocreatine (Pcr) and inorganic phosphate (Pi). The controls did not receive any infusion. On his usual diet, the working capacity of the subject measured at treadmill exercise was approximately one half of that of the controls. ATP/(Pcr+Pi) and Pi/Pcr ratios were within the normal range at rest. During exercise there was a rapid decrease of Pcr and an equivalent rise in Pi, whereas ATP was unchanged at all levels of work load. During the intravenous glucose infusion, the expenditure of Pcr at each level of work load during hyperglycaemia was significantly less than during normoglycaemia. Following an increase of the daily protein intake from 15% to 28% on an isocaloric diet of unchanged carbohydrate content, the endurance at submaximal work load during bicycle ergometry was increased from 5 to 8 minutes and the maximal capacity at graded bicycle exercise improved by 25%. Treadmill exercise performance improved by 40%. The 31P-spectrum showed decreased expenditure of Pcr at the maximum work intensities and the Pi/Pcr ratios improved from 3.1 at the usual diet to 1.5 at high protein diet. In comparison the Pi/Pcr ratios were 1.4 during glucose infusion and 4.4 during infusion of amino acids. Intravenous amino acid infusion at a rate of 0.3g/kg body wt/hr was not associated with any improvement of the phosphorous energy metabolism nor of the working capacity during treadmill exercise. The findings were an increase in performance and high energy kinetics following a high protein diet and glucose infusion, but not following administration of intravenous amino acids. There was, however, no concealment of allocation and statistical analysis was not appropriate because the study included only one patient.

There have been three studies to evaluate glucagon. The study by Day et al. (Day 1985) is included in this review and did not report any demonstrable effect with glucagon supplementation. Two earlier studies excluded from the review merit further discussion. Kono et al. (Kono 1984) gave glucagon to a single female patient aged 26 years. No placebo was used and there were no control subjects. Blood levels for creatine kinase, lactate dehydro-

genase, glucose, free fatty acids and ammonia were measured. The patient was exercised for three minutes. The authors suggested that glucagon improved exercise tolerance. The patient was not assessed blindly and had also co-incidentally been taking coenzyme Q10 for one year which had resulted in a subjective improvement of her symptoms. Subcutaneous glucagon administration improved work tolerance on a bicycle ergometer. Normally the patient was exhausted after three minutes but with glucagon she exercised for 30 minutes with a second wind at three and ten minutes. An ischaemic lactate test undertaken with glucagon led to a rise in plasma lactate. There were no controls, and no concealment of allocation and no statistical parameters were used because this was a single case study. Mineo 1984 studied two female patients with McArdle's disease aged 26 and 29 years, and two male cases with Tarui's disease, aged 44 and 20 years. (Tarui's disease is a glycogen storage myopathy caused by a deficiency of the glycolytic enzyme phosphofructokinase.) One patient with McArdle's disease and one with Tarui's were exercised on a bicycle ergometer with and without glucagon pre-treatment following an overnight fast. All four subjects underwent a modified ischaemic exercise test and were given the following: oral glucose, glucagon and glucose combined with insulin. The authors found that the McArdle's patient achieved a second wind more efficiently with glucagon administration during cycle ergometer exercise. No benefit was seen in the case with Tarui's disease. This study lacked concealment and statistical analysis. Further studies would be necessary to determine whether regular use of glucagon would benefit patients. However, any consideration of the use of glucagon as a form of possible therapy for McArdle's disease should also be considered in context of its long-term side-effects, which include haemolytic anaemia.

Phoenix 1998 reported the effect of withdrawal of daily 50 mg Vitamin B6 in a male patient with McArdle's disease. The patient had been taking vitamin B6 as a supplement for two years. The effect of withdrawal of treatment was assessed. The patient was blind to receiving either vitamin B6 or placebo, which was allocated by the hospital pharmacy after a period of observation. The outcome was assessed using Vitamin B6 status as assessed by erythrocyte aspartate transaminase (eAST) activity. Objective muscle function was evaluated by stimulation of the adductor pollicis muscle via the ulnar nerve at the wrist using PSEM providing information on force and compound muscle action potential (CMAP) together with qualitative data on symptoms. Qualitative changes in feelings of reduced well being were noted off treatment and there was a rapid decline in vitamin B6 status. The PSEM studies showed a reduction in the patient's ability to recover during the post ischaemic recovery phase during withdrawal of vitamin B6 although there was no clear effect of vitamin B6 on the CMAP. Vitamin B6 withdrawal did not affect the serum creatine kinase levels or frequency of myoglobinuria.

Pearson 1961 first described the second wind phenomenon and related this to delayed mobilisation and utilisation by the muscles of free fatty acids as a secondary energy source during muscle exercise. They showed a beneficial action of a continuous infusion of emulsified fat in 4% glucose on the muscle performance of a patient. On the basis of this report, Viskoper 1975 assessed the potential benefit of a high fat diet for three days in a single case study. The patient, an affected 21 year old male, was exercised on a bicycle ergometer at a workload of 60kW for two and a half minutes. Later he was asked to maintain sustained abduction of the deltoid muscle to 90 degrees. Blood pressure was taken at one, two and five minutes, a blood sample was taken to measure free fatty acids, triglycerides and lactic acid, and EMG monitoring was conducted during eccentric exercise. The patient reported subjective feelings of increased fitness, but this could not be confirmed objectively by the researchers. In a second branch of the study isoprotenol was administered as a means of raising plasma free fatty acid levels, a dose of 10 mg three times a day was given for two weeks while the patient was on a normal diet. No beneficial effect was observed.

Wagner 1991 assessed the effect of high dose oral ribose given to a 20 year old patient and six normal controls, which were not matched for age or sex. While the patient was pedaling a cycle ergometer, 3 g oral ribose was given every ten minutes. The study reported an increase in exercise capacity from 60W to 100W. Blood lactate levels were tested before and after exercise. The patient reported fewer cramps although there were no quantitative or qualitative assessments to substantiate this.

Lewis 1985 showed that intravenous glucose is associated with a partial normalisation of an excessive cardiac output in response to exercise together with improved exercise tolerance. They studied a single male McArdle's patient and two normal controls (one male and one female). The 31P-NMR of the forearm flexor muscles was assessed during exercise using a modified handgrip dynamometer with a non-magnetic extension and potentiometer so that maximal handgrip could be recorded. Repetitive exercise was performed two hours post prandially on a normal mixed diet and during an intravenous infusion of 60 ml of a 50% glucose infusion. Under control conditions the McArdle patient fatigued with an impending muscle contracture at 2 minutes and 10 seconds. From rest to fatigue the patient's forearm muscle PCr declined precipitously and Pi increased markedly but ATP was only slightly reduced. Plasma glucose levels rose three times during the glucose infusion, the patient performed maximal handgrip exercise for more than 7 minutes. During glucose infusion PCr fell and Pi increased to a much lesser extent than under control conditions. In the healthy controls forearm PCr tended to decline similarly and Pi tended to increase less in the healthy subjects than the McArdle patient. Exercise in the control patients was no different with the glucose infusion.

Haller 2002 studied the effect of intravenous glucose on the second wind. They studied 9 patients (8 with complete phosphorylase deficiency and 1 with 3% of normal phosphorylase activity). Patients exercised on a cycle ergometer for about 40 minutes. Initial work capacity was determined in the first 6 to 8 minutes, then workload was reduced for 5 to 10 minutes. The workload was again progressively increased to deter-

mine peak performance at 25 minutes. Immediately afterwards 50 ml of 50% glucose was infused over 1 to 2 minutes followed by a continuous infusion of 10% dextrose at a rate of 6 ml/min for the duration of exercise. Exercise was continued for 40 minutes. Patients were assessed three times over a 24 month period and the mean results presented. Heart rate was continuously monitored, gas exchange and cardiac output were measured at rest and during peak exercise within 6-8 minutes. The glucose infusion resulted in a 20% increase in oxidative capacity.

O'Reilly 2003 studied a single case on and off creatine at a dose of 25 g/day for five days. The author was also the subject and thus, there was no concealment, he was exercised to exhaustion in the second wind phase of exercise, achieving a work rate of 275 to 325 W. No benefit was noted with creatine supplementation.

A recurrent theme of therapeutic studies for McArdle's disease is the restricted availability of patients. Future studies will need to be multicentre and probably multinational. However, before such studies can be contemplated several key issues must be resolved. First is the need to specify rigorously defined methods for assessment of muscle performance and fatigue in McArdle's disease. Whilst objective physiological tests are valuable, there is also a need for assessments that relate more to lifestyle and day-to-day demands on skeletal muscle. The features of McArdle's disease are fatigue, pain, speed of recovery and the onset of the second wind phenomenon. Future studies will need to be clear about which aspects of McArdle's disease they wish to improve. There is at the moment too much emphasis on impairment (biochemical and physiological measurements) and not enough on disability (function) and handicap (participation). Other challenges that have emerged from this review relate to the chemical composition of dietary supplements. For example high protein diet does not seem to elicit the same effect as intravenous or oral amino acids. Once such issues have been adequately addressed, the path is clear for new studies to clarify the value of many of the treatments that have been addressed thus far in a limited fashion and to define modalities for new interventions.

AUTHORS' CONCLUSIONS

Implications for practice

As yet it is not possible to recommend any specific treatment for McArdle's disease. Further studies incorporating larger numbers of patients are needed to confirm the effectiveness of low-dose creatine and pre-exercise oral sucrose administration. Research is also required to determine the potential benefit of these treatment modalities in reducing disability and handicap and to assess any long term adverse effects.

Implications for research

Because of the rarity of the disorder, multicentre national and international collaboration will be required to produce high quality effective treatment trials. The development of standardised assessment protocols need to be developed once clear objectives have been agreed as to the phase and type of exercise to be assessed. This will determine the most effective means of measuring functional improvement in affected patients.

ACKNOWLEDGEMENTS

We thank the Muscular Dystrophy Campaign of Great Britain and the Association for Glycogen Storage Diseases (AGSD). We dedicate this review to Nicholas Owston, who sadly died in 2003, in acknowledgement of his untiring support through the AGSD.

POTENTIAL CONFLICT OF INTEREST

Both authors (Beynon and Quinlivan) were involved in the conduct of a randomised cross-over placebo controlled trial of vitamin B6, which did not demonstrate any overall benefit.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Beynon 1998 *{unpublished data only}*

Beynon RJ, Quinlivan RCM, Hopkins P, White L, Bartram C, Phoenix J. McArdle's Disease: molecular genetics, clinical heterogeneity and a therapeutic trial. Muscle & Nerve. 1998;S30.

Day 1985 *{published data only}*

Day T J, Mastaglia F L. Depot-glucagon in the treatment of McArdle's disease. *Australian and New Zealand Journal of Medicine* 1985;**15**(6): 748–50.

Kushner 1990 *{published data only}*

Kushner R F, Berman S A. Are high-protein diets effective in McArdle's Disease. *Archives of Neurology* 1990;**47**(4):383–4.

Lane 1986 *{published data only}*

Lane R J, Turnbull D, Welch J, Walton JL. A double-blind crossover study of verapamil in exertional muscle pain. *Muscle & Nerve* 1986; **9**(7):635–41.

MacLean 1998 *{published data only}*

MacLean D, Vissing J, Vissing S F, Haller RG. Oral branched chain amino acids do not improve exercise capacity in McArdle's disease. *Neurology* 1998;**51**(5):1456–9.

Poels 1990 *{published data only}*

Poels PJ, Braakhekke JP, Joosten EM, Stegeman DF. Dantrolene sodium does influence the second wind phenomenon in McArdle's disease. Electrophysioloical evidence during exercise in a double-blind placebo-controlled, cross-over study in 5 patients. *Journal of the Neurological Sciences* 1990;**100**(1-2):108–12.

Steele 1996 *{published data only}*

Steele I C, Patterson V H, Nicholls D P. A double-blind, placebo controlled, crossover trial of D-ribose in McArdle's disease. *Journal of the Neurological Sciences* 1996;**136**(1-2):174–7.

Vissing 2003 *{published data only}*

*Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *New England Journal of Medicine* 2003;**349**:2503–9.

Vorgerd 2000 *{published data only}*

Vorgerd M, Grehl T, Jager M, Muller K, Freitag G, Patzold T, et al. Creatine therapy in myophosphorylase deficiency (McArdle's disease) A placebo controlled crossover trial. *Archives of Neurology* 2000;**57** (7):956–63.

Vorgerd 2002 *{published data only}*

Vorgerd M, Zange J, Kley R, Grehl T, Husing A, Jager M, et al. Effect of high-dose creatine therapy on symptoms of exercise intolerance in McArdle's disease: double-blind, placebo-controlled crossover study. *Archives of Neurology* 2002;**59**(1):97–101.

References to studies excluded from this review

Haller 2002

Haller RG, Vissing J. Spontaneous "second wind" and glucose-induced "second wind" in McArdle disease. *Archives of Neurology* 2002; **59**(9):1395–402.

Jensen 1990

Jensen K E, J Jacobson, Thomsen C, Henriksen O. Improved energy kinetics following high protein diet in McArdle's syndrome. A 31P magnetic resonance spectroscopy study. *Acta Neurologica Scandinavica* 1990;**81**(6):499–503.

Kono 1984

Kono N, Mineo I, Sumi S, Shimizu T, Kang J, Nonaka K, et al. Metabolic basis of improved exercise tolerance: Muscle phosphorylase deficiency after glucagon administration. *Neurology* 1984;**34** (11):1471–76.

Lewis 1985

Lewis SL, Haller RG, Cook JD, Nunnally RL. Muscle fatigue in McArdle's disease studied by 31P-NMR: effect of glucose infusion. *Journal of Applied Physiology* 1985;**59**(6):1991–94.

Mineo 1984

Mineo I, Kono N, Shimizu T, Sumi S, Nonaka K, Tarui S. A comparative study on glucagon effect between McArdle disease and Tarui disease. *Muscle & Nerve* 1984;**7**(7):552–9.

O'Reilly 2003

O'Reilly D S, Carter R, Bell E, Hinnie J, Galloway P J. Exercise to exhaustion in the second-wind phase of exercise in case of McArdle's disease with and without creatine supplementation. *Scottish Medical Journal* 2003;**48**(2):46–8.

Phoenix 1998

*Phoenix J, Hopkins P, Bartram C, Beynon R, Quinlivan RCM, Edwards RHT. Effect of vitamin B6 supplementation in McArdle's disease: a strategic case study. *Neuromuscular Disorders* 1998;**8**(3-4): 210–12.

Slonim 1985

Slonim A E, Goans PJ. Myopathy in McArdle's syndrome: improvement with a high protein diet. *New England Journal of Medicine* 1985; **312**(6):355–59.

Viskoper 1975

Viskoper R, Wolf E, Chaco J, Katz R, Chowers I. McArdle's syndrome: the reaction to a fat rich diet. *American Journal of Medical Sciences* 1975;**269**(2):217–21.

Wagner 1991

Wagner D R, Zollner N. McCardle's disease: successful symptomatic therapy by high dose oral administration of ribose. *Klinische Wochenschrift* 1991;**69**(2):92.

Additional references

Bartram 1993

Bartram C, Edwards RHT, Clague J, Beynon R. McArdle's disease: a nonsense mutation in exon 1 of the muscle glycogen phosphorylase gene explains some but not all cases. *Human Molecular Genetics* 1993; **2**(8):1291–93.

Bertorini 1982

Bertorini T, Palmieri G, Bhattacharya S. Beneficial effects of Dantrolene sodium in exercise-induced muscle pains: calcium mediated?. *Lancet* 1982;**1**(8272):616–17.

Beynon 1995

Beynon R J, Bartram C, Hopkins P, Toesco V, Gibson H, Phoenix J, et al. McArdle's disease: molecular genetics and metabolic consequences of the phenotype. *Muscle & Nerve* 1995;**3**:S18–22.

Borg 1982
Borg GAV. Psychophysical basis for perceived exertion. *Medicine and Science in Sports and Exercise* 1982;**14**:377–81.

De Stefano 1996
De Stefano N, Argov Z, Matthews PM, Karpati G, Arnold DL. Impairment of muscle mitochondrial oxidative metabolism in McArdle's disease. *Muscle & Nerve* 1996;**19**(6):764–69.

Haller 1983
Haller R G, Dempsey W B, Feit H, Cook J D, Knochel JP. Low levels of muscle pyridoxine in McArdle's syndrome. *American Journal of Medicine* 1983;**74**(2):217–20.

Kubisch 1998
Kubisch C, Wicklein EM, Jentsch TJ. Molecular diagnosis of McArdle's disease: revised genomic structure of the phosphorylase gene and identification of a novel mutation. *Human Mutation* 1998;**43**: 1355–60.

Libonati 1998
Libonati JR, Cox M, Incanno N, Melville SK, Musante FC, Glassberg HL, et al. Brief periods of occlusion and re-perfusion increase skeletal muscle force output in humans. *Cardiologia* 1998;**43**(12):1355–60.

McArdle 1951
McArdle B. Myopathy due to a defect in muscle glycogen breakdown. *Clinical Science* 1951;**10**:13–33.

Mommaerts 1959
Mommaerts WFH, Illingworth B, Pearson CM, Guilorg RJ, Seraydarian K. A functional disorder of muscle associated with the absence of phosphorylase. *Proceedings of the National Academy of Science USA* 1959;**3**:18–22.

Pearson 1961
Pearson CM, Rimor DG, Mommaerts WFHM. A metabolic myopathy due to absence of muscle phosphorylase. *The American Journal of Medicine* 1961;**30**:502–17.

Ruff 1998
Ruff RL. Why do patients with McArdle's disease have decreased exercise capacity?. *Neurology* 1998;**50**(1):6–7.

Schmidt 1959
Schmidt R, Mahler R. Chronic progressive myopathy with myoglobinuria: demonstration of a glycogenolytic defect in muscle. *Journal of Clinical Investigation* 1959;**108**:2044–58.

Tarnopolsky 1997
Tarnopolsky MA, Roy BD, MacDonald JR. A randomised controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. *Muscle & Nerve* 1997;**20**:1502–9.

Vandenberghe 1997
Vandenberghe K, Goris M, Van Hecke P, Van Leemputte M, Vangerven L, Hespel P. Long term creatine intake is beneficial to muscle performance during resistance training. *Journal of Applied Physiology* 1997;**83**:2055–63.

Vissing 1998
Vissing J, Vissing SF, Maclean D, Saltin B, Quistorff B, Haller RJ. Sympathetic activation in exercise is not dependent on muscle acidosis. Direct evidence from studies in metabolic myopathies. *Journal of Clinical Investigation* 1998;**108**:1654–60.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Beynon 1998
Methods	Randomised placebo controlled crossover study.
Participants	8 males and 2 females.
Interventions	50 mg pyridoxine or placebo given for 10 weeks followed by 6 week washout period and then crossover to the alternative treatment.
Outcomes	Erythrocyte AST activity to assess vitamin B6 status, PSEM to assess force generation and fatiguability under ischaemic conditions.
Notes	No significant difference between treatment and placebo.
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	**Day 1985**
Methods	Single blind crossover study.
Participants	A 42 year old affected female.
Interventions	2 mg subcutaneous glucagon, 2 mg of depot glucagon and 1 ml normal saline subcutaneously.
Outcomes	Isometric grip strength under ischaemic conditions. Exercise endurance curves were plotted.
Notes	The patient subjectively felt better after depot glucagon but there was no statistically significant beneficial effect.
Allocation concealment	A

Study	**Kushner 1990**
Methods	Open controlled study.
Participants	3 adults (age and sex not specified). 3 controls (age, sex, height and weight matched).
Interventions	Baseline assessments performed after fasting, 100 g of oral dextrose or 0.33 mg/kg BCAA. Patients were assessed after 1 and 2 months of 0.3 g/kg of dietary BCAAs as a supplement to their habitual diet.
Outcomes	Maximal concentric strength or torque at 60 cycles per minute and muscle endurance measured as absolute work performed to fatigue (60 or 90 cycles per minute with a 2 minute rest between sets).
Notes	No significant immediate or long-term improvement with BCAA supplements.
Allocation concealment	D

Study	**Lane 1986**
Methods	Randomised double- blind placebo controlled crossover study.
Participants	3 adults with McArdle's disease (2 male and 1 female aged 26, 44 and 24 years) and 8 patients with an exertional muscle pain syndrome (6 males and 2 females aged 19 - 40 years).
Interventions	80 mg verapamil once daily for 3 days, twice daily for 4 days then three times daily for 5 weeks. After 6 weeks all patients stopped treatment for 2 weeks and then crossed over to the alternative treatment.
Outcomes	Pain diary which recorded the severity of muscle pain on a scale of 0 to 10, the amount of time spent reclining, sleeping, sitting and standing/ walking/ running for the same three hour period each day for 14 weeks, timed exercise test.
Notes	No effect. None of the McArdle's cases kept satisfactory diaries.
Allocation concealment	A

Characteristics of included studies (*Continued*)

Study	**MacLean 1998**
Methods	Randomised single- blind placebo crossover trial.
Participants	6 subjects, 3 male (50, 39 and 27 years) 3 female (42, 29 and 25 years).
Interventions	77 mg/kg BCAA as a drink and a control 200 ml non- calorific drink.
Outcomes	Performance on cycle ergometer for 20 minutes at maximal intensity without experiencing pain or exhaustion.
Notes	No beneficial effect, exercise capacity was diminished after BCAA.
Allocation concealment	A

Study	**Poels 1990**
Methods	Randomised double- blind placebo controlled crossover trial.
Participants	2 females (23 and 29 years) and 3 males (aged 21, 28 and 41 years).
Interventions	Placebo or dantrolene sodium 150 mg was given for 6 weeks, the dose was built up to 50 mg three times a day over 3 days. There was a 4 week washout period before crossover to the alternative treatment for a further 6 weeks.
Outcomes	Weekly subjective scores of improvement and serum CK . Performance on a cycle ergometer at 30% VO2 max after a 12 hour fast at the end of each treatment phase.
Notes	Four cases had to reduce the daily dose of dantrolene to 100 mg or 75 mg because of side-effects. Subjective improvement in 1 case on treatment and 3 cases on placebo. No change in CK. levels. Positive EMG changes occurred during the treatment phase. Results were thus inconclusive.
Allocation concealment	A

Study	**Steele 1996**
Methods	Randomised double- blind placebo controlled trial.
Participants	4 males and 1 female age range 20 to 60 years.
Interventions	15 g oral ribose four times a day for 7 days or placebo.
Outcomes	Muscle performance on treadmill with respiratory gas analysis.
Notes	No benefit, adverse effects noted, unpleasant taste, symptoms of hypoglycaemia and increased bowel frequency.
Allocation concealment	C

Characteristics of included studies (*Continued*)

Study	**Vissing 2003**
Methods	Randomised single blind placebo controlled cross-over study
Participants	7 males and 5 females aged 22 to 57 years.
Interventions	75 g oral sucrose or placebo.
Outcomes	Heart rate, level of perceived exertion, blood glucose levels.
Notes	Significant reduction in perceived exertion and heart rate. Significant rise in blood glucose levels.
Allocation concealment	A

Study	**Vorgerd 2000**
Methods	Randomised double- blind placebo controlled crossover trial.
Participants	9 cases (6 females and three males aged 9 to 61 years).
Interventions	Placebo or creatine, loading dose for 5 days (150 mg/kg) then 60 mg /kg for 5 weeks then a four week washout period and crossover to the other treatment.
Outcomes	Fatigue severity score, muscle P-31 MRS, 3 minute ischaemic exercise test.
Notes	Dizziness and headache in one patient during the treatment phase, no other adverse efects noted. Five cases reported improvement of muscle symptoms with treatment. Force-time intervals and depletion of creatine was significantly greater during ischaemic and aerobic exercise with creatine. The decrease of median frequency of surface EMG during contraction was significantly larger with creatine. Results were statistically significant.
Allocation concealment	A

Study	**Vorgerd 2002**
Methods	Randomised double- blind placebo controlled trial.
Participants	19 cases (8 females and 11 males aged 11 to 59 years).
Interventions	Creatine 150 mg/kg/day for 5 weeks vs placebo, washout period 4 weeks.
Outcomes	Subjective muscle symptoms, serum CK, creatine, P-31 MRS and surface EMG.
Notes	Increase in exercise induced pain, limitation of daily activity. Surface EMG revealed a smaller increase in amplitude over time with muscle contraction. No significant changes in muscle spectroscopy.
Allocation concealment	A

BCCA: Branched-chain amino acid
CK: Creatine kinase

Characteristics of excluded studies (*Continued*)

Characteristics of excluded studies

Haller 2002	Three McArdle's disease patients, no controls. No concealment of allocation.
Jensen 1990	Single patient study with baseline controls data but controls did not receive intervention therapy. No concealment of allocation, no statistical analysis.
Kono 1984	Single patient, no concealment of allocation. Patient concurrently self medicating with coenzyme Q10.
Lewis 1985	Single patient with two normal controls. No concealment of allocation
Mineo 1984	Two female McArdle's patients (GSDV) compared with two male cases with phosphofructokinase deficiency (GSD-VII). No concealment of allocation. Only one GSDV and one GSD VII patient were assessed with bicycle ergometry.
O'Reilly 2003	Single case study, no concealment of allocation.
Phoenix 1998	Single case study, inadequate concealment of allocation.
Slonim 1985	Single case study, no concealment of allocation.
Viskoper 1975	Single patient, no concealment of allocation.
Wagner 1991	Single patient, no concealment of allocation.

ADDITIONAL TABLES

Table 01 Methodological quality on included studies

Study	Observer blinding	Patient blinding	Diagnostic criteria	Outcome criteria
Beynon 1998	A	A	A	A
Day 1985	D	D	A	A
Kushner 1990	D	D	D	A
Lane 1986	C	A	A	A
Maclean 1998	D	A	A	A
Poels 1990	A	A	A	A
Steele 1996	A	A	A	A
Vissing 2003	D	A	A	A
Vorgerd 2000	A	A	A	A
Vorgerd 2002	A	A	A	A

GRAPHS

This review has no graphs.

COVER SHEET

Title	Pharmacological and nutritional treatment for McArdle's disease (Glycogen Storage Disease type V)
Authors	Quinlivan R, Beynon RJ
Contribution of author(s)	Both reviewers agreed the criteria for inclusion of studies for the review and their methodological quality. Both reviewers independently assessed all of the studies reviewed. RQ completed the first draft with agreement and input from RB, who also approved the final draft of the review.
Issue protocol first published	2002/1
Review first published	2004/3
Date of most recent amendment	26 May 2004
Date of most recent SUBSTANTIVE amendment	01 March 2004
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Rosaline Quinlivan Consultant Paediatrician Muscle Clinic Robert Jones and Agnes Hunt District and Orthopaedic Hospital Gobowen Oswestry SY10 7AG UK Telephone: 01743 261073 E-mail: Ros.Quinlivan@rjah.nhs.uk Facsimile: 01743 261060
Cochrane Library number	CD003458
Editorial group	Cochrane Neuromuscular Disease Group
Editorial group code	HM-NEUROMUSC