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

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

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ABSTRACT

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

Search strategy
We updated the review by searching the Cochrane Neuromuscular Disease Group Trials Register (November 2007), MEDLINE (January 1966 to November 2007) and EMBASE (January 1980 to November 2007) using the search terms 'McArdle disease' and its 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 participant or observer blinding were included in the discussion. Types of interventions included any pharmacological agent or micronutrient or macronutrient supplementation. Primary outcome measures included any objective assessment of exercise endurance (for example aerobic capacity (VO₂ max, walking speed, muscle force or power and improvement in fatigability). 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
Three review authors checked the titles and abstracts identified by the search and reviewed the manuscripts. Two review authors (RQ and RB) independently assessed methodological quality of the full text of potentially relevant studies and extracted data onto a specially designed form.

Main results
We reviewed 24 studies. Twelve trials fulfilled the criteria for inclusion, with two being first identified in this update. The 12 excluded trials are 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
There is no evidence of significant benefit from any specific nutritional or pharmacological treatment in McArdle disease. In one small trial low dose creatine produced slight benefit but high dose creatine caused myalgia. Ingestion of oral sucrose immediately before exercise reduced perceived ratings of exertion and heart rate and improved exercise tolerance. This treatment will not influence sustained or unexpected exercise and may cause significant weight gain. A carbohydrate rich diet did benefit patients. Because of the rarity of McArdle disease, there is a need to develop international multicentre collaboration and standardised assessment protocols for future treatment trials.
**Pharmaceutical and nutritional treatment for McArdle disease**

McArdle Disease (also known as glycogen storage disease type V) is a disorder affecting muscle metabolism and is caused by the absence of an enzyme called muscle phosphorylase. This causes an inability to break down glycogen ‘fuel’ stores. The condition leads to pain and fatigue with strenuous exercise. Sometimes severe muscle damage may develop and occasionally this results in acute reversible kidney failure. Taking low dose creatine supplements has a modest benefit in improving exercise tolerance in a small number of people with McArdle disease. Taking a sugary drink before planned exercise can improve performance but this treatment is not practical for day-to-day living. A diet rich in carbohydrate may be superior to a diet rich in protein. Further research is needed before any specific treatment can be recommended.

**Background**

McArdle 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 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 people is the nonsense mutation at R50X (previously referred to as R49X) (Kubisch 1998). By December 2006 67 mutations in the gene had been identified (Andreu 2007). 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 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. 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 (Vising 1998).

Most people present in the second or third decade, although symptoms are often reported retrospectively from childhood. With advancing age, a small proportion of people develop fixed muscle weakness predominantly affecting the shoulder girdle. 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 people learn to manage their condition using an exercise pattern which exploits a phenomenon known as a ‘second wind’. In McArdle disease, pain occurs within a few minutes of initiating exercise. However, if at this stage the person 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 an elevated 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 give an 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 modifying genes such as the angiotensin converting enzyme gene (ACE) and alpha actinin 3 (ACTN3) (Gomez-Gallego 2007; Lucia 2007; Martinuzzi 2007), differences in lifestyle including diet, fitness and aerobic capability. A study of 99 Spanish participants found a significant gender effect with females presenting with a significantly more severe phenotype than males (Rubio 2007). 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 substrates 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, and in McArdle 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 demands placed on alternative fuel sources in McArdle disease may make people more dependent on vitamin B6. Dantrolene sodium is used as a muscle relaxant for spasticity and for the prevention and treatment of malignant hyperthermia. Dantrolene 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 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 (Vandenbergh 1997) and to increase strength in people with mitochondrial myopathies (Tarnopolsky 1997). In McArdle disease magnetic resonance spectroscopy studies during exercise have demonstrated a rapid depletion of phosphocreatine with exercise, so creatine supplementation therefore might be beneficial. Upregulation of oxidative metabolism through diet, drugs or exercise might potentially increase the availability of a second wind. Thus, for example, an intravenous infusion of glucose during exercise enables glycolysis which in turn up-regulates oxidative phosphorylation (Haller 2002). The efficiency of muscle adaptation to training has been shown to be due to polymorphic variants of ACE. Polymorphisms leading to insertions or deletions (I/D) can affect muscle performance after training. In particular, the I allele which is associated with reduced ACE activity shows improved performance after aerobic training. Carrying the I/D ACE polymorphism affects phenotypic severity in McArdle disease (Gomez-Gallego 2007; Martinuzzi 2003). The use of pharmacological agents which inhibit ACE might improve performance in McArdle disease.

In most people with McArdle disease, the primary genetic abnormality is a missense mutation in the PYGM gene leading to a stop codon. Certain drugs, for example the aminoglycosides, may allow the potential to read through stop codons and thus may induce the synthesis of a full-length protein (Barton-Davis 1999). This potential therapeutic strategy may be exploited with new pharmacological compounds for McArdle disease.

The first version of this review was published in 2004, contained 10 trials and showed no evidence of significant benefit. We have updated this review to include a total of 12 trials.

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 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 were included in the discussion.

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 pharmaceutical agent or micronutrient or macronutrient supplementation.

Types of outcome measures

Primary outcome measures
The primary outcome measure was level of change, after three months from start of treatment in exercise endurance objectively assessed by, for example VO₂ max (aerobic capacity), walking speed, muscle force or power and improvement in fatigue.

Secondary outcome measures
Secondary outcome measures after three months of treatment included:

1. metabolic changes including reductions in serum plasma creatine kinase and frequency of myoglobinuria together with metabolic changes seen on 31 phosphorus- magnetic resonance spectroscopy (31P-MRS).
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 METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Neuromuscular Disease Group methods used in reviews.

Electronic searches
We searched the Cochrane Neuromuscular Disease Group Trials Register for randomised trials using the following search terms:
To search 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 three unpublished studies, one conducted by two of the authors of this review.

Other sources
We reviewed the bibliographies of the randomised trials identified, contacted the authors and known experts in the field and approached pharmaceutical companies to identify additional published or unpublished data.

METHODS OF THE REVIEW

Selection of studies
Three review authors checked titles and abstracts identified and all review authors independently assessed the full text of all potentially relevant studies.

Data extraction and management
Each review author assessed the full text independently using pre-agreed data extraction forms.

Assessment of methodological quality of included studies
Two reviewers (RQ and RB) 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.

Data analysis
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 relative risks or difference in means as a weighted mean difference with 95% confidence intervals to provide pooled estimates.

DESCRIPTION OF STUDIES

Twenty four studies were assessed and in addition to the 10 studies identified for inclusion in the first version of this review, this update identified two new trials (Vissing 2007 and Martinuzzi 2007). The twenty four studies assessed 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, oral sucrose, intravenous gentamicin, ketogenic diet, high carbohydrate diet and ramipril. 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.

METHODODOLOGICAL 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 participants 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 Additional Table 01, '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 participants with McArdle 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). Participants underwent a weekly incremental exercise treadmill test with respiratory gas analysis. All five participants completed the trial, although some developed symptoms of hypoglycaemia which included light-headedness and hunger. One participant 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 participant with McArdle 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 participant was asked to report when the forearm became fatigued or painful, at which point exercise was stopped. Various treatments were assessed and neither the participant 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 participants with McArdle disease (diagnosed by muscle biopsy) were studied compared with eight participants with an exertional pain syndrome of unknown cause. Participants 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 participants were asked to keep a pain and activity diary, at the same time each week the participants 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 participants kept satisfactory diaries, two more participants 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 cases.

Beynon 1998 (unpublished data) undertook a randomised double-blind placebo controlled crossover trial of vitamin B6. Ten participants (eight male and two female) with biochemically and genetically proven McArdle disease were given either placebo or Vitamin B6 in a once daily dose of 50 mg. Ethical approval was obtained and participant 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 participants, 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 participants underwent programmed stimulation electromyogram (PSEM) to assess force generation and fatigability under ischaemic conditions. The investigators were unaware of the phase in the trial for each participant (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 participants were not revealed but the controls were age, sex, height and weight matched. Prior to the two month period of dietary supplementation, the participants 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. Participants 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-caloric drink. The six participants (three males and three females) were unaware of treatment or placebo, but the investigators were not blinded to treatment. The participants 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 participants. 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 participants (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 participants reducing the dose. At the end of both treatment phases participants were tested on a bicycle ergometer at 30% VO2 max during two hours and after a 12 hour fast. Surface EMG was recorded during exercise. Participants 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 disease participants (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. Participants 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 participants 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 participants 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. However 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 participants (seven men and five women) aged 22 to 57 years, known to have McArdle disease were asked to exercise at a fixed intensity 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 disease. When used regularly, however, sucrose ingestion may result in weight gain and would be of no benefit for unprepared exercise where such pre-treatment could not be taken. Oral sucrose would be contraindicated in diabetics.

In an unpublished study, Vissing 2007 compared carbohydrate-rich versus protein-rich diets in a randomised cross-over study design with one week washout. The study could not be blinded. Participants (6 male and one female) were asked to follow a fixed diet with pre-set recipes for three days, compliance was ensured because participants were accommodated in the study site for the duration of the study. The diet consisted of either 20% fat, 15% protein and 65% carbohydrate, or 55% protein, 30% carbohydrate and 15% fat. Assessments were undertaken using cycle ergometry for 15 minutes at two thirds of maximal exertion, followed by incremental work intensity to exhaustion. With the carbohydrate rich diet there was a significant drop in heart rate and work effort.

Martinuzzi 2007 studied eight participants who were given 2.5 mg ramipril for 12 weeks in a double-blind, randomised, placebo controlled, crossover trial with a one month washout. The primary outcome measure was an objective assessment of performance using cycle ergometry. The secondary outcome measure was 31P MRS of the calf muscle during plantar flexion and subjective outcome measures including SF-36 and the WHO-DAS 11 (a disability assessment scale). SF-36 showed improvement in selected areas in both the treatment and placebo arms. No significant difference was found between the placebo and ramipril in objective exercise parameters, although the DAS-11 score improved in ramipril treated participants. The treatment was more effective in participants with the D/D ACE genotype, in whom it was associated with a slight but significant increase in peak VO₂.

Results Summary
There are few good quality controlled treatment trials for McArdle disease. Those trials which do exist have included only small numbers of participants (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 participants, although high dose creatine worsened symptoms. Oral ingestion of sucrose taken 30 minutes before exercise improved exercise tolerance in twelve participants undertaking planned exercise. A diet rich in carbohydrate may be better than a protein-rich diet. Ramipril 2.5 mg orally daily showed possible benefit in participants with the D/D ACE haplotype.

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

Non-randomised studies:

(i) High protein diet
Treatment with a high protein diet has been recommended in the past for people with McArdle 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 person suffered cramps on exertion and had significant upper limb muscle wasting and weakness and was confirmed to have McArdle 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 in-
dividual (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 person was exercised carefully through a second wind phase and then exercised to exhaustion. The person 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 participant 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 person's exercise ability and an improvement in strength in the upper limbs. There was no concealment of allocation and the person'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 participant with McArdle disease, confirmed by muscle biopsy. Bicycle ergometry was performed two hours after meals of the individual'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: two minutes work followed by 10 minutes rest. Endurance at submaximal muscle strength was measured at 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 participant 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 five to eight 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 participant.

(2) High fat diet
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. A beneficial action of a continuous infusion of emulsified fat in 4% glucose on the muscle performance of a participant was demonstrated. On the basis of this case report, Viskoper 1975 assessed the potential benefit of a high fat diet for three days in a single case study. The participant, an affected 21 year old male, was exercised on a bicycle ergometer at a workload of 60 kW 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 participant reported subjective feelings of increased fitness, but this could not be confirmed objectively by the researchers. In a second branch of the study isoproterenol 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 participant was on a normal diet. No beneficial effect was observed. Busch 2005 and Vorgerd 2007 described the effects of a ketogenic diet in one 55 year old male with McArdle disease by increasing the fat content of his diet by 80% with 14% protein for one year. His exercise tolerance was reported to be increased three to 10 fold. Maximum strength and activity also improved and CK levels reduced. Ketogenic diet did not alter 31P-MRS data during rest, work and recovery. A larger controlled study is currently in progress.

(3) Glucagon administration
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 participant aged 26 years. No placebo was used and there were no control subjects. Blood levels for creatine kinase, lactate dehydrogenase, glucose, free fatty acids and ammonia were measured. The participant was exercised for three minutes. The authors suggested that glucagon improved exercise tolerance. The participant 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 participant 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. Mino 1984 studied two female participants with McArdle 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 participant with McArdle disease and one with Tarui’s were exercised on a bicycle ergometer with and without glucagon pre-treatment following an overnight fast. All four participants underwent a modified ischaemic exercise test and were given the following: oral glucose, glucagon and glucose combined with insulin. The authors found that the participant with McArdle disease 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 disease should also be considered in context of its long-term side-effects, which include haemolytic anaemia.

(4) Other interventions
Non-randomised studies for other interventions have included vitamin B6, oral ribose, intravenous glucose, creatine and gentamicin.

Phoenix 1998 reported the effect of withdrawal of daily 50 mg Vitamin B6 in a male participant with McArdle disease. The participant had been taking vitamin B6 as a supplement for two years. The effect of withdrawal of treatment was assessed. The participant 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 programmed stimulation electromyography (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 participant’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. 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 participant 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 participant 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 with McArdle disease and two normal controls (one male and one female). The 31P-NMR of the forearm flexor muscles was assessed during exercise using a handgrip dynamometer (modified to work in the magnetic field) to record maximal handgrip. 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 person with McArdle disease fatigued with an impeding muscle contracture at two minutes and 10 seconds. From rest to fatigue the participant’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 participant performed maximal handgrip exercise for more than seven minutes. During glucose infusion PCr fell and Pi increased to a much lesser extent than under control conditions. In the healthy controls forearm PCr declined to tend to decline similarly and Pi tended to increase less in the healthy participants than the person with McArdle disease. Exercise in the control participants was no different with the glucose infusion. Haller 2002 studied the effect of intravenous glucose on the second wind. They studied nine participants (eight with complete phosphorylase deficiency and one with 3% of normal phosphorylase activity). Participants exercised on a cycle ergometer for about 40 minutes. Initial work capacity was determined in the first six to eight minutes, then workload was reduced for five to 10 minutes. The workload was again progressively increased to determine peak performance at 25 minutes. Immediately afterwards 50 ml of 50% glucose was infused over one to two 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. Participants 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 six to eight 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.

Schroers 2006 tested the short-term efficacy of gentamicin in four participants with McArdle disease who had stop mutations. These were given daily intravenous gentamicin sulphate 8mg/kg/day
each day for ten consecutive days in an open study. Plasma creatine kinase levels decreased but not significantly. Participants were evaluated with 31P-MRS but no difference was detected. Further studies on myoblasts demonstrated no increase in phosphorylase expression. Thus, short-term gentamicin treatment appeared to have no effect on performance in McArdle disease. It might be that the treatment was not given for long enough or the type of non-sense mutation was not amenable to the effects of the drug.

(5) Outcome measures
A recurrent theme of therapeutic studies for McArdle disease is the restricted availability of patients. Future studies will need to be multicentre and probably multinational. The limited evidence suggesting that females with McArdle disease may differ in phenotypic expression to males opens the question of considering a gender effect when planning future treatment trials. 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 disease. Whilst objective physiological tests are valuable in determining proof of principle, there is also a need for assessments that relate more to lifestyle and day-to-day demands on skeletal muscle, for example assessments of walking rather than cycling. The features of McArdle 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 disease they wish to improve. There is at the moment too much emphasis on impairment (biochemical and physiological measurements) and not enough on disability (activities) and handicap (participation). Other challenges that have emerged from this review relate to the chemical composition of dietary supplements. For example a 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 disease.

Implications for research
Further studies incorporating larger numbers of patients are needed to confirm the effectiveness of interventions including: low dose creatine, pre-exercise oral sucrose, dietary manipulation (protein vs carbohydrate) and oral ramipril by defining patient groups according to ACE phenotype. The development of new compounds which induce read-through of stop codons, such as PTC 124, and drugs to up-regulate the brain phosphorylase isoform, such as valproic acid, could be promising, initial studies on cell culture and animal models are required before large scale clinical trials can be contemplated. More research is needed to determine optimum outcome measures, for example some assessments such as 31P-MRS, which is very sensitive at detecting metabolic changes, may be less effective in detecting clinically meaningful improvements, while assessments of daily activities such as walking may capture functional changes with greater sensitivity. Assessments of quality of life will also be useful in determining benefit although it is recognised that such scales have limitations. 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.

POTENTIAL CONFLICT OF INTEREST
Two authors (RB and RQ) were involved in the conduct of a randomised cross-over placebo controlled trial of vitamin B6, which did not demonstrate any overall benefit. One author (AM) was involved in the conduct of a randomised controlled trial of ramipril which did not demonstrate any significant benefit.

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.

SOURCES OF SUPPORT

External sources of support
- No sources of support supplied

Internal sources of support
- No sources of support supplied
References to studies included in this review

Beynon 1998  [unpublished data only]

Day 1985  [published data only]

Kushner 1990  [published data only]

Lane 1986  [published data only]

MacLean 1998  [published data only]

Martinuzzi 2007  [published data only]

Poels 1990  [published data only]

Steele 1996  [published data only]

Visking 2003  [published data only]

Visking 2007  [unpublished data only]

Vorgedor 2000  [published data only]

Vorgedor 2002  [published data only]

References to studies excluded from this review

Busch 2005

Haller 2002

Jensen 1990

Kono 1984

Lewis 1985

Mino 1984

O’Reilly 2003

Phoenix 1998

Schroers 2006

Sloenim 1985

Viskoper 1975

Vorgedor 2007
Bartram 1993

Additional references
Andreu 2007

Barton-Davis 1999

Bartram 1993

Bertorini 1982

Beynon 1995

Borg 1982

De Stefano 1996

Gomez-Gallego 2007

Martinuzzi 2003

McArdle 1951

Mommaerts 1959

Pearson 1961

Rubio 2007

Ruff 1998

Schmidt 1959

Tarnopolsky 1997

Vandenbergh 1997

Vising 1998

* Indicates the major publication for the study
### Characteristics of included studies

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Kushner 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Open controlled study.</td>
</tr>
<tr>
<td>Participants</td>
<td>3 adults (age and sex not specified). 3 controls (age, sex, height and weight matched).</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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).</td>
</tr>
<tr>
<td>Notes</td>
<td>No significant immediate or long-term improvement with BCAA supplements.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>D – Not used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Lane 1986</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised double-blind placebo controlled crossover study.</td>
</tr>
<tr>
<td>Participants</td>
<td>3 adults with McArdle's disease (2 male and 1 female aged 26, 44 and 24 years) and 8 people with an exertional muscle pain syndrome (6 males and 2 females aged 19 to 40 years).</td>
</tr>
<tr>
<td>Interventions</td>
<td>80 mg verapamil once daily for 3 days, twice daily for 4 days then three times daily for 5 weeks. After 6 weeks all participants stopped treatment for 2 weeks and then crossed over to the alternative treatment.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>MacLean 1998</td>
<td>6 participants, 3 male (50, 39 and 27 years) 3 female (42, 29 and 25 years).</td>
</tr>
<tr>
<td>Martinuzzi 2007</td>
<td>8 participants.</td>
</tr>
<tr>
<td>Poels 1990</td>
<td>2 females (23 and 29 years) and 3 males (aged 21, 28 and 41 years).</td>
</tr>
<tr>
<td>Steele 1996</td>
<td>4 males and 1 female age range 20 to 60 years.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Vissing 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Carbohydrate rich diet vs protein-rich diet.</td>
</tr>
<tr>
<td>Participants</td>
<td>8 participants with McArdle disease.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Fixed menu plan with recipes for 3 days. Crossover design.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Incremental cycle test 2/3 max for 15 minutes then max to exhaustion.</td>
</tr>
<tr>
<td>Notes</td>
<td>Reduced heart rate and work load with the carbohydrate rich diet.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>C – Inadequate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Vorgerd 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised double-blind placebo controlled crossover trial.</td>
</tr>
<tr>
<td>Participants</td>
<td>9 cases (6 females and three males aged 9 to 61 years).</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Fatigue severity score, muscle P-31 MRS, 3 minute ischaemic exercise test.</td>
</tr>
<tr>
<td>Notes</td>
<td>Dizziness and headache in one patient during the treatment phase, no other adverse effects 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.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A – Adequate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Vorgerd 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised double-blind placebo controlled trial.</td>
</tr>
<tr>
<td>Participants</td>
<td>19 cases (8 females and 11 males aged 11 to 59 years).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Creatine 150 mg/kg/day for 5 weeks vs placebo, washout period 4 weeks.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Subjective muscle symptoms, serum CK, creatine, P-31 MRS and surface EMG.</td>
</tr>
<tr>
<td>Notes</td>
<td>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.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A – Adequate</td>
</tr>
</tbody>
</table>

**BCCA**: Branched-chain amino acid  
**CK**: Creatine kinase
Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busch 2005</td>
<td>Single case study</td>
</tr>
<tr>
<td>Haller 2002</td>
<td>Three people with McArdle disease, no controls. No concealment of allocation.</td>
</tr>
<tr>
<td>Jensen 1990</td>
<td>Single participant study with baseline controls data but controls did not receive intervention therapy. No concealment of allocation, no statistical analysis.</td>
</tr>
<tr>
<td>Lewis 1985</td>
<td>Single participant with two normal controls. No concealment of allocation</td>
</tr>
<tr>
<td>Mineo 1984</td>
<td>Two female participants with McArdle's (GSDV) compared with two male cases with phosphofructokinase deficiency (GSDVII). No concealment of allocation. Only one GSDV and one GSD VII patient were assessed with bicycle ergometry.</td>
</tr>
<tr>
<td>O’Reilly 2003</td>
<td>Single case study, no concealment of allocation.</td>
</tr>
<tr>
<td>Phoenix 1998</td>
<td>Single case study, inadequate concealment of allocation.</td>
</tr>
<tr>
<td>Schroers 2006</td>
<td>Single case study, no concealment of allocation.</td>
</tr>
<tr>
<td>Slonim 1985</td>
<td>Single case study, no concealment of allocation.</td>
</tr>
<tr>
<td>Viskoper 1975</td>
<td>Single participant, no concealment of allocation.</td>
</tr>
<tr>
<td>Vorgerd 2007</td>
<td>Open design, no concealment of allocation.</td>
</tr>
<tr>
<td>Wagner 1991</td>
<td>Single participant, no concealment of allocation.</td>
</tr>
</tbody>
</table>

ADDITIONAL TABLES

Table 01. Methodological quality of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Observer blinding</th>
<th>Patient blinding</th>
<th>Diagnostic criteria</th>
<th>Outcome criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beynon 1998</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Day 1985</td>
<td>D</td>
<td>D</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Kushner 1990</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>Lane 1986</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Maclean 1998</td>
<td>D</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Poels 1990</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Steele 1996</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Vissing 2003</td>
<td>D</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Vorgerd 2000</td>
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</tr>
<tr>
<td>Vorgerd 2002</td>
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<td>A</td>
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<td>A</td>
</tr>
</tbody>
</table>
Table 02. Ovid MEDLINE Search Strategy

Ovid MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. animals/ not humans/
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
13. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab.
14. placebos/
15. placebo$.ti,ab.
16. random$.ti,ab.
17. research design/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. comparative study/
22. exp evaluation studies/
23. follow up studies/
24. prospective studies/
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. Glycogen Storage Disease Type V/
31. (McArdle$ or Glycogen Storage Disease Type V or GSDV or muscle phosphorylase deficiency).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. 30 or 31
33. 29 and 32

Table 03. Ovid EMBASE Search Strategy

Ovid EMBASE

1. Randomized Controlled Trial/
2. Clinical Trial/
3. Multicenter Study/
4. Controlled Study/
5. Crossover Procedure/
6. Double Blind Procedure/
7. Single Blind Procedure/
8. exp RANDOMIZATION/
9. Major Clinical Study/
Table 03. Ovid EMBASE Search Strategy  (Continued)

Ovid EMBASE
10. PLACEBO/
11. Meta Analysis/
12. phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
14. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
15. placebo$.tw.
16. random$.tw.
17. control$.tw.
18. (meta?analys$ or systematic review$).tw.
19. (cross?over or factorial or sham? or dummy).tw.
20. ABAB design$.tw.
21. or/1-20
22. human/
23. nonhuman/
24. 22 or 23
25. 21 not 24
26. 21 and 22
27. 25 or 26
28. Glycogen Storage Disease Type 5/
29. (McArdle$ or Glycogen Storage Disease Type V or Glycogen Storage Disease Type 5 or GSDV or muscle phosphorylase deficiency).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
30. 28 or 29
31. 27 and 30

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)
∗Dietary Supplements; Glycogen Storage Disease Type V [drug therapy; ∗therapy]; Randomized Controlled Trials as Topic

MeSH check words
Humans

COVER SHEET

Title  Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V)
Authors  Quinlivan R, Beynon RJ, Martinuzzi A
Contribution of author(s)  RQ and RB were involved in the original review and agreed criteria for inclusion of studies and their methodological quality. RQ and MA were involved in assessing the two new studies included in the updated review. RQ completed the first and updated drafts with agreement and approval from RB and MA.
Since the last update of this review in 2004, there have been several new studies. An unpublished study comparing a carbohydrate rich diet with a protein rich diet demonstrated improved exercise performance with the carbohydrate rich diet (Vissing 2007). No benefit was observed with oral ramipril.