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Clinical practice guidelines for glycogen storage disease V & VII (McArdle disease and Tarui disease) from an international study group

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1. Introduction

By an initiative of the International Association of Muscle Glycogen Storage Disease (IamGSD), an international workshop was organised in the form of several digital meetings to provide a document as a resource for clinicians regarding current best practice related to diagnosis and management of Glycogen Storage Diseases (GSDs) V (McArdle) and VII (Tarui).

2. General background

2.1. Overview

Glycogen is the stored form of glucose, which is primarily derived from ingested carbohydrates. In order to break down glycogen for energy, the coordinated action of a number of enzymes is required; GSDs result from a defect in one of these enzymes.

There are three isoforms of phosphorylase, an enzyme encoded by any of three genes depending on cell type, muscle (*PYGM* gene), liver (*PYGL* gene), and brain (*PYGB* gene). GSD V is the most common muscle GSD, and results from a deficiency in the muscle isoform of glycogen phosphorylase (myophosphorylase) [1]. A deficiency of this enzyme disables the breakdown of muscle glycogen into glucose-1-phosphate, resulting in a block in glycogenolysis. However, glycolysis is only partially blocked in GSD V, as muscle fibres can take up serum glucose and convert it to glucose-6-phosphate downstream of the metabolic block [2].

The primary intramuscular and extramuscular substrates of skeletal muscle metabolism include: (a) muscle glycogen; (b) blood glucose derived from liver glycogenolysis and from gluconeogenesis, as well as from the gut when carbohydrate is ingested; and (c) fatty acids derived from both intramuscular triacylglycerides and triacylglyceride in adipose tissue [3]. Because skeletal muscle relies predominantly on anaerobic energy for the first few minutes as it transitions from rest to activity, and throughout more intense activities, individuals with GSD V experience muscle fatigue and pain, tachypnea, and tachycardia very soon after initiating physical activity and during all intense activities. If these warning signs are not heeded, a muscle contracture may occur very rapidly which could lead to rhabdomyolysis.

Unique to GSD V is a phenomenon called 'second-wind', which typically occurs about 6 to 10 min into physical activity. It was originally identified by Pearson et al (1961), and denotes a marked improvement in the capacity for physical activity such that activity that previously caused fatigue becomes more easily tolerated [4]. 'Second-wind' is marked by a dramatic fall in heart rate, commonly by 20 to as much as 50 beats per minute, by an improved ability of working muscle to extract oxygen and substrates from

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arterial blood, by a marked fall in perceived exertion, and often by a decrease in ventilation and breathing effort. The basis of this improved physical activity tolerance has long been recognised to relate to a change in muscle metabolism. At approximately 6 to 10 min of sustained physical activity a nadir of oxidative capacity occurs, which is then followed by improved oxidative capacity attributable to increased delivery, uptake, and metabolism of alternative fuels (such as free fatty acids (FFA), glucose, and amino acids) that increase oxidative capacity, on average, by 25%.

There are three isoforms of Phosphofructokinase, a tetrameric enzyme encoded by any of three genes depending on cell type, muscle (*PFKM* gene), liver (*PFKL* gene), and platelet (*PFKP* gene). In GSD VII there is a complete block in glycolysis due to a deficiency of the enzyme muscle phosphofructokinase, whereas normal isoforms are present in the liver and platelets [5]. Muscle phosphofructokinase is a glycolytic enzyme that catalyses the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate. Accordingly, use of both muscle glycogen and blood glucose is blocked, resulting in a metabolic shift to a non-glycolytic anaerobic pathway, which has by-products of uric acid and ammonia. A GSD V style of 'second-wind' does not occur in GSD VII, thereby increasing the reliance on fat metabolism. Ingestion of glucose prior to exercise in individuals with GSD VII worsens exercise capability, leading to an 'out-of-wind' phenomenon [6].

Isolated and unconfirmed cases of a severe infantile form of GSD VII have been reported.

2.2. History

In the 1920s, several hepatic forms of glycogenosis were described and in 1932 the first muscle glycogenosis, Pompe disease (type II) [7], was described. GSD V was described in 1951 by Dr. Brian McArdle [8]. He elegantly demonstrated that lactate from an effluent vein draining from an exercising muscle did not increase during exercise. At the same time, he showed that glucose could be mobilised from the liver after norepinephrine injection, which indicated intact liver glycogenolysis. He therefore correctly deduced that the patient had a disorder of muscle glycogen breakdown. In 1959, it was shown that the affected enzymatic step was myophosphorylase [9,10]. In 1984, the gene encoding myophosphorylase (*PYGM*) was discovered [11].

GSD VII was first described by Dr. Seiichiro Tarui [12] in Japanese patients, and then in an Ashkenazi Jew [13]. Although more than 50 years have passed since its discovery, GSD VII remains a very rare muscle GSD.

2.3. Nomenclature

GSD V is also referred to as McArdle disease, McArdle's syndrome, Muscle Phosphorylase Deficiency, Myophosphorylase Deficiency, McArdle Myopathy, Muscle Glycogen Phosphorylase Deficiency, GSD Type 5 and GSD5. GSD VII is also referred to as Tarui disease, Muscle Phosphofructokinase Deficiency, GSD Type 7, and GSD7. McArdle disease and Tarui disease will hereafter be referred to as GSD V and GSD VII, respectively.

2.4. Clinical overview

The main feature of both GSD V and GSD VII is 'physical activity intolerance'. In almost all papers to date, this has been referred to as 'exercise intolerance'. However, exercise, a subcategory of physical activity, is planned and controlled, thereby making it easier to manage. By contrast, activities of daily living (ADL) are often spontaneous, and symptoms can occur within seconds to minutes after initiation. Accordingly, we use the term 'physical activity intolerance' throughout.

Despite a long history of activity limitations, many individuals only receive a diagnosis as the result of an incidental finding of elevated serum creatine kinase (CK). The inability to sustain muscle effort can objectively be measured during incremental exercise tests, in which the maximal work performed is usually $< 50\%$ of what might be expected for age- and gender-matched controls. Premature physical activity intolerance is mainly associated with muscle fatigue and activity-induced muscle pain, and 30% of patients with GSD V report chronic pain [14]. Pain intensity is reported as moderate (mean numerical reporting scale (NRS) 5.43/10) and mostly cramp-like. The impact of physical activity intolerance and pain on ADLs and instrumental ADL (iADL) has been investigated and it is reflected in the widely used ordinal (0-3) grading of severity of disease [15]. In the combined Spanish and Italian GSD V cohort (380 patients), there was no reported impact on ADL (grade 0) in 7% of the patients, mild to moderate impact in 70%, and substantially severe impact in 23%.

An assessment of disability in 14 adults with GSD V using the World Health Organisation – Disability Assessment Schedule (WHO-DAS) 2.0, showed an equal distribution of mild difficulties in four activity domains: mobility, social life, household tasks, and work (Martinuzzi, A. unpublished results). The evaluation of perceived quality of life (QoL) with the Short Form 36 (SF36) in the same group yielded the worst results in the domains of health-related role limitation (40), general health, pain, energy/fatigue and emotional wellbeing (50).

When exploring the types of activity that trigger pain or result in a limitation in the intensity and/or duration of the activity, spontaneous iADL such as lifting heavy objects, climbing stairs or running are among the most frequently reported. Most patients with GSD V learn to circumvent the limitations by implementing adaptive strategies, either by taking advantage of the 'second-wind' phenomenon or by avoiding overload of single muscle groups with sustained contraction. To help patients understand when muscle damage may occur, please refer to Supplementary Material - Appendix 1.

The impact of the disease on activities, and the evaluation of the modulating effect of the environmental factors, should be evaluated in patients with GSD V and GSD VII with

appropriate tools: for example, the WHO-DAS 2.0 [16]. The same systematic approach should be followed for the evaluation of the QoL.

GSD VII is also characterised by physical activity intolerance, muscle cramps and, following intense activity, nausea and vomiting. Jaundice, elevated CK, hyperuricaemia, reticulocytosis, and increased serum bilirubin may also be observed. The late onset form presents with myalgia later in life and may lead to severe disability. The unconfirmed infantile form may present as 'floppy babies' with a lifespan of one year. Lastly, the haemolytic form presents with non-spherocytic haemolytic anaemia and no muscle involvement [17].

Job/task specific adaptation is sometimes needed for patients with GSD V or VII, and consideration of these strategies should be part of the treatment protocols.

2.5. Clinical variability

There is heterogeneity in the clinical manifestation of GSD V, which complicates diagnosis and understanding of this condition. In the last update of the Spanish registry of patients [18], 8% of patients reported themselves as asymptomatic during normal daily life. By contrast, 21% of patients reported episodes of recurrent myoglobinuria, fixed muscle weakness mostly affecting the upper body, and sometimes associated muscle wasting. These individuals were severely limited in most ADLs. The *PYGM* gene, which encodes myophosphorylase, has no genotype-phenotype correlation, as reported in various cohorts [18–21]. In one series, most documented *PYGM* mutations have functional consequences, and patients' muscles are devoid of myophosphorylase activity, independent of clinical manifestations [18]. However, splice mutations in *PYGM* have been reported to preserve some myophosphorylase activity and attenuate the phenotype in single cases of GSD V, but this is extremely rare, and thus the overall conclusion of no phenotype-genotype correlation is likely to hold true [22].

Age negatively affects functional capacity in everybody, whereas regular physical activity has the opposite effect. Individuals with GSD V or GSD VII are advised to engage in regular exercise in order to improve cardiorespiratory function (CRF) and ultimately to improve the clinical course of the disease. Factors that may influence functional capacity in GSD V and GSD VII are highlighted in Supplementary Material - Appendix 2.

2.6. Epidemiology

The variance between the prevalence based on genetic data and the prevalence based on diagnosed cases may be due to the average delay in correct diagnosis. In the Dallas/Fort Worth area of the USA, the prevalence of GSD V based on genetic data is estimated to be 1/100,000 [23]. A study of diagnosed cases in Spain indicates a prevalence of ~1/139,543, [18]. However, a study of next-generation sequencing (NGS) data predicts a prevalence of between 1/7650 (based on six common mutations) and 1/42,355 (based on the two most common mutations) [24].

GSD VII is considered to be very rare, with only around 100 to 200 reported cases worldwide. Symptoms may be attributed to poor fitness, so a lack of recognition and diagnosis may mean the true prevalence is much higher. Ashkenazi Jews share two common mutations in the *PFKM* gene, which may account for the higher prevalence amongst this population.

Both GSD V and GSD VII are inherited in an autosomal recessive pattern. In regard to gender, in GSD V cohorts the following ratios of males to females have been observed: Spain 55:45 [18]; Italy 65:35 [25]; UK 50:50 [20]. Equality is expected in an autosomal recessive condition. Where there is a predominance of affected males, this may be due to gender-related reporting bias, as males are more likely to undertake strenuous recreational and occupational activities.

3. Methods/process

3.1. Consensus development panel

An international group of experts was assembled to review the current evidence base in GSD V and GSD VII for (1) clinical variability; (2) clinical and laboratory diagnosis; and (3) management (exercise, nutrition, medical emergencies, general medical care, surgery, and obstetric care) in order to develop management guidelines for these areas. Group members were assigned sections specific to their areas of expertise. The terms cited in Section 2.3 were included in the search of PubMed. Where the current evidence base was insufficient, expert opinion was sought, and consensus was applied. The participants provided conflict of interest statements and these are included in the Disclosure section. An external review group reviewed a penultimate draft of these CPGs. The study group reviewed their suggestions and made amendments as appropriate. All members of the Consensus Development Panel reviewed and approved the final CPG.

3.2. Target audience

The overall impact of GSD V and GSD VII can be nuanced, resulting in a cascading effect on multiple systems, including the skeletal, muscular, nervous, cardiovascular, urinary, respiratory, and ocular systems. For this reason, these guidelines were developed to support clinicians in multiple disciplines across the continuum of care and the lifespan of patients.

4. Diagnosis

4.1. Differential diagnosis

The clinical manifestations of GSD V and GSD VII typically begin in childhood [26,27]. The clinical signs and symptoms of GSD V and GSD VII are common to all

glycolytic disorders. Basal CK is typically raised in GSD V, but may be normal in GSD VII. Other non-glycolytic myopathies can also present with physical activity-induced muscle pain, rhabdomyolysis, myoglobinuria, and raised basal CK (Fig. 1).

The phenomenon of 'second-wind' might not be so easy to detect in young children [28]. It may also prove difficult at this age to perform a non-ischaemic forearm exercise test, and no study has been conducted to determine whether this provides conclusive data. Haematological findings, namely haemolytic anaemia, may point to a diagnosis of GSD VII. In brief, the differential diagnosis for these diseases is highly complex, and diagnosis of these patients is challenging for clinical care professionals. Although these are rare disorders, the first presentation is usually before the age of 10 and paediatricians should consider these pathologies, and nowadays the first approach is often genetic testing. In adults, a patient self-report of 'second-wind' or a flat lactate response with a rise in ammonia levels after a non-ischaemic forearm exercise test may be helpful to guide the differential diagnosis.

4.2. Misdiagnosis

Ninety percent of people with GSD V received a misdiagnosis before a corrected diagnosis (GSD VII unknown), resulting in a median diagnostic delay of 29 years, which can seriously affect QoL [29].

The onset of symptoms typically occurs in childhood with first presentation to a general practitioner (GP) before the age of 10 years; however, the median age of correct diagnosis is age 33. Of the most commonly reported misdiagnoses, children are often dismissed by GPs as 'lazy or unfit' (51% of patients), or having 'growing pains' (44%). Of those who are misdiagnosed, 62% report being misdiagnosed more than once, with 47% receiving incorrect management [29], thereby increasing the risk of muscle damage and episodes of rhabdomyolysis, which can lead to potential life-threatening complications such as acute renal failure (ARF) and acute compartment syndrome (ACS). In addition to the most common misdiagnoses, some patients receive a more generalised diagnosis of myositis [30].

A blood test to evaluate basal CK (particularly in GSD V) is a useful screening test as it is almost certain to be significantly raised indicating the need for further investigation. Misdiagnoses are evenly split between males and females, with the exception of 'psychological conditions', with which females are misdiagnosed six times as frequently as males [29]. The misdiagnosis of neuromuscular diseases is likely to decrease with the increasing use of genetic testing.

4.3. Genetics

From records documenting the study of the genetics of GSD V, 179 pathogenic variants have been described, the combination of which affect all the exons of the *PYGM* gene. Missense pathogenic variants are the most common, and the p.Arg50Ter variant is the most commonly detected variant in European and US Caucasian populations (~60% of the mutated alleles). A recent publication explains the lack of genotype-phenotype correlation in GSD V. Most of the patients in the study did not have myophosphorylase activity, independent of the type of mutation (missense, nonsense, deletion, insertion, splicing, etc.) [31]. This indicates that myophosphorylase is not produced in the presence of *PYGM* mutations, except for very rare cases in which missense mutations lead to preserved myophosphorylase activity and ameliorated phenotypes [22].

There is no clear relationship between clinical severity, *PYGM* genotype and biochemical analysis of muscle samples. The clinical phenotype may be modified by the genotype of the angiotensin-converting-enzyme (ACE) gene [15,32].

The diagnosis of GSD V can be made after taking a careful clinical history, and with the observation of raised serum CK, and is confirmed using minimally invasive methods based on the molecular analysis of the *PYGM* gene on deoxyribonucleic acid (DNA) obtained from peripheral blood samples. Molecular genetic testing is clinically available through Sanger sequencing of *PYGM,* NGS panels which include *PYGM* (such as for all GSDs or for rhabdomyolysis), or whole exome sequencing (WES). Identification of two pathogenic variants in suspected patients is required for confirmation of diagnosis.

Based on the knowledge of common mutations in Caucasian and Japanese patients or individual families, DNA-based targeted mutation testing can be offered. If only one (or no) pathogenic variant is detected, Sanger sequencing of *PYGM*, followed by deletion/duplication analysis may be indicated.

In cases in which variants of unknown significance (VUS) are detected, a functional exercise test such as a cycle test may be helpful, as may a non-ischaemic forearm test and muscle biopsy for muscle phosphorylase enzyme activity.

In the case of GSD VII, 27 pathogenic variants are described in the Human Gene Mutation Database. GSD VII has marked phenotypic and genotypic heterogeneity, and the majority of mutations result in markedly reduced activity of the enzyme [33–36]. Reported variants include deletions, duplications, intronic deletions, insertions, and single nucleotide changes. GSD VII is especially prevalent in the Ashkenazi Jewish population, with the most prevalent pathogenic variant being a splicing defect in the 5′ donor site, which results in an in-frame deletion of exon 5 sequence. Japanese, Ashkenazi, and non-Ashkenazi European ethnic groups account for virtually all known pathogenic variants in the *PFKM* gene [33–36].

Genetic testing can be performed using single-gene Sanger sequencing or using myopathy or rhabdomyolysis gene panels or WES with peripheral blood samples [33,36]. Where disease-causing family mutations are known to exist in a proband, targeted mutation analysis can be performed.

Prenatal diagnosis is not indicated for these disorders [18,37–39].

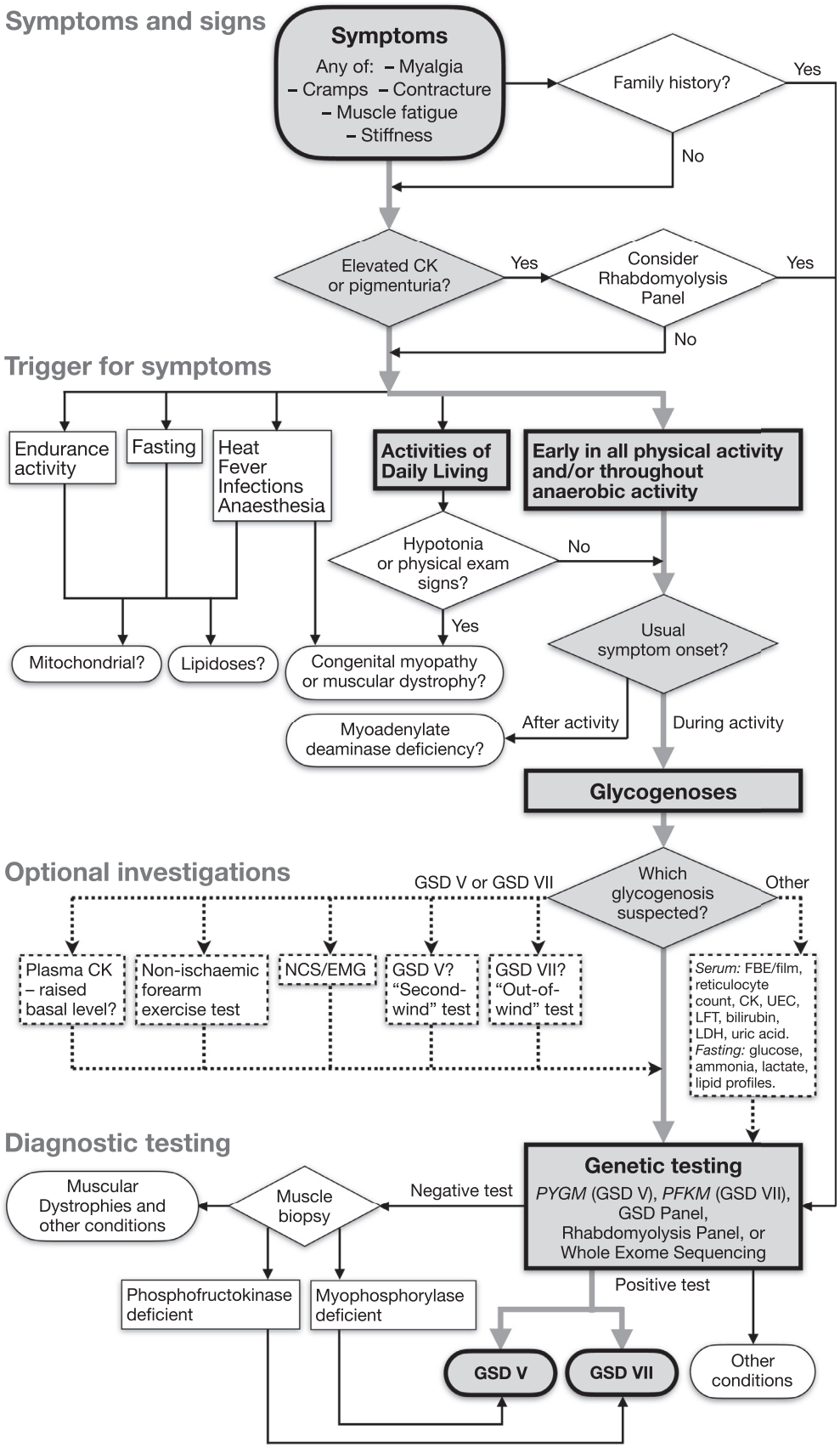

Fig. 1. Differential diagnosis - a decision path to aid diagnosis of GSD V and GSD VII. Note: The typical path is highlighted.

4.4. Muscle biopsy

When VUS are observed, and exercise tests are inconclusive, a biochemical or histochemical demonstration of the enzymatic defect in the muscle biopsy tissue may be used. [18,40,41]. In GSD V, muscle biopsy specimens usually show markedly increased levels of subsarcolemmal glycogen accumulation (3 to 5 times the normal range) with normal glycogen structure [39]. The diagnosis of GSD V is confirmed by enzymatic evaluation of skeletal muscle biopsy, which shows undetectable or very low levels of myophosphorylase activity [37,38]. Myosin-heavy-chain staining has not shown any special pattern of muscle fibre type distribution in GSD V biopsies [42]. Muscle phosphorylase activity can also be suppressed due to phosphorylase kinase deficiency (GSD IXd) [43].

When VUS are observed, and exercise tests are inconclusive, the diagnosis of GSD VII may also be established through biochemical or histochemical demonstration of the muscle phosphofructokinase deficiency in muscle biopsy tissue. The muscle biopsy is characterised by glycogen accumulation by periodic acid-Schiff staining [44] or with ultra-structure analysis. Muscle glycogen content is not markedly elevated in GSD VII, although it can be mildly elevated or in the upper normal limits, with normal distribution. Muscle phosphofructokinase activity can be significantly reduced (< 10% of normal) or mildly reduced, indicating partial enzyme deficiency, in milder cases [45–47].

4.5. 'Second-wind' as a diagnostic aid

The utility of the 'second-wind' as a diagnostic indicator has been explored using both cycle ergometry and walking tests [48,49]. The 12 min walk test can be easily performed in the clinic setting by measuring heart rate and perceived muscle pain at each minute. It is important to remember that the 'second-wind' phenomenon might not be easily detectable in very young patients with GSD V [28], and some individuals may require assistance to recognise 'second-wind'. In recent years these tests have been used not only as a diagnostic aid, but also as outcome measures to detect the effects of various interventions in clinical trials [50–53] and in long term management of patients.

Although the same pattern of the 'second-wind' phenomenon has not been observed in GSD VII patients [54], physical activity stimulates the release of free fatty acids, thereby enabling patients with GSD VII to engage in submaximal physical activity following a period of warm-up.

4.6. Other

The forearm exercise test has been used in patients with muscle GSD. Studies in GSD V have shown that a non-ischaemic version of the test is the better option, as ischaemia triggers cramps and pain in many patients, with the risk of rhabdomyolysis [55]. Even in the absence of cuff-induced ischaemia in forearm muscles, patients with GSD V show a flat lactate response. Therefore, if needed, a non-ischaemic test is recommended for diagnosis of GSD V, and patients should be advised to stop the test if they experience muscle pain.

Although fewer studies have been published on the forearm exercise test for the diagnosis of GSD VII, similar flat lactate responses have been observed [56,57], and therefore the aforementioned recommendations apply. This test only indicates a block in the glycogen degradation pathway, and it is not specific for any individual muscle GSD.

Electrophysiology shows myopathic features, but it is rarely required to assist with the diagnosis of people with GSD V and GSD VII.

5. Overview of management

5.1. Centre of expertise

As with all rare disorders, diagnosis is frequently delayed [20]. Diagnosis and management should be undertaken by an experienced clinical team in a Centre of Excellence (CoE) that has a reasonably sized cohort of patients with GSD V or GSD VII.

The goal of management should be to reduce episodes of muscle breakdown, which may result in hospital admissions for rhabdomyolysis, ARF and ACS, which are serious and potentially life threatening. In addition, patients presenting for the first time later in life are likely to have adopted unhealthy lifestyles and have become deconditioned. As a result, they may struggle to get into 'second-wind', may suffer recurring pain and fatigue and may have a poor QoL. In addition, there are likely to be multiple secondary physical and psychological consequences of diagnostic delay. An expert multi-disciplinary team consisting of a physician, physiotherapist, and/or exercise physiologist, psychologist, clinical nurse specialist and dietitian is recommended to help patients overcome these difficulties and improve their physical activity tolerance.

5.2. Benefits of regular assessment

Annual assessment is recommended for most patients. Assessment may include a functional exercise test to determine physical fitness/functional capacity and the ability of people with GSD V to be able to use the 'second-wind'. This could be either a 12 min walk test [49] or a cycle test [58]. Given the higher prevalence in GSD V compared to the general population of gout (8.5: 5%), diabetes (6.7: 4.8%), myocardial infarction (11: 4%) [Quinlivan,R; unpublished data], a blood draw to test basal CK, urate, HbA1c and lipid profile is recommended on an annual basis. Clinical assessment should include examination for evidence of muscle wasting and muscle weakness, as well as an assessment of gout and other medical issues. An assessment should be made of the impact of the condition on the individual with regard to their ADL, and a QoL assessment

should be made at each visit. A dietetic assessment should be undertaken to support avoidance of excess weight and to discuss dietary options.

Patients who are deconditioned or have difficulty with the 'second-wind' should be offered additional appointments with the physical therapy team to help them practice achieving 'second-wind', to encourage regular physical activity and to demonstrate methods of core strengthening that are suitable for this cohort.

5.3. Laboratory testing

Median basal CK elevation in a cohort of 256 individuals with GSD V was 2643 iu/L, with normal values (< 200 IU/L) reported in only 18 individuals (7%) [53]. With episodes of rhabdomyolysis, CK levels can be much higher, even in excess of 100,000 IU/L. It is important to establish a baseline CK level by testing in the absence of injury and/or prior to initiating new medications (i.e. statins). This will help patients to better manage their condition and avoid serious episodes. It is advisable to set up a mechanism for the patient to access urgent CK testing following an injury, to help inform whether emergency management is required. CK level tends to peak 24 h after injury, and falls by approximately 30–50% per 24 h thereafter.

When CK levels are above the thousands, liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are almost always elevated. This is not a sign of liver disease, but of the physiological dispersion of sarcoplasmic muscle transaminases caused by fibre damage. If ALT and AST are grossly elevated disproportionate to the hyperCKemia, or if alkaline phosphatase (ALP) or bilirubin levels are significantly raised, further investigation may be indicated.

If urine test strips show blood (haemoglobin) or protein this may be myoglobin. Urate levels are often raised in GSD V due to excessive increases in blood ammonia, inosine, and hypoxanthine due to accelerated degradation of muscle purine nucleotides which serve as substrates for the synthesis of uric acid. This may lead to development of hyperuricaemia and gout. In addition, raised urate levels can lead to the development of renal stones.

Routine evaluation of HbA1c and a lipid profile are warranted due to the increased prevalence of diabetes and coronary artery disease for this cohort [Quinlivan, R; unpublished data].

In the case of GSD VII, episodes of rhabdomyolysis may be less frequent. In addition to muscle disease, there is erythrocyte involvement that may cause haemolysis, hyperbilirubinaemia and increased reticulocyte counts [59].

The absence of muscle phosphofructokinase can also be demonstrated in blood cells and fibroblasts. Laboratory analysis may also show myogenic hyperuricaemia, due to metabolic shifting towards a non-glycolytic anaerobic pathway, which has by-products of uric acid and ammonia [60].

5.4. Information & guidance for day-to-day management

5.4.1. Use of second-wind in GSD V

It is essential that patients understand how to achieve 'second-wind' in order to improve physical activity tolerance and reduce muscle damage. The 'second-wind' phenomenon is specific to the muscles being used. Upon initiation of activity, patients with GSD V must go slow and pay attention to the following signals: muscle fatigue or pain, rate of perceived exertion, quickening heart rate and increased breathing effort. If any of these signals occur, patients are advised to slow down (reduce exertion) or pause until symptoms subside. This 'slow-pause-resume' pattern should be repeated as necessary until a marked improvement in physical activity tolerance is achieved. After 6–10 min, resting or stopping as necessary, aerobic metabolism becomes the dominant fuel source, and submaximal physical activity can be carried out more easily. If, however, the intensity of the activity increases (for example, walking uphill), there will be a deficit in the immediate availability of substrates and symptoms will recur. At that time, the 'slow-pause-resume' pattern should be re-initiated.

Patients with GSD VII are unable to metabolise blood glucose, and do not develop a 'second-wind' under conditions that produce one in patients with GSD V. Oxidative metabolism in patients with GSD VII is also substrate-limited, but the inability to utilise blood glucose as an oxidative fuel makes muscle oxidative capacity dependent upon the availability of fatty acids. The most dramatic change in exercise and oxidative capacity in these patients is a reduction in exercise capacity following a carbohydrate meal, a condition that has been dubbed the 'out-of-wind' effect [54]. It is advised that patients with GSD VII follow the same 'slow-pause-resume' pattern outlined for those with GSD V until warning signs subside and physical activity tolerance improves.

5.4.2. Physical activity - aerobic conditioning

Aerobic conditioning is best reflected in 'VO_{2max}'; the maximal amount of oxygen that can be used during physical activity. The higher the value, the lower the risks of morbidity and mortality. Individuals with muscle GSDs tend to be in the range 15–30 ml/kg/min. Improving VO_{2max} by just 1 ml/kg/min results in a 10% decrease in morbidity. [61,62].

Individuals with GSD V or GSD VII should be undertaking some exercise aimed at improving CRF. The 'right' type of exercise can improve VO_{2max}. Individuals with a muscle GSD can only work at low to moderate intensity, ideally for at least 20 min, 2–4 times per week. See Supplementary Material - Appendix 3

5.4.3. Physical activity - strength training

In the case of GSD V, strength training can increase muscle mass, lower the severity class, decrease baseline CK, and avoid fixed muscle weakness. To avoid the risk of

contractures, it is essential to adhere strictly to the guidelines. See Supplementary Material - Appendix 3.

The principle is a warm-up of all muscles into 'second-wind', followed by sets of very few repetitions using a circuit-training structure, rotating on multiple machines to give a recovery time of at least 3 min between sets.

In the case of GSD VII, there is not adequate clinical data to recommend a strength-training programme for this cohort.

5.5. Dietary management

5.5.1. GSD V

The beneficial effects of intravenous glucose and oral sucrose supplementation on exercise capacity in people with GSD V are well established [4,48,63,64]. Oral sucrose shortly before strenuous exercise markedly improves exercise tolerance by providing a stable flux of glucose to fuel the working muscles, independent of the blocked glycogen breakdown, with a blunting of the barrier to 'second-wind' as a result. Currently, the recommendation is to ingest 37 g of sucrose, which approximately corresponds to one can of soda (330 ml), 5–10 min before exercise [63]. Due to the risk of weight gain and related health issues, use of this strategy must be carefully planned. Sucrose supplementation for individuals with diabetes must be closely supervised. The potential effects of repeated sucrose supplementation during prolonged exercise are currently being investigated and any recommendations regarding repeated supplementation must await the results of these investigations.

A carbohydrate-rich diet has proven beneficial compared to a protein-rich diet [65]. The theory is that the carbohydrate-rich diet maintains the hepatic glycogen stores, providing a more stable supply of glucose flux from the liver to the muscle. However, the diet will not eliminate all GSD V symptoms and cannot abolish the barrier to 'second-wind', therefore the risk of muscle damage is still present. Furthermore, the specific diet composition and carbohydrate level needed is still unknown.

Triheptanoin oil supplementation has been shown to be ineffective in people with GSD V, and is therefore not recommended as a dietary management strategy [52]. The low carbohydrate ketogenic diet (LCKD) is currently being investigated as a potential dietary management strategy.

5.5.2. GSD VII

Dietary treatment in GSD VII has not been studied in any detail. In contrast to GSD V, oral or intravenous supplements with sucrose or glucose are detrimental for individuals with GSD VII, as glucose cannot be metabolised. Sucrose/glucose supplementation in GSD VII produces an 'out-of-wind' phenomenon, which is the opposite of the 'second-wind' phenomenon seen in GSD V with sucrose/glucose supplementation [6]. LCKD has shown long-term effects in one patient with GSD VII, with improved exercise tolerance and subjective alleviation of muscle symptoms during a 5-year follow-up period [66]. According to this study, a LCKD can potentially benefit selected patients with GSD VII with proper medical and nutritional supervision. However, placebo-controlled studies with larger cohorts are warranted to provide conclusive evidence on composition and effects of this diet.

5.6. Cramps and contractures

The exact underlying mechanism for muscle cramps is not fully understood. It begins with a nerve-activated muscle contraction. Some investigators suggest that hydrogen ion accumulation in the lumen of a blood vessel results in vasoconstriction, and downstream from that, the muscle tissue becomes partially ischaemic, which triggers cramping [67]. This can occur in any individual. Muscle contractures, which can be observed in patients with GSD V and those with GSD VII, are different from muscle cramps, because they are not elicited by the nerve, but by intrinsic mechanisms in the muscle itself. In consequence, contractures, unlike muscle cramps, are silent on electromyography. Contracture in GSD V and GSD VII is the response to impending muscle damage associated with the energy deficiency, and is longer lasting and generally more painful than muscle cramps.

Muscles will generally recover following a cramp or contracture, but repeated episodes can accumulate muscle damage.

To manage a cramp or contracture, cessation of the causal activity is recommended until pain resolves. Unlike stretching of muscle cramps, stretching of a muscle in contracture may cause further muscle damage, and should be avoided.

5.7. Pain management

The primary goal in management of GSD V and GSD VII is to avoid excessive muscle breakdown. By doing so, the experience of pain is likely to be lessened. Individuals must learn how to recognise the interim warning signs of muscle fatigue and myalgia during the pre-'second-wind' period and respond accordingly. However, generally the pain from cramps is of short duration and should not prompt use of pain medications, as the pain often will be over by the time the pain medications start to work.

Following intense aerobic and anaerobic activities (for example, carrying a heavy object or running for a bus), in which the metabolic demand on the muscle surpasses the ability of this tissue to produce energy fast enough, individuals may develop cramps, contractures, or worse, rhabdomyolysis. To manage episodic occurrences of cramps, paracetamol (acetaminophen) may be taken after activity has ceased. For more severe pain, which lasts for hours, patients may need to seek medical attention.

For patients that experience chronic daily pain, a thorough assessment of their aerobic and muscle conditioning is warranted, as there is an inverse relationship between aerobic fitness/muscle strength and chronic pain. Furthermore, chronic use of opioid medications is not recommended, as they may mask feedback from the muscles, leading to further muscle damage and recurring pain. Instituting a carefully planned

regular exercise programme should help to reduce chronic pain.

Patients with GSD V or GSD VII can anticipate some muscle fatigue and pain, in GSD V especially pre-'second-wind'. These sensations signify the need to respond and modify activity. However, in some cases, pain may not be related to having a muscle GSD, and therefore each complaint should be thoroughly assessed to determine the correct aetiology.

6. Medical emergencies

Individuals with GSD V or GSD VII are at increased risk of rhabdomyolysis. All activity (including ADLs and formal exercise) can lead to muscle breakdown and the potential for rhabdomyolysis, the risk of which increases as the combined demand of intensity and duration of activity increases. While the occurrence is low, there is some potential for ARF and ACS subsequent to rhabdomyolysis [68]. The best prevention against rhabdomyolysis (as well as ARF and ACS) is to apply appropriate caution when engaging in all types of physical activity. This includes sporting activities and ADLs, particularly those involving high mechanical stress on low muscle mass (for example, handgrip and carrying or lifting heavy weights). It is recommended to gradually build up these types of activities (day by day, gently increasing loads). Carbohydrate ingestion (in the case of GSD V), together with abundant hydration before heavy and/or unaccustomed activity/exercise is recommended to prevent – or at least minimise – muscle damage.

6.1. Rhabdomyolysis

Rhabdomyolysis – the breakdown of damaged skeletal muscle fibres as reflected by the efflux of intracytoplasmic proteins such as CK and myoglobin into the bloodstream – is the main medical problem in GSD V and GSD VII.

Myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis does not necessarily result in visible myoglobinuria. Rhabdomyolysis can range from elevated CK to myoglobinuria, ACS or ARF (leading to heart failure, arrhythmias, electrolyte imbalance, and in severe cases, death) [69]. The symptoms of rhabdomyolysis vary individually, but may include myalgia, muscle weakness, nausea, vomiting, fever, myoglobinuria, oliguria, and anuria.

In individuals with GSD V or GSD VII, the threshold for developing rhabdomyolysis is much lower than in unaffected individuals. Mechanical stress imposed by high muscle glycogen stores, down regulation of sodium–potassium pumps and oxidative stress all contribute to structural muscle fibre fragility and membrane disruption, leading to an increase in serum CK [2]. Rhabdomyolysis is predominantly brought on by isometric exercise (for example, lifting weights) or intense 'aerobic' activity (for example, stair climbing or running) [18].

As is the case in healthy individuals, a number of factors can increase the risk of rhabdomyolysis in individuals with GSD V or GSD VII. Primary factors include individual CRF, and intensity, duration and type of activity (concentric, eccentric, isometric). Secondary factors include environmental temperature (heat), electrolyte imbalance, gender (male), and alcohol [69].

The primary treatment goal for rhabdomyolysis is to prevent the factors that lead to ARF. Discharge criteria are contingent upon a lack of myoglobinuria and a return to baseline renal function (creatinine and glomerular filtration rate).

6.2. Acute renal failure

Myoglobinuria due to rhabdomyolysis can produce ARF, but data from large cohorts of patients suggest that this emergency complication is a rare event in both GSD V and GSD VII.

The mechanism of renal dysfunction is predominantly related to myoglobin-direct tubular cytotoxicity, vasoconstriction and tubular obstruction. Volume depletion enhances both vasoconstriction and the formation of obstructing casts.

Patients with severe rhabdomyolysis should be treated with adequate fluid administration to prevent renal impairment or be put on dialysis if warranted. However, it is important to take into account the fluid balance to avoid further complications such as hypervolaemia and acute pulmonary oedema. For patients that develop ARF, consultation with nephrology is required.

Standard criteria for dialysis initiation are: fluid overload unresponsive to loop diuretics, and electrolyte disturbances such as hyperkalaemia, metabolic acidosis and uraemic encephalopathy. The levels of myoglobin and CK are not considered to be parameters upon which to base implementation of renal replacement therapy.

To avoid episodes of myoglobinuria and so to reduce the risk of ARF, strenuous exercise should be avoided but regular moderate exercise can be beneficial by improving CRF, and thus reducing symptoms.

Although acute or chronic renal failure may present a problem, the occurrence of these conditions is quite rare, being reported in only 10 patients (6%) of a large Spanish cohort [18], 5 patients (11%) of a British cohort [20] and 19 patients (7.9%) of the GSD V Euromac registry [53]. According to the literature, ARF is almost always reversible when emergency treatment is provided [26].

6.3. Compartment Syndrome

ACS is characterised by a rise in pressure within a closed fascial space in the absence of a traumatic event. This condition is rarely described in patients with GSD V [70]. In individuals with GSD V, severe sustained physical activity can lead to muscle contracture, thereby reducing blood flow to contracting muscles, which may induce partial ischaemia. Potential development of a feedback loop between

compartment oedema and decreased blood supply may predispose to compartment syndrome.

ACS in the upper or lower limbs has been reported in individuals with GSD V following strenuous exercise, during the postpartum period, and in those who performed an ischaemic forearm test (no longer recommended) for GSD V diagnosis [71]. No associations of ACS and GSD VII are reported in the literature.

ACS is a clinical diagnosis; the classic presentation is relentless pain not relieved by rest. Other signs include pallor, absence of pulse, paralysis and paraesthesia. Diagnosis may be supplemented using intracompartmental pressure measurements.

Individuals with GSD V or GSD VII must be cautioned about the potential for ACS following strenuous activities. The use of continuous blood-pressure monitoring or compressive devices, as well as the use of tourniquets, are contraindicated in this patient population.

Missed diagnosis of ACS may rapidly lead to irreversible muscle and nerve damage, resulting in musculotendinous contractures and sensorimotor deficits. A prompt ACS diagnosis can be facilitated by using limb magnetic resonance imaging; this often leads to an expeditious surgical treatment with decompressive fasciotomies, which maximises functional outcomes for these patients [72].

6.4. Haemolytic anaemia in GSD VII

Muscle phosphofructokinase deficiency impairs the ability of erythrocytes to usecarbohydrates as a bioenergetic substrate supply. Haemolysis can occur because of impaired adenosine-5′-triphosphate (ATP) generation and increased 2,3-bisphosphoglycerate generation from abnormal glycolysis, leading to problems with red blood cell membrane maintenance.

Haemolytic anaemia (HA) can be present in GSD VII. In one apparent sub-type it is characterised by non-spherocytic HA without muscle symptoms.

As a consequence of HA, myogenic hyperuricaemia results from an excessive degradation of muscle purine nucleotides, secondary to impaired ATP generation. This process is sustained by the inability of the kidneys to process an excess ofuric acid due to myoglobin disposal.

High levels of indirectbilirubin are often found in blood, as is a recurrent increase inreticulocytes. These are immaturered blood cells produced by bone marrow, which is highly active in an attempt to replace red blood cell loss.

6.5. Rehabilitation protocol

Once the patient has a clear reduction in clinical symptoms (for example weakness, swelling, and pain), their CK level is trending downward, and laboratory tests for kidney function are normal, discharge from hospital may be considered. There should be a discussion with the patient as to why the episode occurred. Particular consideration should be given to any physical activities or exercises which were unusually intense, of unusually long duration, or with which the patient was previously not familiar. The development of strategies to avoid such episodes in the future should be encouraged. Notably, gradual familiarisation should be encouraged with any new activities.

There is currently no scientific evidence on how the patient should gradually and safely return to baseline ADL and exercise. As such, no specific rehabilitation protocol can be proposed based on published data. This being said, we propose that the patient should not return to normal activity levels until the CK values and pain/cramping have returned to their pre-episode baseline levels. In any event, this should not be in less than one week, bearing in mind that muscle regeneration usually begins during the first week after injury and peaks at about two weeks [73]. Pain medication should be used sparingly throughout rehabilitation, so as not to mask the warning sign of pain, which is an evolutionarily conserved mechanism that ensures full restoration of biological homeostasis. Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended during recovery from ARF due to afferent artery vasoconstriction. In any case, physical activities should be limited to below the threshold of pain; for example, if fitness permits, gentle cycling or walking can be undertaken at intensities that the patient knows are not going to trigger cramps. It is always good to stimulate muscle regeneration through an increased delivery of trophic factors via the bloodstream.

7. General medical care

7.1. Considerations for general practitioners

Diagnosis and management should be provided by an experienced clinical team at a CoE. However, the GP can provide further support by sharing information about: (1) improving overall fitness, (2) limiting anaerobic and static activities, (3) use of ‘second-wind’ (in the case of GSD V); (4) psychological impact and management thereof, (5) recognising symptom onset, and (6) the need for emergency care.

The basal plasma CK level should be established as a reference point, and CK can then be further tested to aid in assessment of any episode of rhabdomyolysis. An elevated CK level is not an immediate alert for a cardiac event; it is preferable to rely on more specific cardiac tests. (Note that an increased troponin T level can also be present in some muscle disorders, possibly including GSD V and GSD VII.) The enzymes AST and ALT may be mildly increased due to skeletal muscle damage, rather than hepatic issues [74]. Further investigation is indicated if ALP or bilirubin levels are significantly increased. Patients should be monitored for concomitant conditions. See Supplementary Material - Appendix 4.

Due to the restriction of blood flow, blood-pressure cuffs can be damaging and should be removed as soon as possible. During routine examinations, the use and duration of positions in which a muscle is held in a static position, or muscles are

compressed, should be minimised, as a cramp or contracture may ensue.

Given the interplay between the muscular and skeletal system, massage and chiropractic treatments may help to alleviate chronic pain. Therapists should be fully briefed on GSD V and GSD VII. Interventions should be mild and should avoid stressing the muscles so as not to cause defence contractions or damaging pressure.

Patients should carry an emergency card or 'in case of emergency' (ICE) app on their smartphone to prompt them about when to seek medical assistance. If, after activity, they have one or more of: myoglobinuria, feeling very unwell with flu-like symptoms, oliguria or anuria, muscle weakness, muscle swelling, and very severe myalgia, they should drink water at 2x maintenance and seek medical attention.

7.2. Concomitant conditions

In addition to the typical muscle-related symptoms, there may be an increased prevalence of other conditions in patients with GSD V or GSD VII. Some conditions, such as gout are well documented in patients with GSD V, whereas others, such as ocular involvement in GSD V, are emerging. Supplementary Material - Appendix 4 provides an overview of established and emerging conditions across the following areas: cardiology, rheumatology, nephrology, psychology/psychiatry, endocrinology, ophthalmology and haematology.

7.3. Potential drug–disease interactions

When prescribing medications for other conditions a check should be made for any side-effects or contraindications in skeletal muscle disorders. It is recommended that a baseline CK level is established before initiating treatment, so that any increase in CK level can be determined.

Although statin medications are generally well tolerated, the most common side-effects relate to skeletal muscle – myalgia, myositis, and rhabdomyolysis [75]. Other cholesterol-lowering drugs may also worsen myopathy in patients with GSD V [76]. Use of systemic steroids may also increase the risk of myalgia and rhabdomyolysis. It is advisable to 'start low and go slow' when prescribing new medications.

Most anaesthetists consider muscle glycogenosis no differently from other muscle diseases in which the potential risk of developing malignant hyperthermia (MH) mandates the use of special precautions in the choice of the anaesthetic and the use of muscle relaxants. However, there is no report in the literature of MH events in patients with GSD V or VII. Despite the lack of evidence for occurrence of MH in GSD V and GSD VII, most authors consider it advisable to apply the same precautions used for conditions prone to MH; that is, to avoid halogenated agents and depolarising relaxants such as succinylcholine, and to keep dantrolene sodium in the operating room [77]. This specific risk might be overestimated, even in the presence of a positive *in vitro* contracture test showing MH susceptibility [78,79].

Care should be taken with regard to the use of pain medications in patients with GSD V and GSD VII as these may mask the signals which patients need in order to adjust activity appropriately.

8. Surgery

As outlined in Section 7.3, anaesthetists should follow MH protocol in patients with GSD V or GSD VII. Hypoglycaemia, tourniquet use, prolonged forced position/compression, hypothermia and shivering are all conditions in which the metabolic block in GSD V and GSD VII might precipitate contractures and rhabdomyolysis in patients, possibly evolving into ARF. The key unifying element is the generalised or focal failure (for lack of supply or excessive use) of the readily available energy source provided to skeletal muscle by blood glucose. It is therefore advisable that patients meet the anaesthetist prior to major procedures to review the precautions detailed below. Recommended preventive measures include: the following of MH protocol; careful monitoring of body temperature (with the use of thermal blanket or warmed fluids if needed); the use of a urinary catheter to enable immediate identification of possible pigmenturia; the avoidance of tourniquets or continuous blood-pressure monitoring by brachial cuff; consideration of the positioning of the patient, especially during lengthy procedures, to avoid focal compression; measurement of blood glucose hourly during the procedure; and strict surveillance during the 24 h following a procedure (for example, monitoring of urine output and blood glucose).

With these precautions in place, any scheduled surgery is not expected to present an excessive risk because of the diagnosis of GSD V or GSD VII.

9. Obstetric care

The uterus is composed of smooth muscle, which has a different isoform of glycogen phosphorylase and is therefore not affected in female patients with GSD V.

There is no published data on pregnancy and childbirth in these conditions, other than individual case reports. Of a cohort of 127 females with GSD V (125) or GSD VII (2), a retrospective review across the obstetric spectrum did not suggest that any particular problems had occurred, either in the antepartum/intrapartum or postpartum periods. Indeed, most women had their babies before the diagnosis of either GSD V or VII was made, and they had the same incidence of interventional delivery (forceps and caesarean section) as did the general population (16%) [Quinlivan, R., unpublished results]. Nevertheless, the strain and efforts associated with the intrapartum phase may pose a potential risk of muscle contractures or energetic crises. A careful exercise adaptation training programme may be advisable to minimise such risk. There are anecdotal reports of improved activity tolerance during pregnancy, possibly due to the peculiar hormonal status

associated with it, and to the hyperglycaemia experienced by some pregnant women.

In order to lessen potential muscle fatigue and cramps associated with newborn care, it is important for women with GSD V or GSD VII to exercise caution during unaccustomed tasks, such as carrying their newborn and frequent feeding.

10. Publications and resources

A wide range of resources is available for patients and medical professionals. These include publications, web sites, videos, and courses. Details are available in Supplementary Material - Appendix 5.

11. Emerging issues and knowledge gaps

11.1. Impact on carriers

Some cases of 'manifesting' heterozygotes or carriers – individuals who show some symptoms characteristic of GSD V despite being carriers of only one pathogenic variant in the *PYGM* gene – have been reported, [80–86] but there is controversy, with misdiagnosis being a possibility. In a recent study, 50 GSD V carriers were assessed to see whether any were actually 'manifesting' heterozygotes of GSD V [87]. Only 14% of carriers manifested some activity-related muscle problems (for example, exacerbated myalgia or weakness), and when present muscle symptoms were milder than those commonly reported in patients. Of note, no carrier (manifesting or not) showed the 'second-wind' phenomenon or a flat blood lactate response to maximal-intensity exercise, both of which are hallmarks of GSD V.

11.2. Third wind in GSD V?

'Third wind' was coined by individuals with GSD V who, from personal experience, suggested that after 2 h of walking there seems to be a further improvement in physical activity tolerance. Research conducted at Brunel University London was able to confirm that 'third wind' is a real phenomenon in GSD V. Metabolism in individuals with GSD V appeared to be quite different from that of non-GSD V individuals, in whom prolonged exercise elicits a slow climb in the percentage of fat used as fuel. By contrast, those with GSD V had a long slow climb in the use of carbohydrate as fuel, suggesting a greater contribution from gluconeogenesis [88].

11.3. LCKD in GSD V

LCKD has shown promise as a treatment option for GSD V. A recent pilot study found that a modified ketogenic diet composed of a minimum of 75% fat and a maximum of 10% carbohydrates seemed to improve exercise capacity and improve GSD V-related symptoms [6,51]. This is in line with published case series [66,89], which also showed promising effects, and with patient experiences published in an IamGSD survey [90]. However, a randomised placebo-controlled trial is lacking, therefore the efficacy of a LCKD in the treatment of GSD V has not been determined and cannot currently be recommended. Studies are currently ongoing in Copenhagen, London and Italy [91].

LCKD works by mimicking the physiological stage of fasting, in which low carbohydrate levels induce hormonal changes (lowering of insulin levels and increasing glucagon levels), stimulating fat oxidation and ketone body production. Ketone bodies (KB) constitute a desirable and fast-working energy source for both the brain and working muscles independent of glycogen breakdown. Thus, KB could be an alternative fuel source, especially during the first critical minutes of exercise before 'second-wind' is achieved. Increased fat oxidation should in theory also benefit people with GSD V, especially during prolonged exercise.

11.4. Cognitive impairment

GSD V and GSD VII are considered to be rare diseases in which brain function is normally spared. GSD V has commonly been regarded as a 'pure myopathy'. Nevertheless, myophosphorylase expression is not muscle-restricted. With regard to the brain, a deficiency of the brain isozyme of creatine kinase (CK-BB) in adults is complemented by an aliquot of the muscle isoform (CK-MM). Glycogen is the main energy reserve in the central nervous system (CNS) and accumulates predominantly in astrocytes, suggesting that the lack of myophosphorylase in the brain may impair its function. To date, the occurrence of CNS symptoms has rarely been reported in GSD V. Some years ago, a pilot study on neuropsychological performances in patients with GSD V showed that patients performed worse than unaffected individuals on tests of verbal fluency and verbal memory [92]. Despite this, further studies would be necessary to establish if there is involvement of the brain in GSD V and GSD VII.

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Supplementary material

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