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A Narrative Review on D-Glucose as a Metabolic Modulator in Amyotrophic Lateral Sclerosis: Mechanistic Insights and Therapeutic Implications

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons. Alongside the classical pathogenic mechanisms of protein aggregation, glutamate excitotoxicity, oxidative stress and mitochondrial dysfunction, a growing body of evidence identifies disturbed D-glucose metabolism as a central and potentially modifiable contributor to disease onset and progression. Patients with ALS frequently display systemic hypermetabolism, glucose intolerance and progressive weight loss, while positron emission tomography studies reveal regional cerebral and spinal glucose hypometabolism that correlates with clinical decline. At the cellular level, animal and cellular models of ALS show impaired glucose transport, defective glycolysis, disrupted pentose-phosphate pathway (PPP) flux, abnormal glycogen handling, reduced tricarboxylic acid (TCA) cycle throughput and mitochondrial oxidative phosphorylation deficits, all of which converge to compromise ATP generation, NADPH-dependent antioxidant defense, ion homeostasis and astrocyte–neuron metabolic coupling. These defects intersect with glutamate excitotoxicity and oxidative stress to accelerate motor neuron death. Conversely, nutritional interventions that increase carbohydrate and overall caloric intake have shown signals of clinical benefit, including a randomized trial in which a high-carbohydrate, hypercaloric diet was associated with longer survival, while epidemiological studies report a paradoxical inverse association between type 2 diabetes mellitus and ALS risk that may hinge on insulin-mediated glucose utilization rather than hyperglycemia itself. Experimental strategies that pharmacologically or genetically enhance neuronal glycolysis, restore PPP flux, or replenish NAD^+ pools have shown neuroprotective effects in preclinical ALS models. This review integrates current mechanistic and clinical evidence to propose that D-glucose functions as a double-edged metabolic determinant in ALS: physiological, well-regulated glucose availability and utilization support neuronal survival, whereas both cellular glucose hypometabolism and unregulated systemic hyperglycemia may be detrimental. We discuss therapeutic and translational implications, including caloric and carbohydrate-based nutritional strategies, glycolysis-targeted pharmacology, and the unresolved role of antidiabetic agents, while highlighting the methodological limitations and unanswered questions that should guide future research.

Key words: D-glucose; amyotrophic lateral sclerosis; motor neurons; hypermetabolism; glucose hypometabolism; GLUT3; glycolysis; pentose phosphate pathway; NADPH; astrocyte-neuron metabolic coupling; hypercaloric nutrition; diabetes mellitus; excitotoxicity; oxidative stress.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal, progressive neurodegenerative disorder characterized by the selective loss of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord, leading to muscle weakness, paralysis and death, typically from respiratory failure,

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within three to five years of symptom onset [1,2]. Approximately 90% of cases are sporadic, while the remainder are familial, most commonly linked to mutations in SOD1, TARDBP (TDP-43), FUS or C9ORF72 [2,3]. Despite decades of research, the mechanisms underlying selective motor neuron death remain incompletely understood, and current disease-modifying therapies confer only modest survival benefit.

Among the several converging pathogenic mechanisms proposed for ALS-glutamate excitotoxicity, protein misfolding and aggregation, impaired axonal transport, neuro-inflammation and oxidative stress-disturbed energy metabolism has emerged as a particularly important and clinically tractable axis [1,3]. Because D-glucose is the principal, and for the central nervous system (CNS) largely obligatory, energy substrate supporting ATP generation, redox defense and neurotransmitter cycling, disruption of glucose availability, transport or intracellular metabolism could plausibly compromise the very processes that protect motor neurons from excitotoxic and oxidative injury. Unlike many upstream genetic or molecular triggers of ALS, glucose metabolism is directly modifiable through diet, pharmacology and metabolic monitoring, making it an attractive translational target.

Clinically, ALS is frequently accompanied by whole-body metabolic disturbances, including hypermetabolism, impaired glucose tolerance and progressive weight loss that independently predict shorter survival [3–6]. At the tissue level, neuroimaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has repeatedly demonstrated regions of cerebral and spinal cord glucose hypometabolism in patients with ALS, in parallel with focal hypermetabolism attributed to glial activation [7–10]. Preclinical work in SOD1, TDP-43 and C9ORF72 models has begun to dissect the molecular basis of these abnormalities, implicating defects at nearly every step of glucose handling, from transporter expression to glycolysis, the pentose-phosphate pathway (PPP), glycogen metabolism, the TCA cycle and oxidative phosphorylation [2].

This review synthesizes current mechanistic evidence linking D-glucose metabolism to ALS pathogenesis, evaluates nutritional and pharmacological strategies that target glucose handling as potential ALS treatments, and considers the complex and still-unresolved relationship between systemic glucose regulation (including diabetes mellitus and antidiabetic medications) and ALS risk and progression. We conclude by outlining a working model in which the appropriate availability and regulated intracellular utilization of D-glucose-rather than glucose abundance alone-is central to motor neuron survival, and we highlight priority questions for future research.

2. A brief overview of CNS glucose metabolism

The mammalian CNS accounts for roughly 2% of body weight yet consumes approximately 20% of resting energy expenditure, most of which supports ion-gradient restoration, synaptic vesicle cycling and postsynaptic signaling [11,12]. Because neurons have limited intrinsic energy reserves, they depend on a continuous supply of D-glucose, which crosses the blood–brain barrier *via* glucose transporter 1 (GLUT1) and is subsequently taken up by neurons predominantly through the high-affinity transporter GLUT3, with astrocytes relying mainly on GLUT1 [11,13].

Once inside the cell, glucose-6-phosphate stands at a metabolic branch point: it may proceed through glycolysis to pyruvate, generating ATP and NADH, be diverted into the PPP to generate NADPH and ribose-5-phosphate for antioxidant defense and nucleotide biosynthesis, or be stored as glycogen (predominantly in astrocytes). Pyruvate derived from glycolysis is largely oxidized in mitochondria *via* the TCA cycle and the electron transport chain, generating the majority of neuronal ATP, while also supplying carbon skeletons for the synthesis of glutamate, GABA and other neurotransmitters [11,14]. Astrocytes and neurons cooperate metabolically through the glutamate–glutamine cycle and, under some conditions, through lactate shuttling, both of which are energetically coupled to glucose metabolism and to clearance of synaptic glutamate [11,15].

Abnormalities at any point along this network-transport, glycolysis, the PPP, glycogen handling, the TCA cycle or oxidative phosphorylation-can reduce ATP availability, compromise NADPH-dependent glutathione regeneration, and impair glutamate clearance, thereby lowering the threshold for excitotoxic and oxidative injury. This interconnected architecture explains why glucose dysmetabolism in ALS produces effects that extend well beyond simple energy deficit.

3. Systemic energy and glucose disturbances in patients with ALS

Energy homeostasis is disturbed in a substantial proportion of people with ALS. Hypermetabolism-an elevation in resting energy expenditure beyond that predicted from body composition-has been documented in 25–68% of patients and is on average about 10% higher than in healthy controls [4–6]. Hypermetabolism is associated with greater functional decline and shorter survival, independent of body weight [4]. Reduced body mass index at diagnosis, and ongoing weight loss during the disease course, are similarly and independently associated with faster functional decline and increased mortality risk, with a U-shaped relationship between body mass index and survival [5,6].

Glucose intolerance and dyslipidemia have also been reported in patients with ALS, in some studies preceding overt motor symptoms, suggesting that metabolic dysregulation may not simply be a consequence of reduced mobility or dysphagia but an intrinsic, and possibly early, feature of the disease [3]. The precise origin of this systemic hypermetabolic, glucose-intolerant state remains unresolved; proposed contributors include increased mitochondrial uncoupling in skeletal muscle, elevated resting energy expenditure from neuro-inflammatory and motor overactivity, and centrally driven neuroendocrine dysregulation of energy balance [1,3].

4. Regional CNS glucose hypometabolism and hypermetabolism in ALS

^{18}F-FDG-PET, which indexes glucose transport into tissue and its initial phosphorylation by hexokinase, has consistently shown reduced glucose utilization in the motor cortex, frontal and prefrontal regions of patients with ALS, independent of cortical atrophy [7–9]. This cortical hypometabolism correlates with disease severity, functional decline on the ALS Functional Rating Scale, and shorter survival [9,10]. By contrast, increased FDG-PET signal has been reported in the midbrain, cerebellum and, in some studies, the spinal cord, and has been attributed to local activation of astrocytes and microglia rather than to increased neuronal glucose oxidation [10,11]. Similar patterns of frontal hypometabolism with midbrain hypermetabolism have been described specifically in C9ORF72-associated familial ALS [12].

Comparable region-specific glucose hypometabolism, preceding symptom onset, has been observed in the motor cortex and spinal cord of SOD1^{G93A} mice and in TDP-43^{A315T} mice using combined FDG-PET-MRI [2,13]. Possible mechanistic contributors include reduced cerebral and spinal blood flow, decreased expression of GLUT1 at the blood–spinal cord barrier, and direct interference by misfolded mutant SOD1 with hexokinase binding to the mitochondrial voltage-dependent anion channel, which may uncouple glycolysis from mitochondrial ATP synthesis [2]. Whether regional glucose hypometabolism is a cause or a consequence of neuronal loss remains debated, but its detection before overt cortical atrophy in both patients and animal models supports a role as an early pathophysiological event rather than a purely secondary phenomenon, and raises the possibility that FDG-PET could serve as a biomarker of disease activity [2,9].

5. Molecular defects in glucose metabolic pathways in ALS

5.1 Glycolysis

Glycolysis provides rapid, locally generated ATP that is particularly important for maintaining synaptic function and fast axonal transport at nerve terminals distant from the cell body [14]. In the CNS of symptomatic SOD1^{G93A} mice, ^{13}C-glucose tracing has demonstrated reduced production of the glycolytic end-products lactate and alanine, reduced pyruvate levels and reduced pyruvate kinase activity, together with diminished incorporation of glucose-derived carbon into TCA-cycle-derived neurotransmitters such as glutamate, glutamine and GABA [2]. Consistent with impaired glycolytic flux, expression of the glycolytic enzyme phosphoglycerate kinase 1 is reduced in SOD1^{G93A} spinal cord [2]. Conversely, some cellular and Drosophila models show compensatory upregulation of glycolytic enzymes, and experimentally boosting glycolysis *via* overexpression of GLUT3 and phosphofructokinase, or restoration of NAD^+ with nicotinamide supplementation has proved neuroprotective and modestly extended survival in ALS models, supporting glycolysis as both a site of pathology and a potential therapeutic lever [2,16,27].

5.2 Glycogen metabolism

Glycogen, stored mainly in astrocytes, is rapidly mobilized to glucose-6-phosphate during periods of high energy demand. In SOD1^{G93A} mice, glycogen accumulates in the spinal cord from disease onset through end stage, attributable to reduced glycogenolysis (lower phosphorylase activity) rather than increased synthesis [2,17]. A parallel reduction in glycogen-mobilizing enzymes has been observed in astrocytes derived from C9ORF72-mutant ALS patients, alongside broader evidence of reduced astrocytic metabolic flexibility [2,18]. Reduced α-glucosidase activity, consistent with glycogen accumulation, has also been reported in spinal cord tissue from people with ALS, indicating that this defect is not confined to animal models [2].

5.3 The pentose-phosphate pathway (PPP) and antioxidant defence

The PPP diverts roughly 5–6% of neuronal glucose to generate NADPH, which is essential for regenerating reduced glutathione and thereby defending neurons against reactive oxygen species (ROS) [34]. In the spinal cord of SOD1^{G93A} mice at disease onset, total ribose-5-phosphate is reduced by roughly one-third and glucose-6-phosphate dehydrogenase activity is decreased by about 15%, consistent with impaired PPP flux rather than accelerated ribose consumption [2,14]. Decreased expression and activity of the PPP enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase have also been found in mutant-SOD1-transfected motor neuron-like cells [2,21]. These defects coincide with reduced glutathione levels and increased oxidative stress markers in ALS motor cortex, reinforcing the mechanistic link between impaired glucose-dependent NADPH production and the oxidative injury implicated throughout ALS pathogenesis [2].

5.4 TCA cycle and oxidative phosphorylation

Downstream of glycolysis, reduced entry of pyruvate into the TCA cycle has been linked to increased expression of pyruvate dehydrogenase kinase 1 (which inhibits pyruvate dehydrogenase) and reduced activity of oxoglutarate dehydrogenase in motor cortex and spinal cord of ALS models [2]. Multiple studies report structural and functional mitochondrial abnormalities in ALS motor neurons, including defective electron transport chain complexes and reduced ATP synthase expression, contributing to diminished oxidative ATP generation and increased ROS production [2]. Mutant SOD1, TDP-43 and FUS proteins have each been shown to accumulate at or within mitochondria and to impair complex I/IV activity, mitochondria-endoplasmic reticulum interactions and mitochondrial dynamics, providing plausible molecular links between the genetic drivers of familial ALS and downstream glucose-oxidative metabolic failure [2].

6. Disrupted astrocyte-neuron glucose-glutamate coupling

Astrocytes support neuronal glucose metabolism not only by supplying glycogen-derived substrate but, critically, by clearing synaptic glutamate through high-affinity transporters (notably EAAT2/GLT-1) in a process that is directly coupled to astrocytic glycolysis and Na^+/K^+-ATPase activity [15]. In ALS, expression of EAAT2/GLT-1 is reduced in the spinal cord and motor cortex of both patients and animal models, and glutamate uptake into synaptosomes is correspondingly diminished [2,19,20,23,24]. In SOD1^{G93A} spinal cord, glucose-derived glutamate and glutamine production, and the transfer of glutamate to glutamine via the astrocytic glutamate-glutamine cycle, are both reduced, indicating that impaired glucose handling and impaired glutamate clearance are mechanistically intertwined rather than independent defects [2]. Because reduced glutamate uptake elevates extracellular glutamate and increases the risk of excitotoxic NMDA-receptor over-activation, disrupted astrocyte-neuron metabolic coupling represents a key convergence point between glucose dysmetabolism and the classical excitotoxicity hypothesis of ALS [23,24]. Restoring astrocytic EAAT2/GLT-1 expression pharmacologically has been shown to protect motor neurons and extend survival in ALS models, underscoring the therapeutic relevance of this glucose-glutamate axis [2].

7. Convergence of glucose dysmetabolism, oxidative stress and excitotoxicity

The mechanistic threads reviewed above converge on a self-reinforcing cycle. Impaired glycolysis and oxidative phosphorylation reduce ATP available for Na^+/K^+-ATPase activity and astrocytic glutamate uptake, favoring extracellular glutamate accumulation and excitotoxic Ca^{2+} influx through NMDA and AMPA receptors [15,25]. Simultaneously, impaired PPP flux limits NADPH-dependent glutathione

regeneration, reducing the neuron's capacity to detoxify the ROS generated by excitotoxic calcium overload and by dysfunctional mitochondria [14,34]. The resulting oxidative damage can further inhibit glycolytic and TCA-cycle enzymes several of which are directly inhibited by hydrogen peroxide closing a vicious cycle in which glucose dysmetabolism, oxidative stress and excitotoxicity each amplify the others [2]. This integrated view helps explain why interventions directed at any single node (antioxidants, glutamate-modulating drugs or metabolic support) have shown only partial benefit in isolation, and it strengthens the rationale for combination strategies that simultaneously support energy metabolism and antioxidant capacity [9].

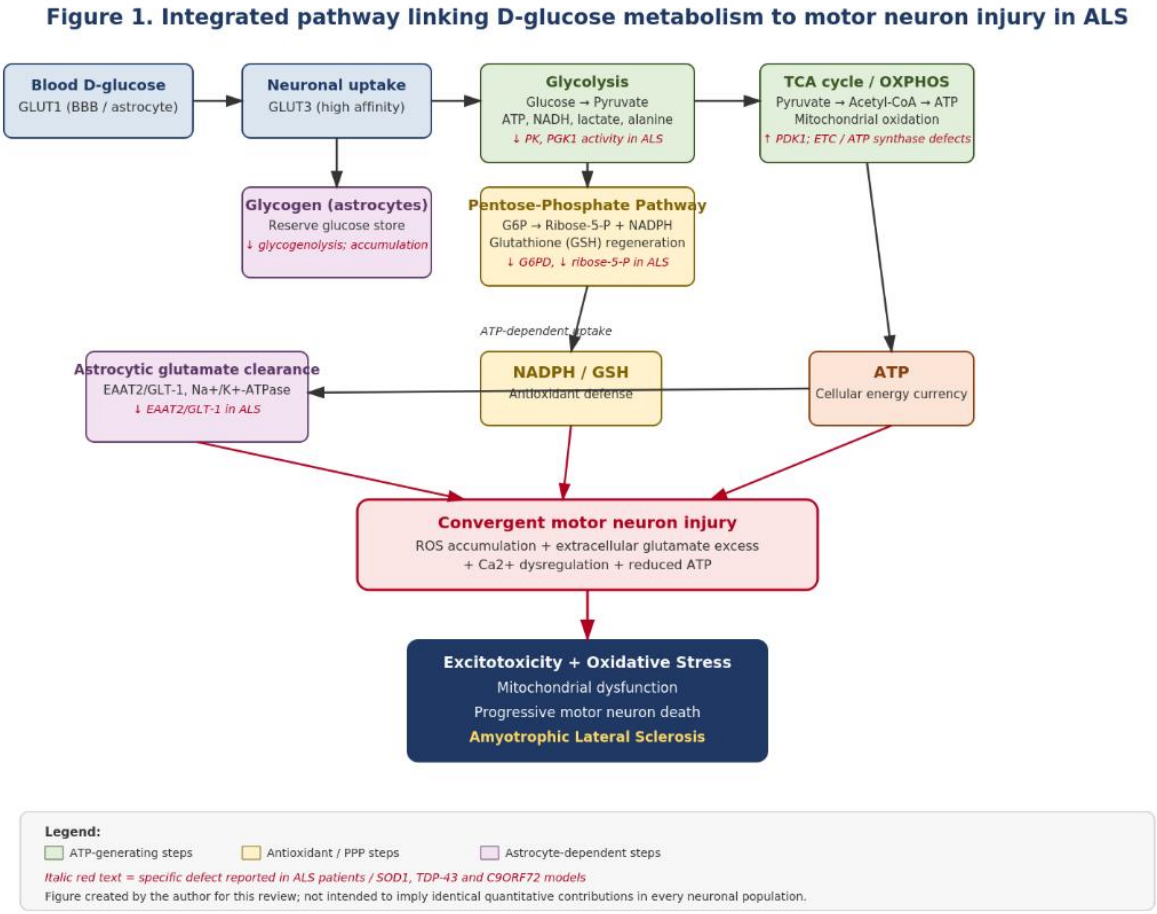


Figure 1. *Integrated pathway linking D-glucose transport, glycolysis, the pentose-phosphate pathway, glycogen metabolism and the TCA cycle/OXPHOS to ATP generation, antioxidant defense and astrocytic glutamate clearance, and their convergence on excitotoxic and oxidative motor neuron injury in ALS (defects reported in ALS shown in red italics; see Sections 5–7).*

8. D-glucose and carbohydrate-based nutritional interventions in ALS treatment

Given the strong association between weight loss, hypermetabolism and poor prognosis, correcting energy balance has been directly tested as an ALS therapy. In a randomized, double-blind, placebo-controlled phase 2 trial in 24 patients with ALS fed *via* percutaneous endoscopic gastrostomy, a hypercaloric, high-carbohydrate diet (125% of estimated energy requirements) was safe, well tolerated, associated with fewer adverse events than a high-fat hypercaloric diet, and notably associated with longer survival during the follow-up period compared with both the high-fat and isocaloric control arms [26]. This trial provided the first controlled clinical signal that increasing carbohydrate-derived caloric intake could extend survival in ALS.

A larger, double-blind, randomized phase 3 trial (n = 208) subsequently tested a high-caloric fatty (rather than carbohydrate-based) supplement and found no overall survival benefit, although a pre-specified subgroup of patients with rapidly progressing disease showed prolonged survival and

stabilized body weight [8]. Taken together with the earlier carbohydrate-focused trial, these results suggest that the macronutrient composition of caloric supplementation and specifically the inclusion of carbohydrate/D-glucose-yielding substrate may matter, not merely total caloric load, although head-to-head comparisons in adequately powered trials are still lacking.

Observational and smaller randomized studies reinforce the broader principle that adequate nutritional and caloric support improves outcomes: a randomized trial of complete high-caloric nutrition (n = 40) in ALS patients after gastrostomy significantly improved nutritional indicator proteins, body weight and cumulative survival compared with routine diet alone [27], and high caloric intake (>1,500 kcal/day) sustained *via* percutaneous endoscopic gastrostomy has been correlated with prolonged survival in prospective cohorts. Collectively, these data support hyper-caloric, carbohydrate-inclusive nutritional support as a pragmatic, low-risk adjunct to standard ALS care, while highlighting the need for larger trials that isolate the specific contribution of D-glucose/carbohydrate content from total caloric intake.

9. Diabetes mellitus, glucose intolerance and ALS risk: A paradox

The relationship between systemic glucose regulation and ALS risk is more complex, and at first glance paradoxical, relative to the nutritional data above. A large Danish population-based case-control study (3,650 ALS cases; 365,000 matched controls) found that a pre-existing diagnosis of type 2 diabetes mellitus was associated with a significantly reduced risk of subsequently developing ALS, with the protective association strengthening with increasing age at ALS diagnosis, whereas type 1 diabetes and obesity were not protective [28]. A Taiwanese nationwide cohort study of over 600,000 diabetic patients similarly found a moderate but significant positive association overall between diabetes and later ALS in some analyses, illustrating that findings have not been fully consistent across populations and study designs [29]. A systematic review and meta-analysis likewise concluded that diabetes mellitus, and type 2 diabetes in particular, is associated with a lower risk of ALS [30].

More recent pharmaco-epidemiological studies have attempted to disentangle the diabetic state itself from antidiabetic drug exposure. A Swedish nested case-control study found an inverse association between antidiabetic medication use and ALS risk, consistent with the diabetes-ALS protective association, while also identifying an increased statin prescription rate in women in the year preceding ALS diagnosis, raising the separate possibility that statin initiation reflects prodromal metabolic change rather than a causal effect on disease risk [31]. A subsequent Israeli case-control study reported that overall type 2 diabetes diagnosis was not associated with ALS risk, but that a history of insulin use specifically was associated with a substantially reduced risk of ALS, suggesting that the protective signal linked to diabetes may be mediated by improved glucose disposal (insulin-driven glucose utilization) rather than by hyperglycemia or diabetes status per se [32].

This body of evidence should be interpreted cautiously: reverse causation is a persistent concern, since the hypermetabolic, glucose-intolerant, catabolic state that can precede clinical ALS diagnosis by years could itself lower measured rates of diabetes diagnosis or diabetes-related prescribing in the pre-diagnostic window. Nonetheless, the convergent finding that agents which enhance cellular glucose disposal (such as insulin) may be protective, while diabetes-associated hyperglycemia itself is not, is broadly compatible with the mechanistic picture developed in Sections 5–7: motor neuron survival appears to depend on adequate glucose delivery and utilization at the cellular level, not on elevated circulating glucose concentration.

Consistent with this interpretation, direct pharmacological activation of glucose-sensing pathways has not uniformly translated into benefit. Metformin, an AMPK activator used in type 2 diabetes that lowers hepatic glucose output and improves insulin sensitivity, showed no survival benefit and was harmful in female mice in a blinded, dose-response survival study in the $SOD1^{G93A}$ model [33], underscoring that pharmacologically lowering systemic glucose availability is not a viable therapeutic strategy in ALS and that the beneficial signal associated with insulin more plausibly reflects enhanced intracellular glucose utilization than reduced circulating glucose per se.

10. Emerging therapeutic strategies targeting D-glucose metabolism

Beyond whole-diet caloric strategies, several approaches aim to directly restore glucose flux or its downstream metabolic products at the cellular level:

- Glycolysis activation: Overexpression of GLUT3 and phosphofructokinase selectively in motor neurons improved locomotor function and was neuroprotective in a TDP-43 Drosophila model, indicating that boosting neuronal glycolytic capacity can compensate for downstream metabolic deficits [16].
- NAD^+ restoration: Nicotinamide supplementation, which restores NAD^+ required to sustain glycolytic flux, modestly improved survival and increased glycolytic ATP production in $SOD1^{G93A}$ mice [27]. A combination of two NAD^+-elevating compounds (EH301) improved the ALS Functional Rating Scale score, pulmonary function and muscle strength in a small randomized, double-blind, placebo-controlled pilot study, providing early clinical proof of concept for this strategy [28].
- Alternative TCA-cycle fuels: Provision of energy substrates that bypass upstream glycolytic and PPP defects and feed the TCA cycle directly - pyruvate, acetoacetate, triheptanoin and β-hydroxybutyrate has counteracted oxidative stress in preclinical models and represents a complementary, rather than competing, strategy to glucose-centered approaches [2].
- Astrocytic glutamate transporter upregulation: Pharmacological induction of EAAT2/GLT-1 (for example, *via* β-lactam antibiotics in earlier preclinical work) restores glucose-coupled glutamate clearance and has extended survival in ALS models, targeting the glucose–glutamate convergence point described in Section 6 [2].
- Hypercaloric, carbohydrate-inclusive nutrition: As detailed in Section 8, dietary carbohydrate supplementation remains the most clinically advanced, low-risk strategy for supporting systemic and, indirectly, CNS glucose availability [8,26,27].

11. Therapeutic considerations: A metabolic optimum rather than “more glucose is better”

The evidence reviewed here does not support a simple “more glucose is better” model of ALS treatment. Rather, it points to a metabolic optimum analogous to that described for neuronal glucose handling more broadly: insufficient CNS glucose delivery and impaired intracellular utilization compromise ATP production, NADPH-dependent antioxidant defence and glutamate clearance, favoring excitotoxic and oxidative injury (Sections 4–7); adequate, well-regulated glucose availability and metabolism support these same protective processes; but unregulated systemic hyperglycemia, chronic glucose excess, or pharmacological manipulation that does not translate into improved cellular glucose disposal is not established as beneficial and may carry independent risks of oxidative stress and glycation-related injury by analogy with glucose toxicity mechanisms described in other neurodegenerative contexts. The apparent benefit of insulin exposure in epidemiological data, contrasted with the lack of benefit (and harm in female mice) with metformin, is consistent with the hypothesis that facilitating cellular glucose uptake and utilization, rather than simply raising or lowering circulating glucose, is the relevant therapeutic lever [32,33].

Practically, this suggests that nutritional strategies in ALS should prioritize preventing energy deficit and hypermetabolism-driven catabolism through individualized, calorimetry-guided caloric and carbohydrate provision, while avoiding uncontrolled hyperglycemia, particularly in patients with comorbid diabetes or during enteral or parenteral feeding, until dedicated safety and efficacy data are available. Any pharmacological strategy aimed at glucose metabolism should be evaluated for its effect on cellular glucose disposal and downstream antioxidant and glutamate-clearance pathways, not solely on circulating glucose concentration.

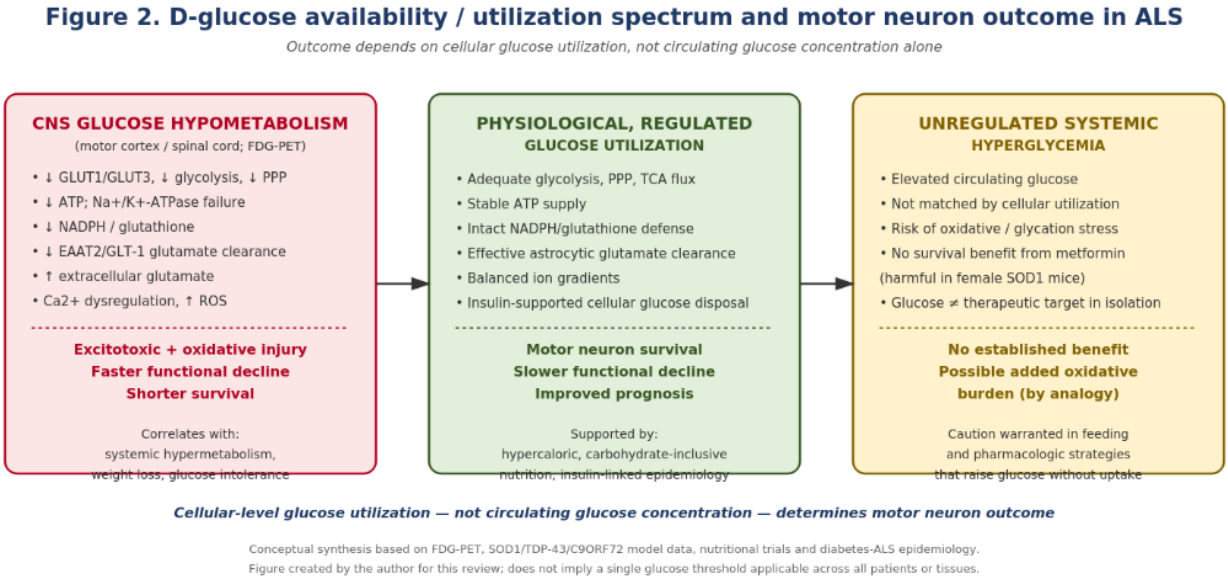


Figure 2. *Conceptual D-glucose availability / utilization spectrum and predicted motor neuron outcome in ALS, contrasting CNS glucose hypometabolism, physiological regulated glucose utilization, and unregulated systemic hyperglycemia (see Section 11).*

12. Limitations and future research priorities

Several important limitations qualify the current evidence base. First, FDG-PET and related imaging techniques index glucose transport and initial phosphorylation, not the full downstream metabolic fate of glucose, so hypometabolic and hypermetabolic PET signals cannot fully distinguish neuronal from glial contributions [2,9]. Second, most mechanistic data derive from SOD1 rodent models, which may not fully recapitulate sporadic ALS or other genetic subtypes (TDP-43, FUS, C9ORF72); cross-model validation is needed. Third, clinical nutritional trials to date have been small (the pivotal carbohydrate-focused trial enrolled only 24 patients) or have tested fat-based rather than carbohydrate-based supplementation at larger scale, leaving the macronutrient-specific contribution of D-glucose/carbohydrate underpowered relative to total caloric effects [8,26]. Fourth, epidemiological studies of diabetes and ALS risk are susceptible to reverse causation and require designs with long lag periods and, ideally, mechanistic biomarkers (e.g., glucose disposal rates, HbA1c trajectories) rather than diagnosis codes alone [28,29,32].

Priority directions for future research include: adequately powered, randomized trials directly comparing carbohydrate-predominant versus fat-predominant hypercaloric nutrition with survival and functional endpoints; cell-type-resolved metabolic flux studies (stable-isotope tracing, genetically encoded metabolic sensors, single-cell metabolomics) to clarify neuron-specific versus astrocyte/microglia-specific contributions to CNS glucose hypo- and hypermetabolism; mechanistic studies of why insulin, but not metformin, shows a protective signal; and controlled evaluation of glycolysis and PPP-targeted pharmacological agents (building on preclinical GLUT3/phosphofructokinase overexpression and NAD^+-restoration data) in human ALS.

Table 1. Summary of D-glucose-related mechanisms and therapeutic approaches in ALS

Level / Process	Alteration observed in ALS	Consequence	Therapeutic approach and evidence
Systemic energy balance	Hypermetabolism; weight loss; glucose intolerance	Faster functional decline; shorter survival [4–6]	Individualized hypercaloric nutrition; calorimetry-guided feeding [8,26,27]
CNS glucose uptake (FDG-PET)	Motor cortex / frontal hypometabolism; midbrain / glial hypermetabolism	Correlates with disease severity and survival [9,10]	Potential biomarker of disease activity and progression [2,9]
Glycolysis	Reduced pyruvate, lactate, alanine; reduced PK and PGK1	Impaired rapid ATP supply at synapses [2,14]	GLUT3/PFK overexpression; NAD^+ restoration (nicotinamide, EH301) [16,27,28]
Pentose-phosphate pathway	Reduced G6PD activity; reduced ribose-5-phosphate	Impaired NADPH/glutathione antioxidant defense [2,14,34]	Investigational; PPP-activating strategies under study
Glycogen metabolism	Astrocytic glycogen accumulation; reduced glycogenolysis	Reduced rapid-access glucose reserve [2,17,18]	Not yet targeted clinically
TCA cycle / OXPHOS	Reduced PDH activity; ETC and ATP synthase defects	ATP depletion; increased ROS [2]	Alternative TCA fuels: pyruvate, acetoacetate, triheptanoin, β-hydroxybutyrate [2]
Astrocyte–neuron coupling	Reduced EAAT2/GLT-1; reduced glutamate–glutamine cycling	Excitotoxicity via extracellular glutamate accumulation [2,15,23,24]	EAAT2 upregulation; combined metabolic/antioxidant support [2]
Systemic glucose regulation	Inverse diabetes–ALS association; insulin protective, metformin not beneficial	Suggests cellular glucose disposal, not hyperglycemia, is protective [28,32,33]	Caution with antidiabetic pharmacology; avoid uncontrolled hyperglycemia

Abbreviations: *FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography; PK: pyruvate kinase; PGK1: phosphoglycerate kinase 1; G6PD: glucose-6-phosphate dehydrogenase; TCA: tricarboxylic acid; OXPHOS: oxidative phosphorylation; ETC: electron transport chain; ROS: reactive oxygen species; EAAT2/GLT-1: excitatory amino acid transporter 2 / glutamate transporter 1.*

13. Conclusions

D-glucose occupies a central and multifaceted position in ALS pathophysiology. It is not simply a fuel whose scarcity or abundance passively tracks disease severity; rather, coordinated disturbances in its transport, glycolytic and pentose-phosphate handling, glycogen storage, TCA-cycle oxidation and coupling to astrocytic glutamate clearance converge with excite-toxicity and oxidative stress to accelerate motor neuron degeneration. Clinically, hyper metabolism, glucose intolerance and weight loss are established, modifiable prognostic markers, and a hyper caloric, carbohydrate-inclusive nutritional strategy has shown a survival signal in a controlled trial, supporting nutritional optimization as a pragmatic component of ALS management. At the same time, the paradoxical epidemiological association between diabetes, insulin use and reduced ALS risk together with the lack of benefit from metformin cautions against equating “more circulating glucose” or generic antidiabetic pharmacology with neuroprotection. The most defensible current synthesis is that motor neuron survival depends on adequate, well-regulated cellular glucose delivery and utilization, and that future therapeutic strategies

should aim to restore this cellular-level metabolic competence through nutrition, glycolysis and PPP-targeted pharmacology, and astrocyte-directed approaches rather than manipulating systemic glucose levels in isolation.

Declarations

The contents of the review provided herein are developed using AI tools; and the review is prepared and published to help researchers who are currently working on neurological diseases such as ALS/MND.

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