Insulin-Based Treatment for Amyotrophic Lateral Sclerosis

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Abstract

Background. Amyotrophic Lateral Sclerosis (ALS) is a devastating disease involving motor neuron degeneration. The few drugs approved for treatment have at most a marginal benefit, and death usually occurs 2-5 years after diagnosis.

Methods. A thorough manual examination of the relevant literature, covering over 35,000 papers.

Results. Two major phenomena that are generally not known to clinicians were found. First, insulin signaling is impaired in ALS even in patients not diagnosed with diabetes (DB). Almost all studies that have explicitly tested insulin function in non-DB ALS patients using glucose tolerance tests (18 out of 21, 1964-2022, different groups) have found it to be impaired. Second, there is strong evidence for excessive insulin-independent glucose uptake (IIGU) in ALS. In addition, (i) early/late diabetes are associated with increased/decreased risk, respectively; (ii) insulin-based diabetes drugs are protective in ALS in large retrospective human studies; and (iii) strong animal and human evidence shows that insulin opposes all of the major pathological processes in ALS.

Conclusion. Most ALS patients have insulin impairment, yet this is commonly not diagnosed, likely because excessive IIGU normalizes glucose levels. The impairment promotes disease progression. Late diabetes is associated with decreased risk because high glucose levels indicate non-excessive IIGU, and because diabetes drugs are protective. Insulin-based treatment (e.g., GLP1 agonists, insulin) is beneficial and can be disease-modifying in ALS and in frontotemporal dementia variants comorbid with ALS. ALS patients should be routinely tested for insulin function and treated if test results are positive.

Keywords. ALS, frontotemporal dementia, insulin, diabetes

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Introduction

ALS is a disease of unknown etiology involving the degeneration of motor neurons (MTNs).[1,2] There are two variants, sporadic ALS (sALS), which affects 80-90% of the patients, and familial ALS (fALS), usually associated with gene mutations. There is strong comorbidity with frontotemporal dementia (FTD), mainly its behavioral variant (bvFTD).[3,4] The few approved treatments have only a marginal benefit,[5–7] and death usually occurs two to five years after diagnosis.

Here I point to a promising immediately available therapy, which, although based on strong existing evidence, is not recognized by the medical community. I highlight wide evidence that insulin function is impaired in a large subset of ALS patients, and explain why it is usually not detected and why insulin-based therapy (insulin itself or drugs promoting its secretion) should provide benefit. The account is supported by wide epidemiological data on the relationship between ALS and diabetes mellitus (DB), studies showing that DB drugs are associated with decreased ALS risk, imaging and molecular evidence in ALS, and a diversity of other preclinical results.

Methods

An extensive manual examination of the relevant literature has been conducted over several years. Papers were identified via searches of Google Scholar and PubMed between 1950 and November 2022, and references from and citations of relevant articles. The search terms used were ALS, FTD, glucose, insulin, diabetes, AMPK, cellular stress, unfolded protein response, oxidative stress, glutathione, TDP-43, and calcium. Hundreds of thousands of papers were examined, with over 35,000 papers thoroughly read.

Note that although the methodology used is similar to that used for reviews, this paper is not a review. It reports novel results, which are based on previously reported empirical evidence.

Known ALS pathophysiology

The etiology of ALS is not known, but much is known about its pathophysiology. Both sALS and fALS cells show clear cellular stress and stress responses, including endoplasmic reticulum (ER) stress,[8–11] unfolded protein and heat shock responses (UPR, HSR),[12–20] oxidative stress[9,21] with reduced glutathione (GSH)[22,23] and increased lipid peroxidation,[24–30] and immune reactivity.[31,32] Indeed, almost all patients show pathological accumulation of the TDP-43 protein, which is associated with stress responses.[33] ALS cell stress involves excitotoxicity, with much evidence pointing to calcium overload.[34–40] Mitochondria are impaired, with reduced oxidative phosphorylation[9,41–45] and permeability pore opening.[46]

These phenomena are widely recognized and comprise the logical foundation of the drugs approved for ALS and of almost all clinical trials done over the years.[47]

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Insulin is impaired in ALS

A thorough search and examination of the literature revealed that ALS exhibits an additional strong pathophysiology, insulin impairment. Twenty one papers published during the last sixty years have reported the results of explicit glucose tolerance or insulin tests (mainly using the oral glucose tolerance test (OGTT)) in ALS patients who were not previously diagnosed with diabetes. Of these, eighteen reported impaired insulin secretion[48–53] or signaling,[54–62,64–66] and one reported an inverse correlation between gluocse disposal rate and disease severity.[63] Only two early papers reported normal glucose tolerance, one using neurological patients rather than healthy controls,[67] and one not using controls at all.[68] Another paper found increased plasma and CSF alpha-hydroxybutyrate (a pre-diabetes marker),[69] and another reported insulin resistance (IR) in bvFTD.[70]

In other words, **almost anybody who has ever tested insulin function in ALS has found it to be impaired in patients not previously diagnosed with diabetes** (at the group level). We can conclude that insulin is impaired in a significant subset of ALS patients.

In addition to these results, there are strong epidemiological data pointing to a link between ALS and DB. Studies examining whole-country registers in England, Sweden, Taiwan, and Denmark have shown that early DB (diagnosed before the age of 50 in Sweden and Denmark or 65 in Taiwan) is associated with increased ALS risk.[71–75] In addition, high HbA1c (indicating high blood glucose levels over a time period) is significantly associated with higher ALS mortality.[76]

These data suggest that type-2 DB (DB2) would be associated with increased ALS risk. However, there is strong country, regional, and single clinic evidence that late age DB is associated with *decreased* ALS risk,[72,74,75,77–82] delayed onset,[83–86] and longer survival.[83,84] We explain this apparent paradox further below.

These results are generally not mentioned at all, or mentioned very little, in relation to ALS,[2,87,88] even in papers focusing on metabolism.[89,90] The vast majority of researchers and clinicians are thus probably not aware of these strong ALS-DB links and of insulin impairment in ALS.

Why insulin impairment is not detected

We saw that explicit testing of insulin function in ALS points to an impairment. However, if this is the case, ALS patients should have been routinely diagnosed with late DB, which is not the case. How can this be explained?

Here I present a novel answer to this question: in ALS, there is excessive insulin-independent glucose uptake (IIGU), which in most patients masks their insulin problem. DB2 is normally discovered when blood glucose levels are abnormally high. When glucose levels seem normal, deeper tests of insulin function (e.g., OGTT) are usually not done.

Insulin induces glucose uptake mainly by stimulating the translocation of the Glut4 glucose

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transporter to the plasma membrane.[91] However, Glut4 translocation is also stimulated independently of insulin, including by AMPK,[92] (nor)epinephrine,[93,94] and calcium.[95,96] Contraction-induced glucose uptake is a major and well-known skeletal muscle mechanism,[95] and so is glucose-induced uptake ('glucose effectiveness').[97] Even calcium concentrations that are below the contraction threshold trigger glucose uptake.[98] Note that Glut4 expression is not limited to skeletal muscle but occurs in brain motor areas as well, including in MTNs.[99,100]

Insulin-independent glucose uptake can be excessive due to several causes. As noted above, calcium overload is one of the major phenomena of ALS. AMPK is activated by ATP deficiency, which can in turn be induced by two of the major ALS phenomena, mitochondria dysfunction (since mitochondria normally produce most of the cell's ATP) and calcium overload (since the plasma membrane and ER calcium pumps consume ATP). A complete theory of ALS that explains why IIGU occurs is presented in a companion paper.

There is very strong evidence supporting this masked IIGU account. Hypermetabolism identified via FDG-PET clearly occurs in skeletal muscle and low brain motor areas in ALS.[101–106] When added to the widespread evidence for increased resting energy expenditure in ALS detected via indirect calorimetry (including in early-stage patients),[107–114] hypermetabolism is one of the major documented ALS phenomena. While indirect calorimetry does not point to a specific mechanism, FDG-PET directly points to excessive Glut4-mediated glucose uptake. Strong evidence of cortical hypometabolism, especially in non-motor areas, where Glut4 expression is weak,[101–104,115,116] points to excessive glucose uptake by the motor system, which is the main glucose consumer in the body. Frontal hypometabolism is also a core feature of FTD.[117–121]

At least some of this excessive uptake is insulin-independent, as shown by increased activated AMPK in patient MTNs,[122,123] early increased sympathetic activity,[124–128] and chronic intracellular MTN calcium. The increased sympathetic activity in skeletal muscle is not correlated with ALS disability, duration, or prognosis, showing that it is a core characteristic of the disease.[129,130] In the large subset of patients with impaired insulin function, almost all of this excessive Glut4-mediated uptake would be insulin-independent.

The existence of a chronic energy consuming process in ALS is also supported by the fact that patients exhibit severe weight loss that is not fully accounted for by reduced food intake.[131–133]

Readers might still wonder why such a gross dysregulation in glucose homeostasis is so commonly not detected. Recall that there are mechanisms to protect from both hyperglycemia (insulin) and hypoglycemia (counter-regulatory responses, CRRs). As long as CRRs work and excessive IIGU masks insulin impairment, glucose dysregulations would not be noticed. Our account implies that CRRs should be moderately hyperactivated, and indeed, all of the CRR components (sympathetic activation (cited above), growth hormone, glucagon, cortisol) are mildly increased in ALS.[66,134–138]

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The effect of insulin in ALS

Insulin should be protective in ALS. Insulin is known to promote glucose uptake and protein synthesis.[91] As part of these role, it streamlines cellular energy production and health in a variety of ways. It opposes oxidative stress by promoting GSH synthesis,[139,140] opposes with GSH the apoptosis-promoting effects of H2O2,[141] acts as an anti-inflammatory agent in the immune system,[142] promotes mitochondria health, oxidative phosphorylation, ATP production, and protein synthesis,[143,144] promotes synaptic plasticity,[145] and opposes calcium overload and toxicityand opposes calcium overload and toxicity.[146–153] The insulin-induced GSH inhibits stress-induced formation of stress granules,[154] which are strongly associated with TDP-43 accumulation.[33] Conversely, chronic intracellular calcium[155,156] and mitochondria impairment[157,158] induce insulin resistance. Beta cell stress and IR are associated with unfolded proteins,[159–164] permeability pore opening,[165] and calcium toxicity.[155,156,163,166–168]

In other words, **insulin opposes all of the detrimental phenomena that clearly occur in ALS, and these in turn impair insulin signaling**.

DB drugs, including insulin, are indeed protective in ALS. No clinical trials have been done using insulin therapy for ALS[1]. However, in addition to the general DB2 association with reduced ALS risk, several large studies (including all Medicare and a large Swedish population) have found that usage of DB drugs is specifically associated with decreased risk of developing ALS.[170–172] In an all-Taiwan study, moderate insulin use for DB was associated with decreased risk specifically for patients taking non-oral DB drugs.[78]

Why is insulin impaired in ALS? In light of these data, consider the papers cited earlier reporting insulin impairment in ALS. These papers have discussed various possible explanations for their results, including reduced glucose uptake in wasted skeletal muscle, physical inactivity inducing IR, stress opposition of insulin signaling via cortisol and (nor)epinephrine, and malnutrition ('starvation diabetes'). However, it has also been acknowledged that these explanations cannot account for the overall pattern of results, which include reduced insulin secretion and receptor expression.

The analysis above on the expected effects of insulin in ALS leads to a simpler and better-supported explanation: *the core pathological processes that damage MTNs in ALS can also damage insulin secretion and/or signaling*, directly or indirectly.

Insulin, DB2, and disease risk

Trajectories. There are several possible scenarios for the lifetime trajectory of insulin in ALS and its relationship with disease symptoms.

First, insulin secretion can be reduced at an early age (either due to an ALS-related process

[1]The only trial done using a DB drug was with pioglitazone, which does not directly act on the insulin path.[169]

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(e.g., calcium) or independently of ALS). In this case the protection insulin provides is not present, resulting in increased ALS risk. This explains the data cited above of increased risk with early DB, which is usually insulin-dependent (DB1).

In a second scenario, insulin secretion is basically normal. Since ALS involves excessive insulin-independent glucose uptake, glucose levels should be on the lower side, and the person is expected to be leaner than the average (mainly because muscle takes more glucose than it normally does, so less glucose is available for adipose tissue). Indeed, in a large study in Sweden, ALS was associated with lower blood glucose from 20 years pre-onset to onset,[173] and in both country-wide and single clinic studies, pre-onset low/high BMI were strongly associated with increased/decreased ALS risk, respectively.[174–181] High BMI was also found to be associated with longer survival in a meta-analysis.[182]

In this scenario, insulin and other factors protect the person until aging-induced decline overcomes this protection. In many cases, the normal aging-related decreases in insulin[183,184] and steroids (which reverse the aging-related increase in brain calcium currents[185]) would trigger the appearance of symptoms.

Third, insulin secretion can be higher than normal. This can be ALS-independent, or be linked to ALS, e.g., if the underlying process in ALS is chronically high calcium that also occurs in beta cells (since chronically high beta cell calcium would drive chronic insulin release). In this case, the person would be initially protected as in the second scenario. However, with aging, the chronic insulin secretion and the calcium toxicity in beta cells would impair insulin secretion and/or signaling.

In this scenario, insulin impairment might be the specific event that triggers the appearance of ALS symptoms. This scenario explains the finding that as the disease progresses, fat mass increases and fat-free mass decreases (both are IR markers).[186]

In all three scenarios, the impairment of insulin function is directly associated with the appearance of the disease.

Fourth, there is a possible scenario in which insulin secretion is increased as in the third scenario, but ALS symptoms appear before IR does. This is possible when the core problem or IR affect MTNs faster than they affect beta cells, such that even increased insulin does not manage to protect MTNs after a certain age.

Finally, it is possible that insulin secretion is intact throught life, including during disease appearance and progression. In this scenario, the disease is driven by its core causes (e.g., calcium toxicity) and insulin signaling has no causal effect.

DB2. The above still does not explicitly state why DB2 is associated with reduced risk. There are three possible answers to this question.

First, elevated blood glucose may indicate that there is no serious chronic insulin-independent glucose uptake. In this account, DB2 is not protective per se, but reflects a reduced risk of having the core cause of ALS.

Second, the main pathophysiology in DB2 is IR. IR involves higher blood insulin, which, although promoting further IR, also manages to induce some insulin signaling, which should be

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directly protective in ALS as explained above.

Finally, many DB2 patients are treated with insulin-based drugs (GLP-1 agonists, insulin itself), which should again oppose the core ALS mechanisms. Here, it is DB2 treatment that opposes the development of ALS. Evidence supporting this account was cited above. In both the second and third scenarios, insulin is protective.

Tests and Treatment

Therapy. There are several lines of ALS treatment implied by the analysis here. The main one is to use DB drugs, specifically insulin-based therapy. DB drugs generally improve insulin function, and since insulin opposes the main ALS processes, this might slow down disease progression. In MTNs whose axons have only started degenerating, treatment may even reverse the process and show improvement.

The specific insulin-based treatment to be used depends on beta cell insulin secretion capacity. In cases where endogenous insulin secretion is possible (as in most DB2 patients), GLP-1 agonists are currently preferred over insulin due to reduced risk of hypoglycemia.[187] However, if beta cells are already damaged to the extent that endogenous insulin secretion in meaningful amounts is not possible, exogenous insulin should be used.

To reduce hypoglycemia risk, a hypercaloric carb diet (HCD) can be used. Such a diet should have additional benefits in ALS, since additional glucose would relieve cellular stress, promote protein folding, and provide raw material for lipogenesis, countering the tissue wasting shown in ALS. Indeed, HCD (without insulin) showed better results than a control diet in a small ALS clinical trial.[188]

Tests. Using insulin-based therapy for all ALS patients would require clinical trials and an approval process. However, such therapy is already justified in patients with demonstrated insulin dysfunction. This paper implies that as part of ALS diagnosis, patients should undergo a standard DB classification test focused on insulin function.

The simplest test is the oral glucose tolerance test, but there are several additional options (intravenous glucose, insulin or glucagon tolerance tests with or without clamps). A highly informative test is a clamp along with somatostatin infusions to suppress endogenous insulin secretion. This test isolates the insulin-independent component of glucose uptake,[97] and can directly alert when it is excessive. Thus, it is capable of identifying many of the cases where insulin secretion and insulin-stimulated glucose uptake are low but are still within the 'normal' range, along with seemingly normal glucose levels.

In many patients, the test results would show insulin impairment at levels standardly defined as DB or pre-DB, justifying DB therapy. In these cases, insulin-based rather than other DB drugs should be preferably used, because they are expected to have a greater benefit in ALS. Metformin reduces hepatic glucose production and thus alleviates IR, but it also activates

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AMPK,[189] which might stimulate the excessive glucose uptake shown in ALS [2].

It is reassuring that a systematic review found no evidence of DB drugs being associated with higher ALS risk.[191]

All treated patients should obviously be monitored. Patients showing increased insulin secretion (e.g., the fourth scenario above) should be periodically re-tested, since high insulin may accelerate the appearance of IR. In the all-Taiwan study, high insulin use, indicating a prolonged severe damage to insulin function, showed a non-significant association with increased risk.[78]

Other treatment. Insulin-based therapy can be combined with other drugs. Calcium channel blockers, which reduce calcium load, are associated with reduced ALS risk.[171,172] Clinical trials using nimodipine alone did not help in ALS,[192,193] but daily oral use of verapamil, with insulin treatment, improved beta cell function in adult recent onset DB1 in a human phase II clinical trial.[194] Anti-oxidative stress agents such as the drugs currently approved for ALS might also help, but it is not clear that using them would be cost-effective.

Discussion

In this paper I analyzed the existing ALS literature to conclude that

- Insulin opposes all of the salient pathophysiological phenomena identified in ALS, and these in turn oppose insulin signaling.
- Insulin secretion and/or signaling have been found to be impaired in non-DB ALS in almost all of the studies that have explicitly tested for them.
- Insulin impairment is usually not diagnosed, most likely because it is masked by excessive insulin-independent glucose uptake.
- Different insulin impairment trajectories can explain why early/late DB are associated with increased/decreased risk of ALS, respectively.
- DB drugs including insulin-based therapy have been found to be protective in ALS in several large retrospective studies.

The analysis is supported by very strong existing evidence that is not recognized by most of the research and medical communities. This paper is the first to point to the wide extent of the problem, and provides novels accounts of the seeming paradoxical glucose and DB phenomena.

Insulin impairment is not the core cause of ALS, which is most likely related to calcium overload. However, insulin impairment strongly facilitates ALS and is a major trigger of ALS symptoms. Insulin-based therapy would not be able to reverse MTN death or total axonal degeneration, but it has a good chance of considerably slowing disease progression if started early enough.

[2] Metformin was also harmful to females in the SOD1 mouse ALS model.[190]

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Almost anybody who has ever examined insulin signaling in ALS has found that it is impaired at the group level. DB2, which involves higher blood insulin and in many cases insulin-based drugs, is associated with reduced risk. DB drugs have been independently found to be associated with reduced risk. These three data points alone, even without the new theoretical analysis presented here, justify DB screening tests in ALS patients, followed by DB treatment if positive.

All of the professional infrastructure for insulin-based therapy in ALS is already in place. The OGTT and other related tests are standard tests routinely administered in medical centers. If test results show that the patient has DB according to standard norms, treatment using DB drugs is fully justified. The only non-standard recommendation made here is that treatment would not start with metformin or other non-insulin-based drugs (or life-style changes), but immediately with insulin-based therapy.

Most of the evidence brought here is from sALS[3]. Although the etiology of sALS and fALS is probably different, they show a converging pathophysiology. Thus, our conclusions may be applicable to fALS as well. This should be corroborated in future research.

The analysis here applies to FTD patients showing ALS symptoms, so at least to behavioral variant FTD. Unlike in ALS, the link between dementia and IR is well-known,[195,196] to the extent that some forms of dementia are thought to be 'type-3 diabetes'.[197] FTD patients were specifically shown to have DB much more than controls.[198] Thus, insulin-based therapy is a natural direction in FTD.

I hope that this paper will contribute to reducing the suffering of ALS patients and their families and caretakers.

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Conflicts of interest

The author declares no conflicts of interest.

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List of Abbreviations

ALS: amyotrophic lateral sclerosis.
AMPK: AMP-activated protein kinase.
ATP: adenosine triphosphate.
CRR: counter-regulatory response.
CSF: cerebrospinal fluid.

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DB: diabetes mellitus.
DB1, DB2: type 1, type 2 diabetes mellitus.
ER: endoplasmic reticulum.
fALS: familial ALS.
FDA: food and drug administration.
FTD: frontotemporal dementia.
GLP-1: glucagon-like peptide 1.
Glut4: glucose transporter type 4.
GSH: glutathione.
H2O2: hydrogen peroxide.
HCD: hypercaloric carb diet.
IIGU: insulin-independent glucose uptake.
IR: insulin resistance.
MTN: motor neuron.
OGTT: oral glucose tolerance test.
sALS: sporadic ALS.
SOD: superoxide dismutase.
TDP-43: TAR DNA-binding protein 43.