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Trials of Antidiabetic Drugs in Amyotrophic Lateral Sclerosis: Proceed with Caution?

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder with limited therapeutic options. Clinical trials of several drugs shown to be effective in the superoxide dismutase (SOD1) model of ALS have shown no or negative effects when tested in humans. Here we discuss the role of pioglitazone, a peroxisome proliferator-activated receptor-γ agonist, which failed to show efficacy in a recently published phase II clinical trial of ALS patients. The antioxidant and anti-inflammatory properties of pioglitazone make it an attractive therapeutic candidate for neurodegenerative disorders. However, its antidiabetic and antidyslipidemic effects might be detrimental, as emerging evidence suggests that some features of the metabolic syndrome may be protective in ALS. A number of clinical studies show that dyslipidemia, high body mass index, and possibly diabetes mellitus type 2 are associated with better clinical outcomes in ALS. This is further corroborated by studies on transgenic animal models and immortalized neuronal cell lines. Finally, the intricate interplay between glucose/lipid metabolism and susceptibility to oxidative damage in neurons warrants a judicious approach in further trials of antidiabetic drugs in ALS.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease leading to progressive degeneration of both upper and lower motor neurons. Most ALS cases occur sporadically, but about 10% of individuals with ALS have at least 1 other affected family member and are said to have familial ALS. ALS has a well-established clinical overlap with frontotemporal lobar degeneration (FTLD) [1]. Furthermore, the occurrence of TAR-DNA-binding protein 43 kDa (TDP-43) aggregates in patients with ALS, FTLD and ALS-FTLD suggest a pathophysiological continuum between these disorders [1]. In addition to TDP-43, FTLD is also characterized by pathological aggregation of other RNA-binding proteins: fused in sarcoma (FUS), TATA-binding protein-associated factor 15 (TAF15) and Ewing's sarcoma (EWS) [2].

The field of ALS research was revolutionized by the discovery of superoxide dismutase (SOD1) mutations in familial ALS patients roughly 2 decades ago [3]. Subsequently, transgenic mouse models of ALS-related SOD1 mutations were successfully developed, which recapitulated the motor phenotype representative of human pathology [4]. These animals have been used extensively for the preclinical screening of potential novel therapeutic agents. However, only 10–20% of familial cases of ALS in humans, and almost none of the sporadic cases, are associated with SOD1 mutations. None of the SOD1 mutant

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cases show a clinical overlap with FTLD [5]. Additionally, SOD1-related ALS does not show the hallmark aggregation of TDP-43/FUS/TAF15/EWS [2]. These discrepancies might explain, at least in part, why positive results in SOD1 transgenic animals have consistently failed to predict therapeutic efficacy in humans [5].

In the July 2012 issue of the journal *PLoS One*, Dupuis et al. [6] reported a phase II, multicentric, placebo-controlled trial of the oral antidiabetic, pioglitazone, in patients with ALS as an add-on therapy to riluzole. The rationale for the trial was based on positive preclinical data obtained in SOD1 transgenic mice by at least three independent groups [7, 8]. Contrary to their hypothesis and to the preclinical data, Dupuis et al. [6] did not observe a survival benefit in the pioglitazone group. Instead, pioglitazone was associated with a 21% increased hazard ratio for mortality, which was not statistically significant ($p = 0.48$).

Pioglitazone is a peroxisome proliferator-activated receptor-γ agonist, which has known antihyperglycemic, antidyslipidemic, antioxidant and anti-inflammatory properties [9, 10]. While pioglitazone is used in clinical practice as an antidiabetic agent, its antioxidant and anti-inflammatory roles make it an attractive candidate drug for ALS since oxidative stress and inflammation are implicated in ALS pathophysiology [6].

There are, however, a number of issues of concern regarding the preclinical potential of pioglitazone as a therapeutic agent for ALS. Despite the established disease-modifying effect of gender in ALS, one preclinical study used only male mice [7], the animal cohorts were small ($n < 8$) in size [7, 8] and the observers were not blinded [7]. In addition, pioglitazone has not shown a beneficial effect in any non-SOD1 models of ALS or FTLD. This becomes crucial considering the drawbacks of the SOD1 model of ALS as mentioned previously.

While there may be multiple reasons underlying the failure of the phase II trial of pioglitazone in humans, here we propose the hypothesis that its effects on whole body metabolism, including its antidiabetic and antidyslipidemic effects, might play a significant role. A growing body of evidence suggests that ALS is associated with systemic metabolic changes and abnormal energy metabolism [11]. Impaired lipid metabolism, in particular, is receiving increasing attention since it was found that, in SOD1-ALS mouse models, increasing the fat content of the diet prolongs lifespan and maintains motor neuron numbers [12], whereas restricting fat intake hastens disease onset and death [13]. In humans, several studies have reported an association between dyslipidemia and improved survival in ALS [14, 15]. We observed that change in body mass index (BMI) after ALS onset correlated inversely with the rate of ALS motor disease progression [15], i.e. weight loss was associated with faster rates of progression. Also, in two independent studies we showed that there is a 'U-shaped' association between mortality and BMI in ALS, with people with mild obesity or stable BMI having the least mortality [16, 17]. Data about glucose metabolism in ALS is more limited but is the subject of active research efforts suggesting that premorbid diabetes mellitus type 2 (DM2) might affect disease onset and progression [18]. Taken together, our findings and those of several others have led to an emerging hypothesis that some features of the 'metabolic syndrome' are associated with reduced risk and/or slower disease progression in ALS (table 1). Several molecular as well as prospective studies are now underway to corroborate this hypothesis.

It is important to consider that there is plausible biological rationale for the protective effect of the metabolic syndrome in ALS. There is evidence to suggest that the proteins whose mutated forms are associated with ALS and FTLD might have a physiological role in lipid metabolism. It has been shown that conditional knockdown of TDP-43 leads to downregulation of Tbc1d1, a gene linked to obesity. These mice exhibited a lean phenotype and features of hypermetabolism, besides reduced survival [19]. Progranulin, which is mutated in some cases of FTLD, has been shown to play a role in high-fat-mediated insulin resistance and obesity [20].

Similarly, alterations in glucose metabolism may lead to altered susceptibility to oxidative stress – one of the postulated pathways leading to neurodegeneration in ALS/FTLD. Of particular interest here is glycolysis, which is partly regulated by insulin-glucagon signaling and has important implications for survival of cells. Cancer cells are known to enhance their glycolysis under aerobic conditions, which is associated with decreased production of reactive oxygen species and confers a survival advantage to the cancer cells under hostile conditions [21]. There is evidence to suggest that resistance to amyloid-β toxicity in neuronal lines is also related to enhanced glycolysis and a subsequent decrease in the production of reactive oxygen species [22]. Hyperglycemia in DM2/metabolic syndrome provides increased substrate for glycolysis and also replenishes the active reduced form of the antioxidant enzyme, glutathione, through stimulation of the pentose phosphate pathway, hence countering oxidative stress through different pathways. Thus, in the pioglitazone trial, the antioxidant effect of the medication through stabilization of SOD1 could be counterbalanced by its concomitant antihyperglycemic effects.

The relationship between hypoxia and glucose metabolism is also complicated by complex and sometimes disparate regulation of the two at the molecular level. A notably relevant study would be that of Mergenthaler et al. [23], which showed that the glycolytic enzyme, hexokinase 2 (HK2), acts as a molecular switch and controls the fate of neurons depending on the ongoing metabolic state. Hypoxia leads to activation of hypoxia-induced factor 1, which upregulates HK2. HK2 in turn protects primary neurons from hypoxia through its interaction with phosphoprotein enriched in astrocytes (PEA15). Alternatively, HK2 also acts as a sensor for glucose starvation and initiates a cascade, leading to apoptotic neuronal death in reaction to prolonged glucose starvation [23]. There is evidence to suggest that pioglitazone is associated with upregulation of HK2 [24]. Hence, pioglitazone may confer increased sensitivity of neurons to glucose starvation. There are a number of reasons for which patients with ALS may be glucose starved, including dysphagia, hypermetabolism, physical disability or riluzole-associated nausea and fatigue. The hypoglycemic action of antidiabetics itself may further aggravate the glucose starvation.

In conclusion, we hypothesize that the potential protective antioxidant and anti-inflammatory properties of pioglitazone might be countered in ALS by its effects against the metabolic syndrome. This hypothesis is also consistent with the finding that another widely used antidiabetic drug, metformin, was associated with worse neurological scores and faster symptom progression in female SOD1 mice in a dose-dependent manner [25]. However, another class of antidiabetics, glucagon-like peptide 1 analogs, has demonstrated neuroprotection against kainate-induced excitotoxicity and trophic-factor withdrawal in SOD1 in vitro and in vivo models [26, 27]. The generalizability of this data is currently limited because of lack of reproducibility in the ALS-TDP model, besides the fact that there was no viability/survival benefit against the oxidative stress induced by SOD1 mutation itself. Nevertheless, these studies do raise a possibility that some antidiabetics may be beneficial in particular forms of ALS, and future studies should judiciously account for this paradox.

It would be extremely interesting to further analyze the data from the pioglitazone study to test whether changes in weight, glucose and/or lipid levels were associated with worse survival. It is urged that the disease-modifying effect of dyslipidemia, BMI, DM2 and other metabolic perturbations should be accounted for in future trials of ALS. This might lead to valuable clues about the pathophysiology of ALS and would help to delineate which patients might benefit from one therapy versus another.

Table 1. Studies that support the hypothesis that metabolic syndrome is associated with reduced risk of ALS or improved ALS survival

Dupuis et al. [14], 2008 (France)	ALS patients with high LDL/HDL ratio had a 12-month longer survival compared to ALS patients with low LDL/HDL ratio
Jawaid et al. [18], 2010 (USA)	ALS patients with premorbid DM2 had a 4-year later onset of motor symptoms and a 6-month longer survival compared to patients without DM2
Jawaid et al. [17], 2010 (USA)	Loss of BMI >1 over 2 years after ALS diagnosis was associated with significantly shorter survival and faster progression of motor symptoms
Sutedja et al. [28], 2011 (The Netherlands)	ALS patients more likely to have lower BMI and favorable lipid profile compared to healthy age-matched controls
Marin et al. [29], 2011 (France)	36% increased risk of death per unit decrease in BMI Malnourished patients at diagnosis had an increased (RR 2.15) risk of death, whereas overweight and obese patients had a decreased (RR 0.71) risk of death
Dorst et al. [15], 2011 (Germany)	ALS patients with higher triglycerides and TC had longer survival
Huisman et al. [30], 2011 (The Netherlands)	Reduced prevalence of vascular disease in ALS patients and their relatives compared to age-matched controls
Paganoni et al. [16], 2011 (USA)	Inverted U-shaped relationship between BMI and survival in ALS patients, with the maximum survival at BMI 30–34.9
Shimizu et al. [31], 2012 (Japan)	Faster reduction in BMI postonset was associated with significantly shorter survival
Ikeda et al. [32], 2012 (Japan)	Elevated TC and LDL levels were associated with worsened ALS-FRS and FVC
Gallo et al. [33], 2013 (UK)	Increased prediagnostic body fat was associated with decreased risk of ALS mortality
Reich-Slotky et al. [34], 2013 (USA)	For ALS patient with BMI <30, higher initial BMI predicted slower functional decline
O'Reilly et al. [35], 2013 (USA)	For each 5-unit increase in BMI, ALS rates were 21% lower

LDL = Low-density lipoproteins; HDL = high-density lipoproteins; RR = relative risk; TC = total cholesterol; ALS-FRS = ALS functional rating scale; FVC = forced vital capacity.

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