Trends in
Endocrinology & Metabolism

CellPress
OPEN ACCESS

Review

Hidden players in the metabolic vulnerabilities of amyotrophic lateral sclerosis

Marco Rosina[1,2,6], Silvia Scaricamazza[1,3,6], Gianmarco Fenili[1,4], Valentina Nesci[1,5], Cristiana Valle[1,3], Alberto Ferri[1,3,7,*], and Maria Paola Paronetto[1,4,7,*]

Amyotrophic lateral sclerosis (ALS) is a complex and rapidly progressive motor neuron disorder with a fatal outcome. Despite the remarkable progress in understanding ALS pathophysiology, which has significantly contributed to clinical trial design, ALS remains a rapidly disabling and life-shortening condition. The non-motor neuron features of ALS, including nutritional status, energy expenditure, and metabolic imbalance, are increasingly gaining attention. Indeed, the bioenergetic failure and mitochondrial dysfunction of patients with ALS impact not only the high energy-demanding motor neurons but also organs and brain areas long considered irrelevant to the disease. As such, here we discuss how considering energy balance in ALS is reshaping research on this disease, opening the path to novel targetable opportunities for its treatment.

Highlights

Amyotrophic lateral sclerosis (ALS) is an adult neurodegenerative disease leading to progressive muscle weakness and atrophy.

Metabolic alterations are widely associated with the onset of ALS. Beyond motor neurons, other central and peripheral tissues contribute to metabolic dysfunctions in ALS.

Early weight loss in patients with ALS may indicate a worse prognosis.

Targeting energy metabolism could represent a promising therapeutic approach for ALS.

Therapeutic strategies targeting energy metabolism should consider both central and peripheral organs to effectively address the multifaceted nature of ALS.

Metabolic derangement in ALS

ALS is an adult neurodegenerative disease characterized by the selective loss of upper and lower motor neurons, resulting in progressive muscle weakness and atrophy. The motor phenotypes exhibited by patients is highly heterogeneous. This variability is associated with three independent factors: the anatomical region of onset, the combination of upper motor neuron (UMN) and lower motor neuron (LMN) deficits, and the rate of progression [1]. ALS is a fatal disease, with death typically resulting from respiratory failure within 2 to 5 years of diagnosis. About 50% of patients die within 30 months of onset, and only 20% survive 5 to 10 years after symptoms appear [2,3]. With a global incidence of approximately 2.5 cases per 100 000 and a prevalence of 4–6 cases per 100 000 annually, ALS is the most common motor neuron disease, with higher incidence in men than in women [3]. ALS phenotypes can be classified on the basis of the affected area of motor neurons and the pattern of onset: the typical or 'classic' form, which involves both UMNs and LMNs, is fatal within a few years, while the atypical form, affecting only UMNs or LMNs, has a longer survival rate [4].

ALS is classified in two forms that are clinically indistinguishable and that have similar features: sporadic ALS (sALS), about 90% of total cases, and familial ALS (fALS), based on the presence of gene mutations in the family lineage. The hereditary character of this latter form, accounting for about 10% of cases, generally exhibits autosomal dominant transmission; cases of X-linked or recessive transmission are rare. The mutations involve a heterogeneous group of genes, including *SOD1*, *FUS*, *TDP-43*, and *C9orf72* [5,6].

Notwithstanding the presence of mutations, ALS is considered a multifactorial disease in which several events contribute to determine the degeneration of the neuromotor unit. Among the molecular mechanisms leading to ALS, disorders of RNA metabolism, alterations of protein homeostasis, mitochondrial dysfunctions, oxidative stress, disruption of axonal transport, neuroinflammation, and vesicular transport defects have been described over approximately three decades [7]. Sex difference further complicate this scenario (Box 1).

[1]Laboratories of Neurochemistry and of Molecular and Cellular Neurobiology, IRCCS, Fondazione Santa Lucia, Rome, Italy
[2]Department of Neuroscience, Italian National Institute of Health (ISS), Rome, Italy
[3]National Research Council (CNR), Institute of Translational Pharmacology (IFT), Rome, Italy
[4]Department of Movement, Human, and Health Sciences, University of Rome 'Foro Italico', Rome, Italy
[5]Department of Systems Medicine, University of Roma 'Tor Vergata', Rome, Italy
[6]These authors contributed equally to this article.
[7]These authors are joint senior authors of this work.

© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Correspondence:
alberto.ferri@cnr.it (A. Ferri) and
mariapaola.paronetto@uniroma4.it
(M.P. Paronetto).

Box 1. Sex differences in ALS disease

Sex steroids might exert protective or detrimental effects on disease occurrence and progression. On the basis of the later age of the onset in females, estrogens might be neuroprotective for motor neurons. In this regard, an increased risk of ALS exists in females with later menarche and earlier menopause [85], demonstrating that longer exposure to endogenous female sex steroids can increase survival and reduce ALS susceptibility. Since estrogens modulate secretion of neurotrophic factors such as IGF-1 and brain-derived neurotrophic factor (BDNF), longer reproductive conditions could also play a neuroprotective role on motoneurons in ALS [86,96].

In males, ALS initiates in motoneurons of the lumbar tract of the spinal cord, whereas in females, ALS tends to begin in bulbar regions [83]. Furthermore, females show a later onset and a less severe disease progression than males, suggesting the involvement of hormonal factors through either a toxic effect of androgens or a protective effect of estrogens or both. Remarkably, these reported differences become less significant with age, since postmenopausal women show the same probability as men to develop ALS.

In addition to sex hormones, sex differences in patients and animal models have been reported also for the expression of the orexigenic hormone ghrelin and anorexigenic hormone leptin. Male patients show lower plasma levels of ghrelin and leptin than females, which were associated with poor prognosis [97,98]. It is noteworthy that leptin level is strictly related to BMI [99] and particularly to fat body composition, given the role of adipose tissue in leptin secretion [100]. Interestingly, consistent with the role of AT, the decreased leptin plasma level observed in male patients is associated with reduced subcutaneous adiposity, a pattern not observed in females [97].

Patients with ALS, regardless of sex differences, also show reduced post-prandial ghrelin levels, along with increased LEAP2:ghrelin molar ratios, suggesting the presence of ghrelin resistance [36]. It is worth mentioning that despite the female patients in this study having grater fat mass, the results do not show sex differences in the LEAP2:ghrelin molar ratio. The authors suggest that this finding may be attributed to the small size of the analyzed cohort. Ghrelin affects appetite and metabolism while also exerting neuroprotective effects; therefore, alterations in ghrelin levels, as well as an altered response to this hormone, could influence the course of the disease [36].

There are currently few drugs approved by the FDA to treat ALS and its symptoms, although these compounds exert modest effects on survival and quality of life [8]. Over the past two decades, nearly all clinical trials designed to develop a successful therapeutic strategy for this disease have failed. Genetic complexity, limitations of animal models, diagnostic delays, and the multisystemic nature of the disease are potential factors hindering significant progress in ALS clinical trials.

Regardless of the molecular mechanisms that contribute to the degeneration of motor neurons, the role of metabolic dysfunctions has recently emerged and is gaining increasing significance. More than 60% of patients with fALS and sALS exhibit increased energy expenditure, particularly at rest, attributable to a hypermetabolic state [9]. Paradoxically, although resting metabolic rate tends to rise, fat-free mass – the primary factor influencing resting energy expenditure – declines. This reduction is primarily due to a denervation process, along with dysphagia and subsequent malnutrition. The metabolic dysfunction in ALS is not just a marginal detail, since patients with hypermetabolism demonstrate greater lower motor neuron involvement, faster functional decline, and reduced survival compared with those with normal metabolism [10–12]. Additionally, a lower premorbid body mass index (BMI) is linked to increased risk of ALS and a poorer prognosis, whereas obesity seems to decrease the likelihood of developing ALS and is associated with a better prognosis [13,14]. Remarkably, metabolic alterations precede neuromotor symptoms by up to 10 years in patients [15], and they occur well before the increase of serum **neurofilament light chain (NfL)** (see Glossary) levels in individuals with ALS-related gene mutations [16]. As a result, metabolic profiling may assist in diagnosing ALS, although it should not be regarded as a specific clinical characteristic of the disease. Instead, it should be seen as a potential new prognostic biomarker, while metabolic targeting could offer a promising therapeutic approach [8]. Indeed, pharmacological interventions in mouse models of ALS indicated the potential of restoring energy balance, slowing disease progression [17,18]. Furthermore, considering the contribution of physical activity on energy metabolism, several studies suggest a link between high levels of physical

activity and increased ALS risk; the patient's genetic background affects symptom onset in cases of previous or juvenile intense physical activity [19–21]. In this context, the effect of exercise training in ALS is still controversial. Indeed, evidence suggests that moderate, well-designed exercise programs offer significant benefits for patients with ALS, including improvements in muscle strength, functional capacity, and quality of life, without speeding up disease progression [22]. Overall, these reported findings strengthen the relevance of energy expenditure and hypermetabolism in ALS pathology.

Metabolic dysfunctions of the central nervous system (CNS) and skeletal muscle in ALS have been widely explored, and for in-depth analysis on these topics, we refer to accurate and comprehensive reviews [18,23–25]. However, metabolic alterations were observed not only in the neuromotor unit but also in organs and brain areas long considered irrelevant to the pathology. Changes in the adipose tissue (AT), the endocrine system, and the liver are beginning to be documented in both patients and mouse models. Additionally, dysfunctions in the hypothalamus have only recently been described. Interestingly, sex differences in disease-related endocrine dysfunction have also been identified. Some of these differences, particularly those related to sex hormones, may explain the higher susceptibility to ALS in males than in females.

Given the growing evidence linking peripheral metabolism and energy balance to ALS and the absence of a comprehensive overview on the topic, here we explore the metabolic alterations in ALS apart from the CNS and skeletal muscle, highlighting instead the roles of metabolic organs and the endocrine system and potential sex differences.

Energy homeostasis in ALS

Hypothalamus: the hub of metabolic homeostasis

Energy homeostasis is controlled by a complex network maintaining the balance of energy intake, expenditure, and storage, and central and peripheral organs tightly cooperate to coordinate these processes. The hypothalamus plays a pivotal role in coordinating many vital functions of the body, including regulating body temperature; controlling food and water intake; managing circadian rhythms; overseeing autonomic functions such as heart rate, blood pressure, and digestion; and regulating emotions and behaviors, including sexual behaviors.

The hypothalamus is being increasingly recognized as a critical brain structure that, when dysfunctional, may contribute to the metabolic derangements observed in ALS. Indeed, several findings align with the metabolic changes observed in patients well before the onset of the disease [26] and with those detected in presymptomatic ALS gene mutation carriers [16]. In this context, morphological alterations of the hypothalamus, characterized by a volumetric reduction of 22%, on average, were consistently observed in asymptomatic individuals carrying ALS mutations [27]. It is noteworthy that such alterations precede NfL changes in serum, although the timeline and consistency of hypothalamic changes relative to NfL alterations remain unresolved and may vary between cohorts.

This hypothalamic alteration was related to an early onset and a decreased BMI. Particularly, lower hypothalamic volume with lower BMI was associated with weight loss and earlier death [28]. Patients with lower BMI and lower hypothalamic volume tended to lose more weight and fat mass over the course of their disease and presented with an increased risk of earlier death. Lower hypothalamic volume alone trended toward greater risk of earlier death.

The correlation between hypothalamic volume and disease progression is controversial, however. Marked atrophy of specific subregions was observed in patients; in particular, atrophy of

Glossary

ALS-Functional Rating Scale-Revised (ALSFRS-R): the most widely used instrument for assessing functional deficits in amyotrophic lateral sclerosis.

Arcuate nucleus (ARC): region of the hypothalamus located near the third ventricle and median eminence, it is involved in feeding, metabolism, fertility, and cardiovascular regulation. It contains different populations of neurons, including neuroendocrine neurons, centrally projecting neurons, and astrocytes.

Lateral region of the hypothalamus (LHA): subcortical brain region that contains the primary orexinergic nucleus within the hypothalamus, which extensively projects throughout the nervous system. It exerts control over motivated behavior, feeding, and energy balance.

Neurofilament light chain (NfL): a cytoplasmic protein found in neurons, predominantly expressed in both large- and small-caliber myelinated axons, although levels are higher in large axons. Its levels rise in both cerebrospinal fluid and blood in proportion to the extent of axonal damage, serving as a biomarker in various neurological conditions, including inflammatory, neurodegenerative, traumatic, and cerebrovascular disorders.

Orexins: endogenous ligands for two orphan G protein-coupled receptors in the lateral hypothalamus. First identified as regulators of feeding behavior, orexins are key modulators of the sleep–wake cycle. They activate orexin neurons as well as monoaminergic and cholinergic neurons.

Paraventricular nucleus (PVN): located next to the third ventricle of the hypothalamus, it plays a key role in hormone regulation by secreting hormones such as oxytocin, vasopressin, corticotropin-releasing hormone (CRH), and thyrotropin-releasing hormone (TRH).

Wobbler mice: animal model for ALS. The spontaneous, recessive wobbler mutation causes degeneration of upper and lower motor neurons, leading to progressive muscle weakness resembling the ALS pathology. The wobbler point mutation affects Vps54 protein, a component of the Golgi-associated retrograde protein (GARP) complex, and leads to a destabilization of the whole GARP complex.

the posterior hypothalamus was associated with weight loss and poor survival [29]. By contrast, a different study did not find correlation between the volume of the hypothalamic subregions and BMI, as well as ALS-Functional Rating Scale-Revised (**ALSFRS-R**) in patients [30]. These discrepancies may be attributable to an intrinsic volumetric variability of the hypothalamic area, regardless of any pathological state. In addition, most volumetric studies of the hypothalamus rely on 3-T imaging, which has limitations for segmenting such a small structure. Remarkably, it was also suggested that lower hypothalamic volume in ALS could contribute to both positive and negative energy balance and not be 'universally' associated with loss of appetite or hypermetabolism [28]. A consistent observation instead is the presence of TDP-43 aggregates in the **lateral region of the hypothalamus (LHA)** and basal forebrain of patients. TDP-43 pathology was correlated with lower BMI only in patients with protein aggregation in the lateral hypothalamus and not in the basal forebrain [31]. In line with this, similar alterations were observed in LHA and linked to TDP-43 inclusions with neuronal cell damage, thus contributing to metabolic modifications such as weight loss and decreased appetite [32].

Hypothalamic alterations are not confined to large-scale changes in organ volume but also encompass selective modifications within specific neural populations. Particularly, patients show a significant reduction in oxytocin-producing neurons within the **paraventricular nucleus (PVN)** and in **orexin**-producing neurons in the lateral hypothalamus. Interestingly, reduction in these two neuronal populations correlates with the presence of TDP-43 inclusions [33]. It is noteworthy that loss of oxytocin and orexin neurons has profound implications in modulating appetite and energy expenditure, known to be altered in ALS [34]. Similarly, the loss of orexin-producing neurons, which are essential for maintaining wakefulness and regulating energy metabolism, could underlie the excessive daytime sleepiness and metabolic disturbances observed in ALS [35].

The hypothalamus can integrate signals from peripheral hormones that contribute to maintaining the proper energy balance. Indeed, the alterations in feeding behaviors described in patients may include altered production of peripheral orexigenic and anorexigenic hormones such as liver-expressed antimicrobial peptide 2 (LEAP2), leptin, and ghrelin, which target specific hypothalamic neuronal populations. Interestingly, changes in plasmatic levels of the mentioned hormones are related to disease progression and metabolic profiles in patients [36]. It is noteworthy that alterations in several neuronal hypothalamic populations could impair metabolic hormone signaling, since they represent their natural targets. In this context, preclinical studies in mouse models of ALS demonstrated the alteration of the proopiomelanocortin (POMC) system in the **arcuate nucleus (ARC)**, as well as in the LHA.

The ARC, which is composed of neuroendocrine neurons as neuropeptide Y (NPY), Agouti-related protein (AgRP), POMC, and cocaine- and amphetamine-regulated transcript (CART), represents the center of feeding and energy balance regulation. A decrease of POMC-positive neurons and a simultaneous increase of AgRP-positive neurons was observed in the ARC of mouse models of ALS at the presymptomatic stage. The LHA plays a crucial role in regulating metabolic homeostasis through neuropeptides such as orexin and melanin-concentrating hormone (MCH). In ALS mouse models and in patients with sALS, MCH-positive neurons are significantly reduced. Interestingly, MCH supplementation through intracerebroventricular delivery led to weight gain and improved metabolic balance, restoring normal AgRP-positive neurons [32] (Figure 1).

Interestingly, reduced levels of growth hormone (GH) in patients were linked to impaired hypothalamic regulation of GH secretion through the release of growth hormone-releasing hormone

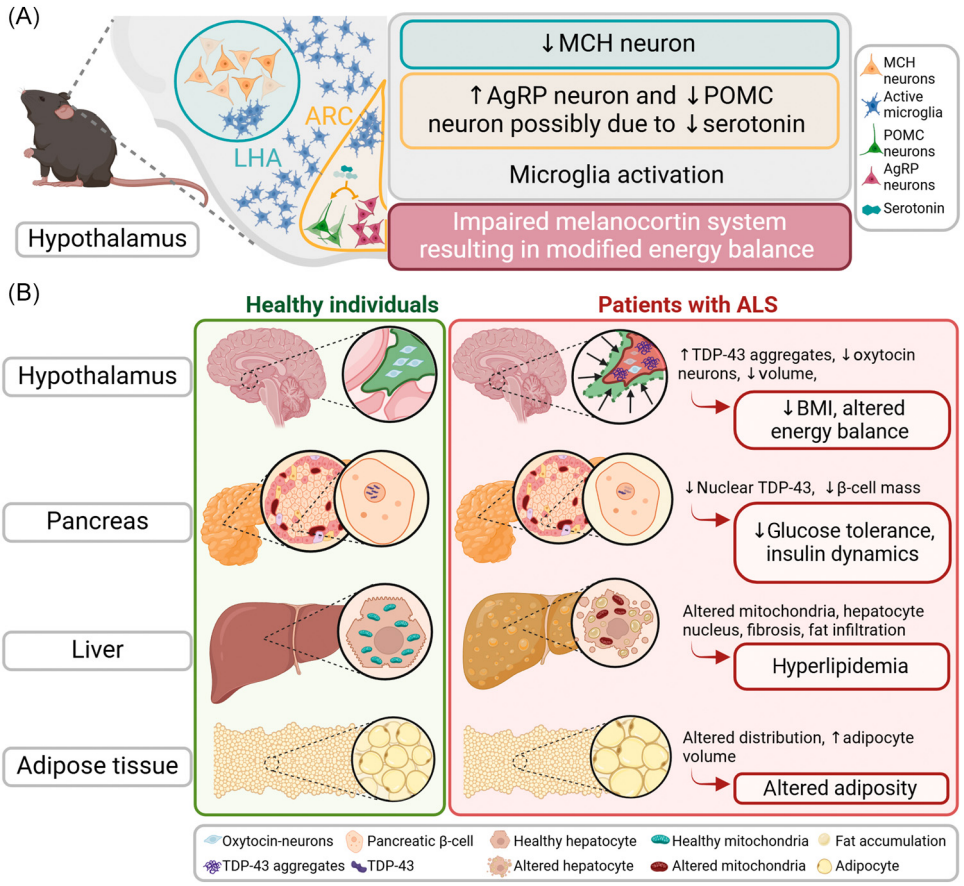

Figure 1. Hypothalamus, pancreas, liver, and adipose tissue alterations in amyotrophic lateral sclerosis (ALS). (A) Defects detected in the hypothalamus of ALS animal models, particularly in the lateral hypothalamic area (LHA) and arcuate nucleus (ARC). These alterations primarily affect the melanocortin system. In the ARC, there is an increase in Agouti-related protein (AgRP) neurons, while proopiomelanocortin (POMC) neurons decrease, likely due to serotonin loss, which normally maintains the balance between POMC-AgRP activation/inactivation. In the LHA, there is a loss of melanin-concentrating hormone (MCH) neurons. The increased activation of microglia in the ARC and throughout the hypothalamus further contributes to the disruptions in the melanocortin system, leading to impaired energy metabolism. (B) Alterations in the hypothalamus, pancreas, liver, and adipose tissue in patients compared with healthy individuals. The hypothalamus of patients is atrophic (reduced volume); additionally, it exhibits TDP-43 aggregates and loss of oxytocin neurons. These hypothalamic alterations may contribute to decreased body mass index (BMI) and disrupted energy balance. In the pancreas, the reduction in β-cell mass and nuclear accumulation of TDP-43 may result in impaired glucose tolerance and altered insulin dynamics. The liver shows alterations in hepatocyte nuclear size, irregular mitochondria, fat infiltration, and steatosis, which could contribute to the hyperlipidemia commonly observed in patients. Additionally, altered adipose tissue distribution and increased adipocyte volume may contribute to the changes in BMI. Figure created using BioRender.

(GHRH) [37]. GH plays a key role in maintaining muscle mass and metabolic health, and its deficiency in ALS may contribute to the severe muscle wasting and metabolic imbalances characterizing the disease. GH deficiency was observed both in patients and in mouse models of the disease [38,39]. GH and insulin-like growth factor 1 (IGF-1) have strong anabolic actions; indeed, modulation of GH/IGF-1 preserves muscle mass, protecting motor neurons. Accordingly, studies in *SOD1-G93A* mice revealed that a higher level of endogenous GH secretion was associated with improved innervation of skeletal muscle [40]. However, the anabolic and neuroprotective effects of endogenous GH are likely lost as the disease progresses. Indeed, GH-IGF-1 therapies in

patients did not show benefits [41]. Decreased GH secretion could contribute to reduced muscle IGF-1, which is related to more rapidly progressing disease. Indeed, lower levels of IGF-1 in patients are associated with faster disease progression and shorter survival [42]. Consistently, IGF-1-directed interventions prolonged survival in mouse models [43–45].

Notably, neuroinflammation is a significant aspect of ALS pathophysiology: the elevated levels of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α detected in patients [46] could disrupt hypothalamic function, further exacerbating the metabolic dysregulation [47]. Indeed, increased activation of microglia within the hypothalamus was observed in a murine model of ALS. Interestingly, inhibiting microglial activation reverted the alterations in melanocortin system and increased food intake and weight gain, strongly suggesting that local inflammatory response might contribute to the degeneration of hypothalamic neurons and the disruption of homeostatic functions [47].

Finally, sleep disturbances, including insomnia and sleep-disordered breathing, are common in ALS and are closely linked to hypothalamic dysfunction [35]. The hypothalamus regulates sleep–wake cycles, and its degeneration in ALS may lead to disruptions in these cycles, resulting in poor sleep quality and excessive daytime sleepiness. Sleep disturbances not only impair quality of life but also have a direct impact on metabolic regulation [35,48].

Overall, the emerging evidence on the involvement of hypothalamus in ALS underscores the importance of considering metabolic and neuroendocrine factors in the disease's pathogenesis. Addressing hypothalamic dysfunction may provide new therapeutic targets to mitigate metabolic imbalances in patients.

Defects in the pancreatic regulation of glucose homeostasis

Glucose homeostasis is accomplished through an elaborate network of hormones and neuropeptides released from the brain, pancreas, liver, intestine, and AT. Within this complex interplay, the pancreas plays a prominent role by secreting insulin and glucagon. Patients with ALS show defects in pancreatic exocrine function and glucose tolerance [49], although the specific underlying mechanism has not yet been completely elucidated. Furthermore, patients display impaired insulin dynamics with reduced early-phase glucose-induced secretion and loss of TDP-43 in the nuclei of beta cells [50]. Consistently, conditional beta cell-specific knockout (KO) of *Tardbp*, the gene encoding TDP-43, led to decreased exocytosis due to reduced transcription of L-type voltage-dependent calcium channels in mice [50]. Overexpression of $Ca_V1.2$ was sufficient to restore early-phase insulin secretion in cells knocked down for *Tardbp* [50]. In ALS mouse models, the capacity of pancreatic islets to secret insulin was normal, whereas a lower beta cell mass has been observed [51]. Despite the elevated circulating glucagon, fasting glucose homeostasis was defective, leading to increased glycogen stores [51].

Liver: detoxification and antioxidant defense

Analysis of a large cohort of individuals from the UK Biobank has recently revealed that individuals with liver disease had a significantly higher risk of developing ALS. Furthermore, increase in the corrected T1 (cT1) liver marker, which is a novel magnetic resonance imaging (MRI)-based metric quantifying liver inflammation and fibrosis, was associated with a higher risk of ALS [52].

Several structural and functional changes, including increased size of pale hepatocytes, abnormalities in hepatocellular mitochondria, and variability in the hepatocellular nuclear size, have been observed in the livers of patients with ALS. Moreover, fibrosis around the hepatocytes and fat infiltrations were reported [49]. Pronounced hepatic fat accumulations, known as

'steatosis,' has also been observed in patients [53], and it is considered a prognostic indicator of patient survival [54,55]. Concurrently, steatosis is frequently associated with a hyperlipidemic state in ALS, characterized by elevated levels of total cholesterol and low-density lipoprotein (LDL) in plasma. Interestingly, an increased LDL/high-density lipoprotein (HDL) ratio initially associated with longer survival in patients and elevated LDL levels may actually display a protective effect [56], although higher total cholesterol levels have generally been linked to an increased ALS risk [57,58]. Taken together, these findings imply that enhanced lipid circulation could serve as an adaptive response to increased energy expenditure, potentially protecting vital organs from energy failure [55,59].

The expression of IGF-1 protein, which protects the liver from atrophy and promotes regeneration, is decreased in *SOD1-G93A* mice [60]. IGF-1 is not typically associated with liver atrophy under normal, healthy conditions. However, in cirrhosis, which involves progressive liver damage, the depletion of IGF-1 can worsen the pathology [61]. IGF-1 plays a key role in maintaining liver cell function and promoting regeneration. A decline in IGF-1 levels leads to malnutrition and worsens liver function, increasing liver susceptibility to inflammation and oxidative stress [62]. This creates a harmful environment that contributes to liver mitochondrial dysfunction, already observed in patients [63], further impairing the liver's ability to self-repair and to maintain metabolic balance.

Interestingly, in the *SOD1-G93A* mouse model of ALS, the liver shows high levels of atrophy, a significant increase of natural killer (NK)T cell infiltration [64], and AMPK activation, reported also in the spinal cord at symptomatic stages [65,66]. Activation of AMPK, which is the master regulator of energy metabolism and stress-induced pathways, is indicative of catabolic activity and hypermetabolism and results in augmented fatty acid oxidation, glucose uptake, glycogen and cholesterol synthesis, and decreased protein translation [65].

In conclusion, liver dysfunction, including structural changes, steatosis, and metabolic abnormalities, are pathogenic features of ALS. Hyperlipidemia and liver atrophy are linked to survival in patients, while decreased IGF-1 expression and AMPK activation highlight disrupted energy metabolism. Targeting these pathways may offer therapeutic potential in ALS.

Clinical and cellular contribution of the AT

Body composition plays a significant role in ALS progression: while a lower BMI is common in patients [67], an increase in body fat percentage may be protective. Early and ongoing weight loss, especially in the form of fat-free mass, is associated with faster disease progression, and individuals with lower visceral fat at baseline tend to progress more rapidly [14]. Observational studies have shown a temporal link between BMI over the life course and the risk of ALS, with evidence suggesting that a higher BMI is associated with a reduced risk of developing ALS [68]. Longitudinal cohort and case-control studies have consistently found that a higher BMI prior to disease onset is linked to a lower risk of ALS many years later [26]. This suggests that early-life factors such as birth weight and childhood BMI could be modifiable long-term factors influencing the likelihood of ALS onset, whereas a causal role of higher adiposity on lower risk of ALS was established [69]. Moreover, the anatomical distribution of AT seems to play a role in disease progression, although poor evidence is available, requiring more clinical validation. In this context, patients with ALS experience loss of subcutaneous adipose tissue (SAT), particularly in the limbs, during weight loss at follow-up, while no significant changes are observed in visceral fat or waist-to-hip ratio. This pattern may result from altered energy metabolism in skeletal muscle and possible neural denervation of SAT. Physiological differences between SAT and visceral adipose tissue (VAT) – such as VAT's higher insulin resistance and different responses to lipolysis –

may also contribute to this process. Furthermore, survival analysis indicates that greater SAT, rather than VAT, is associated with a better prognosis in ALS [14]. Overall, AT distribution, particularly between VAT and SAT, could exert a significant role in ALS pathogenesis and progression, although the discrepancies reported in the literature could be due to the different methods of imaging/evaluation of SAT and VAT. Remarkably, sex, BMI, and fat loss impact both disease risk and survival outcomes, suggesting that monitoring fat distribution and body composition could provide important insights for managing ALS, especially in its early stages.

One of the most important functions of AT is its prominent role as an endocrine organ and its ability to modulate different physiopathological conditions through secretion of cytokines, hormones, and adipokines [70]. Human-derived adipose stem cells (hADSCs) from healthy individuals exert a protective effect on *SOD1-G93A* mouse-derived primary astrocytes through secretion of IGF-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF), in coculture experiments [71]. hADSCs have been used in transplantation studies in an ALS mouse model, demonstrating that intravenous or intracerebroventricular injection of hADSCs, their conditioned medium, or cellular extracts can delay symptom onset, prolong the lifespan, and reduce the fraction of apoptotic cells [72–75]. Furthermore, presymptomatic transplant of human mesenchymal AT played a protective role in the early stages of the disease, because it improved the structural integrity of the spinal cord ventral horn, increased neuronal survival, reduced gliosis, and increased synapse protection in *SOD1-G93A* mice [76]. In *in vitro* and *in vivo* studies, hADSCs can exert their beneficial effect on neuronal stem cells also via exosome secretion, which can be therapeutically administered both intravenously and intranasally [77,78]. Autologous transplant of hADSCs has been applied during a clinical trial in 2018 (NCT03296501), demonstrating improved cytokine levels and neurological amelioration [79], whereas allogeneic transplant of hADSCs showed significant amelioration of forced vital capacity (FVC) and ALSFRS-R scores [80].

In conclusion, evidence highlights the putative bioactive role of AT as an important source of trophic factors to sustain tissue homeostasis in ALS. Furthermore, how the pathology directly affects the homeostasis of AT is an interesting topic needing more attention.

Sex hormones in ALS dysmetabolism

Given their relevance in modulating energy expenditure beyond their role in reproductive function, sex hormones could be players in ALS pathogenesis. Estrogens play a role in almost all aspects of energy homeostasis and metabolism; estrogen deficiency, such as menopause or ovariectomy, correlates with decreased energy expenditure, metabolic abnormalities, and obesity, resolved, at least in part, or even reversed, by estrogen therapy [81]. Interestingly, the administration of 17β-estradiol ameliorated motor performance, extended survival of lumbar motoneurons, and reduced inflammation in *SOD1-G93A* male mice [82]. In line with the protective effect of estrogens, 17β-estradiol treatment also delayed disease progression, whereas ovariectomy displayed the opposite effects [83]. Estrogen signaling triggers Akt phosphorylation, which in turn leads to the activation of the antiapoptotic signaling pathway involving GSK-3 beta and BCL2 [83]. This protective effect was abrogated by the antiestrogen ICI 182780. Consistently, the expression of aromatase, an enzyme responsible for the conversion of androgens into estrogens, is altered in the spinal cords of *SOD1-G93A* mice. This enzyme is expressed in the motor neurons of the anterior horns of the spinal cord at the presymptomatic stage, in the reactive astrocytes after the onset, and then reduced progressively during disease progression [84]. Hence, aromatase expression in glial cells could presumably induce a local increase of estradiol levels to activate Akt phosphorylation and the downstream neuroprotective signaling pathways, which is reduced or even lost during disease progression.

Remarkably, findings from clinical studies suggest that prolonged exposure to endogenous female sex steroids enhances survival and reduces susceptibility to ALS, whereas exogenous sex steroids display the opposite effect [85]. In particular, women who experienced menopause before age 50 were significantly more likely to be diagnosed with ALS before age 60, compared with those who entered menopause after age 50 [86,87]. However, a replication study with a larger cohort of female patients is necessary to strengthen the results, incorporating factors such as the patients' neuroendocrine profiles, disease progression, and genetic characteristics to better identify potential risk or protective factors.

The influence of estrogens on energy metabolism seems to be largely mediated by estrogen receptor (ER) alpha (α). Mice lacking ERα show an increase of body weight and food intake compared with wild-type littermates [87], while administration of ERα-selective agonists (but not ERβ-selective agonists) exerts anorexigenic effects [87]. Notably, ERα activates the proteasome and the mitochondrial intermembrane space protease (IMS), belonging to the mitochondrial unfolded protein response (UPRmt), aimed at restoring proteostasis in mitochondria. Interestingly, genetic inactivation of ERα leads to an impairment of this safeguard system. Since in female *SOD1-G93A* mice the UPRmt is increased, the sex differences in the ALS phenotype could be due to the differential activation of the ERα-IMS-UPRmt axis [88]. Thus, estradiol may exert a protective effect by delaying mitochondrial dysfunction [89].

Notably, both testosterone and androgen receptor (AR) display a direct effect on energy metabolism. Testosterone inhibits lipid uptake and differentiation of adipocyte precursors, while it activates lipolysis via lipolytic β-adrenergic receptors in adipocytes. Cytosolic AR signaling controls several mitochondrial functions, such as biogenesis and alteration of mitochondrial ultrastructure and mtDNA copy number [90]. In the nucleus, AR regulates the expression of several genes involved in metabolic homeostasis, including the ATP-binding cassette subfamily A member 1 (*Abca1*), whose knockdown causes mitochondrial dysfunction, indicating an intimate link between androgens, cellular lipid trafficking, and mitochondrial bioenergetics [91]. A direct link between androgen signaling and motor neuron disease is provided by Kennedy's disease, which combines motor neuron signs (bulbar and proximal arm weakness) and endocrine signs (gynecomastia, diabetes mellitus, azoospermia). This X-linked condition is due to a mutation in the *AR* gene [83]. The phenotype is worse in males; female carriers can have mild symptoms such as tremor [83]. Notably, the serum level of free testosterone is significantly lower in patients with ALS of both sexes, thus involving androgens in the pathophysiology of ALS. Testosterone exerted a neuroprotective and neuroinflammatory effect on **wobbler mice**, resulting in delayed paw atrophy and improved motor performance [92].

In summary, sex hormones could be relevant to understanding the mechanism at the basis of ALS onset, progression, and metabolic implications (Figure 2) and may offer therapeutic benefits in ALS treatment. Other sex differences in ALS are discussed in Box 1 and Figure 2.

Novel therapeutic opportunities

The role of metabolic disorders in the pathogenesis of ALS has recently assumed a prominent position, as numerous studies have highlighted the precociousness of metabolic alterations compared with neuromotor dysfunction [16].

Nutritional interventions designed to increase caloric intake did not achieve their primary endpoint, showing positive effects only in patients with a more rapid neuromotor decline [93]. On the basis of this evidence, some clinical trials have explored or are exploring ALS as a metabolic disorder. It is worth noting that while improving energy metabolism has

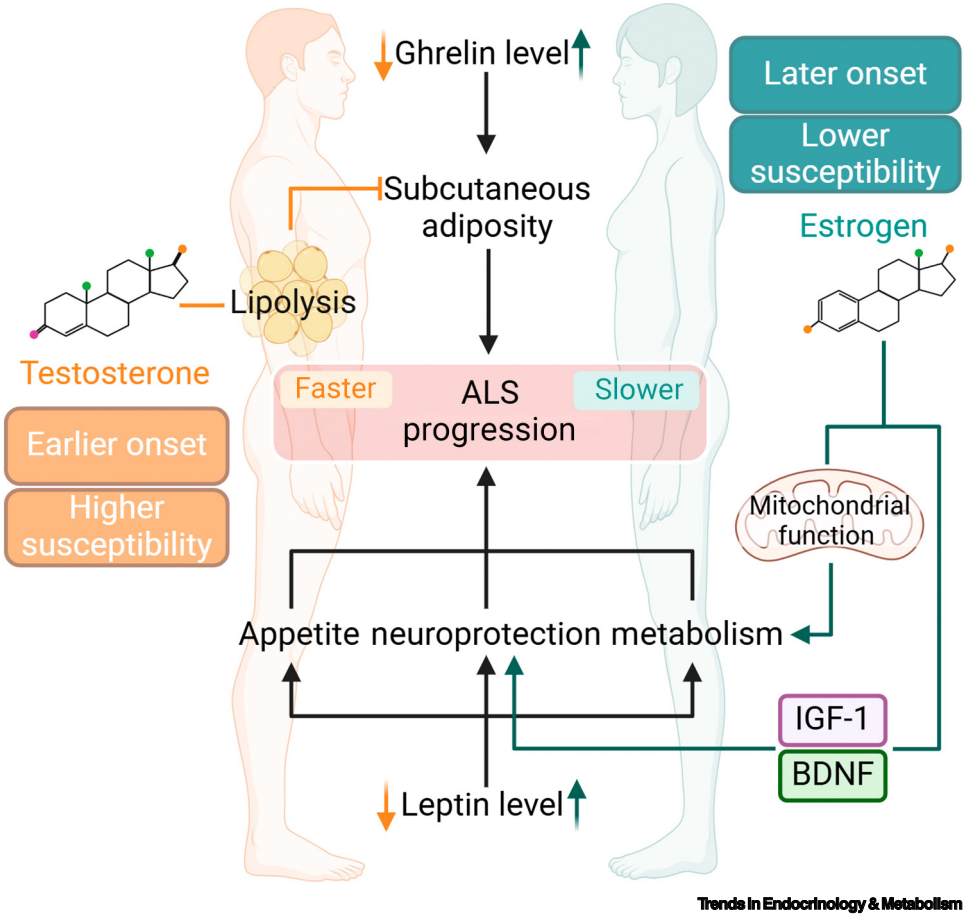

Figure 2. Sex differences in amyotrophic lateral sclerosis (ALS) and the role of sex hormones in the molecular pathways affected in ALS pathology. Illustration of key factors differentiating males and females in the onset, susceptibility, and progression of ALS. The potential role of sex hormones and other hormones regulating energy balance and appetite, which differ between sexes, in influencing energy metabolism. Males exhibit higher susceptibility to ALS and an earlier onset. The faster progression of the disease observed in male patients may be associated with reduced subcutaneous adiposity. Lower levels of ghrelin and leptin may influence adiposity accumulation. Additionally, testosterone-induced lipolysis may contribute to this effect. Conversely, females have a lower susceptibility to ALS and a later onset. Higher levels of ghrelin and leptin may protect against the loss of subcutaneous adiposity. Furthermore, estrogens may exert a protective effect by modulating metabolism and supporting neuroprotection. Specifically, estrogens potentially improve energy metabolism by enhancing mitochondrial function and promote neuroprotection by modulating the secretion of neurotrophic factors, such as insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF). These factors may act as protective mechanisms, contributing to slower ALS progression. Figure created using BioRender.

shown promising results, these outcomes have thus far been observed only in preclinical models [17].

It must be acknowledged that metabolic intervention in ALS is challenged by structural and functional alterations of the brain areas responsible for integrating the body's signals in orchestration of the energy expenditure balance. Indeed, drugs leading to weight gain, if administered during the later stages of the disease when the brain structural and/or functional alterations have already manifested, may prove ineffective because of the absence of their specific targets [32,94,95]. In Table 1, we report the main studies aimed at modulating energy metabolism in ALS, together with the supporting preclinical evidence.

Table 1. Clinical trials and supporting preclinical evidence intervening on energy metabolism in ALS[a]

Therapeutic molecule	Mechanism of action	Clinical trial	Trial description	Supporting preclinical evidence	Clinical status and results
Metformin	Biguanide, orally used as a first-line antidiabetic medication for T2DM, activated mTOR and AMPK pathways in the liver, thus prompting glucose uptake and lowering gluconeogenesis	NCT04220021	Phase 2, open label study to assess the safety and tolerability of metformin in subjects with *C9orf72* ALS	It was shown to lower oxidative stress, neuroinflammation, and neurodegeneration. In *C9orf72* transgenic mice, was shown to reduce the mitochondrial damage and cytotoxicity excess, thus improving ALS/FTD phenotypes [101]	Active, not recruiting
Tideglusib	Small thiazolidinedione (TZD), non-ATP competitive GSK-3β inhibitor	NCT05105958	Phase 2, randomized placebo-controlled trial (TIDALS) (excluded carriers of SOD1 or FUS mutations)	It has shown neuroprotective, anti-inflammatory, and neurogenic properties in different neurodegenerative models [102]. Oral administration of tideglusib in *Tardbp-A315T* transgenic mice was shown to reduce TDP-43 phosphorylation in the spinal cord [103]	Not yet recruiting
Creatine	Nutritional supplement that improves mitochondrial function and ameliorates oxidative stress, glutamatergic excitotoxicity, and apoptosis	NCT00070993	Phase 2 trial to assess the effect of creatine treatment on short-term muscle strength and long-term muscle deterioration in patients with ALS	Oral administration was shown to produce a dose-dependent improvement in motor performance and extended survival of *SOD1-G93A* transgenic mice while protecting mice from loss of motor neurons [104]	Completed, results not disclosed yet
CNM-Au8	Aqueous suspension of nanocrystalline gold able to convert the energetic metabolite NADH into NAD+	NCT04098406	Phase 2, randomized, double blind, placebo-controlled study in early symptomatic patients with ALS to assess bioenergetic catalysis with CNM-Au8 to slow disease progression	Oral gavage in *SOD1* transgenic mice resulted in improved clinical scores and extended lifespan. In iPSC-derived motor neurons cocultured with iPSC-derived astrocytes from a patient with ALS resulted in neuroprotection [105]	CNM-Au8, in combination with riluzole, is well-tolerated in ALS with no identified safety signals [105]
Trimetazidine (TMZ)	Anti-ischemic drug used for the treatment of coronary artery disease, classified as a metabolic modulator that inhibits the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase (ACAA2), catalyzing the oxidation of long-chain fatty acids and improving glucose metabolism	NCT04788745	Phase 2 trial to determine the safety and tolerability of TMZ for the treatment of ALS Targeting metabolic flexibility in ALS (MetFlex)	TMZ increases mitochondrial biogenesis and muscle strength in aged and cachectic muscles [106,107]. It improves muscle performance and energy metabolism in *SOD1-G93A* mice, also extending survival [17]	Completed, results not disclosed yet
Ranolazine	Metabolic modulator and FDA-approved drug for angina, which inhibits the late Na^+ current and intracellular Ca^{2+} accumulation	NCT03472950	Phase 2 trial to determine the safety and efficacy of ranolazine for the treatment of ALS	It was shown to decrease energy expenditure in symptomatic *SOD1-G93A* mice, with a transient recovery of the pathological phenotype [66]	Completed Ranolazine is well tolerated in ALS, with gastrointestinal side effects. It reduced cramp frequency and severity [108]
High fat/high calorie	Compensate the energetic imbalance	NCT00983983	Phase 2 study to assess the safety and tolerability of high fat/high calorie in subjects with ALS	It was shown to compensate for the energetic imbalance extending survival by 20% in animal models of ALS [109]	Hypercaloric enteral nutrition is safe and tolerable in patients with ALS and support the study of nutritional interventions in larger randomized controlled trials at earlier stages of the disease
Pioglitazone	PPARγ agonistic ligand belonging to the TZD class of drugs, used to lower blood glucose levels in T2DM either alone or in combination with metformin or insulin. It binds and activates PPARγ in the cytosol of eukaryotic cells, thus promoting its nuclear translocation and transcriptional activation of target genes	NCT00690118	Phase 2 study to assess the efficacy, safety, and tolerability of 45 mg pioglitazone in patients with ALS receiving standard therapy (riluzole)	It was shown to display anti-inflammatory properties in animal and cell models of neurodegenerative disorders such as Alzheimer and Parkinson diseases and in ALS [110]	Pioglitazone had no beneficial effects on survival as add-on therapy to riluzole [111]

[a]Abbreviations: FTD, frontotemporal dementia; iPSC, induced pluripotent stem cell; PPARγ, peroxisome proliferator-activated receptor gamma; T2DM, type 2 diabetes mellitus.

Concluding remarks

Traditionally, ALS has been regarded primarily as a neurodegenerative disorder, often overlooking the significant contributions of other tissues and organs. In recent years, ALS research has begun to highlight the crucial role played by metabolic organs, increasingly recognized as a central factor to ALS pathogenesis [28] (see Outstanding questions).

Metabolic dysfunction is not merely a hallmark of ALS but also represents a potential therapeutic target. Although neurocentric approaches remain essential, focusing on the metabolic roles of organs previously underexplored in this disease could reveal novel therapeutic opportunities.

It is still unclear whether metabolic dysfunction originates in the CNS or if it develops independently alongside motor neuron degeneration. However, clinical studies of presymptomatic ALS mutation carriers have shown early changes in BMI before the onset of neuromotor symptoms, as well as elevated plasma NfL levels [16]. Indeed, alterations in body weight can be observed in patients decades before the clinical onset of the disease and have been linked to a worse prognosis [26], suggesting that an impaired ability to maintain energy reserves during the presymptomatic phase could exacerbate the condition, particularly when hypermetabolism develops in tandem with the onset of symptoms.

Thus, interventions aimed at restoring metabolic homeostasis could help slow disease progression [54]. A promising example is the positive impact of the high-calorie diet observed in a small cohort of patients [93]; nevertheless, broader and more sophisticated strategies are needed. These could include enhancing bioenergetic performance and promoting the balanced use of essential nutrients such as glucose.

Future research into the metabolic vulnerabilities of these previously unappreciated factors in ALS could lead to innovative therapies that not only address the neurological aspects of this disease but also target the systemic metabolic dysfunctions that contribute to disease progression.

Outstanding questions

Is it still correct to consider ALS as purely a motor neuron disease, or should peripheral organs be considered key players in this condition?

Are peripheral alterations primary or secondary to motor system degeneration?

To what extent does hypothalamic deregulation affect energy homeostasis in ALS?

How does metabolism factor in the sex differences among patients with ALS?

What are the implications of AT localization for disease outcome?

Can energy balance be targeted for therapeutic purpose?

Acknowledgments

M.R.'s salary was supported by the Italian Ministry of Health Ricerca Finalizzata Starting Grant Under-33 (SG-2019-12368589). G.F. was supported by a PhD Scholarship funded by EU - PNRR - Ministerial Decree 351 2022 – Next Generation EU; RF-2019-12369105 (Italian Ministry of Health Ricerca Finalizzata) to A.F.; PRIN 2022 Prot. 20223RXEEC (Italian Ministry of University and Research) to A.F.; PRIN 2022 Prot. 20222KSN2N (Italian Ministry of University and Research) to C.V.; PNRR-MR1-2022-12376821 (Italian Ministry of Health) to M.P.P.

Declaration of interests

The authors declare that they have no competing interests.

References

1. Ravits, J.M. and La Spada, A.R. (2009) ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 73, 805–811
2. Cozzolino, M. and Carrì, M.T. (2012) Mitochondrial dysfunction in ALS. *Prog. Neurobiol.* 97, 54–66
3. Kiernan, M.C. *et al.* (2011) Amyotrophic lateral sclerosis. *Lancet* 377, 942–955
4. Grad, L.I. *et al.* (2017) Clinical spectrum of amyotrophic lateral sclerosis (ALS). *Cold Spring Harb. Perspect. Med.* 7, a024117
5. Gois, A.M. *et al.* (2020) In vitro and in vivo models of amyotrophic lateral sclerosis: an updated overview. *Brain Res. Bull.* 159, 32–43
6. Morgan, S. and Orrell, R.W. (2016) Pathogenesis of amyotrophic lateral sclerosis. *Br. Med. Bull.* 119, 87–98
7. Goutman, S.A. *et al.* (2018) Emerging understanding of the genotype-phenotype relationship in amyotrophic lateral sclerosis. *Handb. Clin. Neurol.* 148, 603–623
8. Tzeplaeff, L. *et al.* (2023) Current state and future directions in the therapy of ALS. *Cells* 12, 1523
9. Fayemendy, P. *et al.* (2021) Hypermetabolism is a reality in amyotrophic lateral sclerosis compared to healthy subjects. *J. Neurol. Sci.* 420, 117257
10. Jésus, P. *et al.* (2018) Hypermetabolism is a deleterious prognostic factor in patients with amyotrophic lateral sclerosis. *Eur. J. Neurol.* 25, 97–104
11. Steyn, F.J. *et al.* (2018) Hypermetabolism in ALS is associated with greater functional decline and shorter survival. *J. Neurol. Neurosurg. Psychiatry* 89, 1016–1023
12. Roscoe, S.A. *et al.* (2024) Mapping the evidence for measuring energy expenditure and indicating hypermetabolism in motor neuron disease: a scoping review. *Nutr. Rev.*, Published online October 7, 2024. https://doi.org/10.1093/nutrit/nuae118

13. Dardiotis, E. *et al.* (2018) Body mass index and survival from amyotrophic lateral sclerosis: a meta-analysis. *Neurol. Clin. Pract.* 8, 437–444
14. Li, J.Y. *et al.* (2022) Correlation of weight and body composition with disease progression rate in patients with amyotrophic lateral sclerosis. *Sci. Rep.* 12, 13292
15. Burg, T. and Van Den Bosch, L. (2023) Abnormal energy metabolism in ALS: a key player? *Curr. Opin. Neurol.* 36, 338–345
16. Dorst, J. *et al.* (2023) Metabolic alterations precede neurofilament changes in presymptomatic ALS gene carriers. *EBioMedicine* 90, 104521
17. Scaricamazza, S. *et al.* (2022) Repurposing of trimetazidine for amyotrophic lateral sclerosis: a study in SOD1. *Br. J. Pharmacol.* 179, 1732–1752
18. Scaricamazza, S. *et al.* (2021) Skeletal muscle in ALS: an unappreciated therapeutic opportunity? *Cells* 10, 525
19. Julian, T.H. *et al.* (2021) Physical exercise is a risk factor for amyotrophic lateral sclerosis: convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. *EBioMedicine* 68, 103397
20. Raymond, J. *et al.* (2021) History of vigorous leisure-time physical activity and early onset amyotrophic lateral sclerosis (ALS), data from the national ALS registry: 2010-2018. *Amyotroph. Lateral Scler. Frontotemporal Degener.* 22, 535–544
21. Fenili, G. *et al.* (2024) Physical exercise in amyotrophic lateral sclerosis: a potential co-adjuvant therapeutic option to counteract disease progression. *Front. Cell Dev. Biol.* 12, 1421566
22. Ferri, A. *et al.* (2019) Tailored exercise training counteracts muscle disuse and attenuates reductions in physical function in individuals with amyotrophic lateral sclerosis. *Front. Physiol.* 10, 1537
23. Kubat, G.B. and Picone, P. (2024) Skeletal muscle dysfunction in amyotrophic lateral sclerosis: a mitochondrial perspective and therapeutic approaches. *Neurol. Sci.* 45, 4121–4131
24. Shefner, J.M. *et al.* (2023) Skeletal muscle in amyotrophic lateral sclerosis. *Brain* 146, 4425–4436
25. Tefera, T.W. *et al.* (2021) CNS glucose metabolism in amyotrophic lateral sclerosis: a therapeutic target? *Cell Biosci.* 11, 14
26. Peter, R.S. *et al.* (2017) Life course body mass index and risk and prognosis of amyotrophic lateral sclerosis: results from the ALS registry Swabia. *Eur. J. Epidemiol.* 32, 901–908
27. Gorges, M. *et al.* (2017) Hypothalamic atrophy is related to body mass index and age at onset in amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry* 88, 1033–1041
28. Chang, J. *et al.* (2023) Lower hypothalamic volume with lower body mass index is associated with shorter survival in patients with amyotrophic lateral sclerosis. *Eur. J. Neurol.* 30, 57–68
29. Michielsen, A. *et al.* (2024) Association between hypothalamic volume and metabolism, cognition, and behavior in patients with amyotrophic lateral sclerosis. *Neurology* 103, e209603
30. Ghaderi, S. *et al.* (2024) Volume loss in the left anterior-superior subunit of the hypothalamus in amyotrophic lateral sclerosis. *CNS Neurosci. Ther.* 30, e14801
31. Cykowski, M.D. *et al.* (2014) TDP-43 pathology in the basal forebrain and hypothalamus of patients with amyotrophic lateral sclerosis. *Acta Neuropathol. Commun.* 2, 171
32. Bolborea, M. *et al.* (2023) Loss of hypothalamic MCH decreases food intake in amyotrophic lateral sclerosis. *Acta Neuropathol.* 145, 773–791
33. Gabery, S. *et al.* (2021) Loss of the metabolism and sleep regulating neuronal populations expressing orexin and oxytocin in the hypothalamus in amyotrophic lateral sclerosis. *Neuropathol. Appl. Neurobiol.* 47, 979–989
34. Jani, M.P. and Gore, G.B. (2016) Swallowing characteristics in amyotrophic lateral sclerosis. *NeuroRehabilitation* 39, 273–276
35. Gnoni, V. *et al.* (2023) Hypothalamus and amyotrophic lateral sclerosis: potential implications in sleep disorders. *Front. Aging Neurosci.* 15, 1193483
36. Howe, S.L. *et al.* (2024) Associations of postprandial ghrelin, liver-expressed antimicrobial peptide 2 and leptin levels with body composition, disease progression and survival in patients with amyotrophic lateral sclerosis. *Eur. J. Neurol.* 31, e16052
37. Pellecchia, M.T. *et al.* (2010) The GH-IGF system in amyotrophic lateral sclerosis: correlations between pituitary GH secretion capacity, insulin-like growth factors and clinical features. *Eur. J. Neurol.* 17, 666–671
38. Morselli, L.L. *et al.* (2006) Growth hormone secretion is impaired in amyotrophic lateral sclerosis. *Clin. Endocrinol.* 65, 385–388
39. Steyn, F.J. *et al.* (2012) Impairments to the GH-IGF-I axis in hSOD1G93A mice give insight into possible mechanisms of GH dysregulation in patients with amyotrophic lateral sclerosis. *Endocrinology* 153, 3735–3746
40. Steyn, F.J. *et al.* (2013) Growth hormone secretion is correlated with neuromuscular innervation rather than motor neuron number in early-symptomatic male amyotrophic lateral sclerosis mice. *Endocrinology* 154, 4695–4706
41. Sorenson, E.J. *et al.* (2008) Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. *Neurology* 71, 1770–1775
42. Nagel, G. *et al.* (2020) Association of insulin-like growth factor 1 concentrations with risk for and prognosis of amyotrophic lateral sclerosis - results from the ALS Registry Swabia. *Sci. Rep.* 10, 736
43. Dobrowolny, G. *et al.* (2005) Muscle expression of a local Igf-1 isoform protects motor neurons in an ALS mouse model. *J. Cell Biol.* 168, 193–199
44. Dobrowolny, G. *et al.* (2008) Local expression of mIgf-1 modulates ubiquitin, caspase and CDK5 expression in skeletal muscle of an ALS mouse model. *Neurol. Res.* 30, 131–136
45. Kaspar, B.K. *et al.* (2003) Retrograde viral delivery of IGF-1 prolongs survival in a mouse ALS model. *Science* 301, 839–842
46. Femiano, C. *et al.* (2024) Inflammatory signature in amyotrophic lateral sclerosis predicting disease progression. *Sci. Rep.* 14, 19796
47. Cocozza, G. *et al.* (2021) The feeding behaviour of amyotrophic lateral sclerosis mouse models is modulated by the Ca. *Br. J. Pharmacol.* 178, 4891–4906
48. Silva, F. *et al.* (2024) Sleep disturbances in amyotrophic lateral sclerosis and prognostic impact – a retrospective study. *Life (Basel)* 14, 1284
49. Maksimovic, K. *et al.* (2023) Evidence of metabolic dysfunction in amyotrophic lateral sclerosis (ALS) patients and animal models. *Biomolecules* 13, 863
50. Araki, K. *et al.* (2019) TDP-43 regulates early-phase insulin secretion via $Ca_V1.2$-mediated exocytosis in islets. *J. Clin. Invest.* 129, 3578–3593
51. McDonald, T.S. *et al.* (2021) Glucose clearance and uptake is increased in the SOD1. *FASEB J.* 35, e21707
52. Zhu, L. *et al.* (2025) Fighting amyotrophic lateral sclerosis by protecting the liver? A prospective cohort study. *Ann. Neurol.* 97, 270–280
53. Johnson, B. *et al.* (2022) Nonalcoholic fatty liver disease in patients with inherited and sporadic motor neuron degeneration. *Genes (Basel)* 13, 936
54. Ludolph, A. *et al.* (2023) Nutritional and metabolic factors in amyotrophic lateral sclerosis. *Nat. Rev. Neurol.* 19, 511–524
55. Dupuis, L. *et al.* (2008) Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. *Neurology* 70, 1004–1009
56. Nakamura, R. *et al.* (2022) Investigation of the prognostic predictive value of serum lipid profiles in amyotrophic lateral sclerosis: roles of sex and hypermetabolism. *Sci. Rep.* 12, 1826
57. Michels, S. *et al.* (2023) Association of blood lipids with onset and prognosis of amyotrophic lateral sclerosis: results from the ALS Swabia registry. *J. Neurol.* 270, 3082–3090
58. Chalitsios, C.V. *et al.* (2024) Apolipoproteins, lipids, lipid-lowering drugs and risk of amyotrophic lateral sclerosis and frontotemporal dementia: a meta-analysis and Mendelian randomisation study. *J. Neurol.* 271, 6956–6969
59. Dorst, J. *et al.* (2011) Patients with elevated triglyceride and cholesterol serum levels have a prolonged survival in amyotrophic lateral sclerosis. *J. Neurol.* 258, 613–617
60. Adamek, A. and Kasprzak, A. (2018) Insulin-like growth factor (IGF) system in liver diseases. *Int. J. Mol. Sci.* 19, 1308
61. de la Garza, R.G. *et al.* (2017) Insulin-like growth factor-1 deficiency and cirrhosis establishment. *J. Clin. Med. Res.* 9, 233–247
62. Gui, R. *et al.* (2023) Effects and potential mechanisms of IGF1/IGF1R in the liver fibrosis: a review. *Int. J. Biol. Macromol.* 251, 126263

63. Masui, Y. *et al.* (1985) Functional and morphometric study of the liver in motor neuron disease. *J. Neurol.* 232, 15–19
64. Finkelstein, A. *et al.* (2011) Abnormal changes in NKT cells, the IGF-1 axis, and liver pathology in an animal model of ALS. *PLoS One* 6, e22374
65. Perera, N.D. *et al.* (2014) Mutant TDP-43 deregulates AMPK activation by PP2A in ALS models. *PLoS One* 9, e90449
66. Scaricamazza, S. *et al.* (2020) Skeletal-muscle metabolic reprogramming in ALS-SOD1. *iScience* 23, 101087
67. Ngo, S.T. *et al.* (2014) Body mass index and dietary intervention: implications for prognosis of amyotrophic lateral sclerosis. *J. Neurol. Sci.* 340, 5–12
68. Nakken, O. *et al.* (2019) High BMI is associated with low ALS risk: a population-based study. *Neurology* 93, e424–e432
69. Zhang, L. *et al.* (2020) Life course adiposity and amyotrophic lateral sclerosis: a Mendelian randomization study. *Ann. Neurol.* 87, 434–441
70. Buti, S. *et al.* (2022) Reassessing human adipose tissue. *N. Engl. J. Med.* 386, e61
71. Gu, R. *et al.* (2010) Human adipose-derived stem cells enhance the glutamate uptake function of GLT1 in SOD1(G93A)-bearing astrocytes. *Biochem. Biophys. Res. Commun.* 393, 481–486
72. Andrzejewska, A. *et al.* (2021) Mesenchymal stem cells for neurological disorders. *Adv. Sci. (Weinh)* 8, 2002944
73. Jeon, G.S. *et al.* (2016) Neuroprotective effect of human adipose stem cell-derived extract in amyotrophic lateral sclerosis. *Neurochem. Res.* 41, 913–923
74. Kim, K.S. *et al.* (2014) Transplantation of human adipose tissue-derived stem cells delays clinical onset and prolongs life span in ALS mouse model. *Cell Transplant.* 23, 1585–1597
75. Tokutake, Y. *et al.* (2015) ALS-associated P56S-VAPB mutation restrains 3T3-L1 preadipocyte differentiation. *Biochem. Biophys. Res. Commun.* 460, 831–837
76. Chiarotto, G.B. *et al.* (2022) Delayed onset, immunomodulation, and lifespan improvement of SOD1. *Brain Res. Bull.* 186, 153–164
77. Lee, I. *et al.* (2021) Fat mass loss correlates with faster disease progression in amyotrophic lateral sclerosis patients: exploring the utility of dual-energy X-ray absorptiometry in a prospective study. *PLoS One* 16, e0251087
78. Bonafede, R. *et al.* (2020) ASC-exosomes ameliorate the disease progression in SOD1(G93A) murine model underlining their potential therapeutic use in human ALS. *Int. J. Mol. Sci.* 21, 3651
79. Kuzma-Kozakiewicz, M. *et al.* (2018) Intraspinal transplantation of the adipose tissue-derived regenerative cells in amyotrophic lateral sclerosis in accordance with the current experts' recommendations: choosing optimal monitoring tools. *Stem Cells Int.* 2018, 4392017
80. Nabavi, S.M. *et al.* (2021) Safety and efficacy of allogeneic adipose tissue mesenchymal stromal cells in amyotrophic lateral sclerosis patients, single-center, prospective, open-label, single-arm clinical trial, long-term follow-up. *Cell J.* 23, 772–778
81. Mauvais-Jarvis, F. and Lindsey, S.H. (2024) Metabolic benefits afforded by estradiol and testosterone in both sexes: clinical considerations. *J. Clin. Invest.* 134, e180073
82. Heitzer, M. *et al.* (2017) Administration of 17β-estradiol improves motoneuron survival and down-regulates inflammasome activation in male SOD1(G93A) ALS mice. *Mol. Neurobiol.* 54, 8429–8443
83. Vegeto, E. *et al.* (2020) The role of sex and sex hormones in neurodegenerative diseases. *Endocr. Rev.* 41, 273–319
84. Sun, C. *et al.* (2017) Characterization of aromatase expression in the spinal cord of an animal model of familial ALS. *Brain Res. Bull.* 132, 180–189
85. Gonzalez Deniselle, M.C. *et al.* (2023) Exposure to endogenous and exogenous sex hormones and reproductive history influence prognosis in women with ALS. *Muscle Nerve* 68, 414–421
86. Raymond, J. *et al.* (2021) Reproductive history and age of onset for women diagnosed with amyotrophic lateral sclerosis: data from the National ALS Registry: 2010-2018. *Neuroepidemiology* 55, 416–424
87. Rasic-Markovic, A. *et al.* (2024) Neuroactive steroids in the neuroendocrine control of food intake, metabolism, and reproduction. *Endocrine* 85, 1050–1057
88. Riar, A.K. *et al.* (2017) Sex specific activation of the ERα axis of the mitochondrial UPR (UPRmt) in the G93A-SOD1 mouse model of familial ALS. *Hum. Mol. Genet.* 26, 1318–1327
89. Cacabelos, D. *et al.* (2016) Early and gender-specific differences in spinal cord mitochondrial function and oxidative stress markers in a mouse model of ALS. *Acta Neuropathol. Commun.* 4, 3
90. Yin, L. *et al.* (2021) Mitochondria in sex hormone-induced disorder of energy metabolism in males and females. *Front. Endocrinol. (Lausanne)* 12, 749451
91. Ducasa, G.M. *et al.* (2019) ATP-binding cassette A1 deficiency causes cardiolipin-driven mitochondrial dysfunction in podocytes. *J. Clin. Invest.* 129, 3387–3400
92. Lara, A. *et al.* (2021) Neuroprotective effects of testosterone in male wobbler mouse, a model of amyotrophic lateral sclerosis. *Mol. Neurobiol.* 58, 2088–2106
93. Ludolph, A.C. *et al.* (2020) Effect of high-caloric nutrition on survival in amyotrophic lateral sclerosis. *Ann. Neurol.* 87, 206–216
94. Bayer, D. *et al.* (2021) Disruption of orbitofrontal-hypothalamic projections in a murine ALS model and in human patients. *Transl. Neurodegener.* 10, 17
95. Vercruysse, P. *et al.* (2016) Alterations in the hypothalamic melanocortin pathway in amyotrophic lateral sclerosis. *Brain* 139, 1106–1122
96. Pape, J.A. and Grose, J.H. (2020) The effects of diet and sex in amyotrophic lateral sclerosis. *Rev. Neurol. (Paris)* 176, 301–315
97. Fernández-Beltrán, L.C. *et al.* (2024) Leptin haploinsufficiency exerts sex-dependent partial protection in SOD1. *Sci. Rep.* 14, 2671
98. Nagaoka, U. *et al.* (2022) Decreased plasma ghrelin in male ALS patients is associated with poor prognosis. *Neurosci. Res.* 177, 111–117
99. Ngo, S.T. *et al.* (2015) Altered expression of metabolic proteins and adipokines in patients with amyotrophic lateral sclerosis. *J. Neurol. Sci.* 357, 22–27
100. Picó, C. *et al.* (2022) Leptin as a key regulator of the adipose organ. *Rev. Endocr. Metab. Disord.* 23, 13–30
101. Feng, Y. *et al.* (2024) Metformin ameliorates mitochondrial damage induced by C9orf72 poly(GR) via upregulating AKT phosphorylation. *J. Cell. Biochem.* 125, e30526
102. Morales-Garcia, J.A. *et al.* (2012) Glycogen synthase kinase 3 inhibition promotes adult hippocampal neurogenesis in vitro and in vivo. *ACS Chem. Neurosci.* 3, 963–971
103. Gutiérrez-Rodelo, C. *et al.* (2023) Modulating cyclic nucleotides pathways by bioactive compounds in combatting anxiety and depression disorders. *Mol. Biol. Rep.* 50, 7797–7814
104. Klivenyi, P. *et al.* (1999) Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nat. Med.* 5, 347–350
105. Vucic, S. *et al.* (2021) Study protocol of RESCUE-ALS: a phase 2, randomised, double-blind, placebo-controlled study in early symptomatic amyotrophic lateral sclerosis patients to assess bioenergetic catalysis with CNM-Au8 as a mechanism to slow disease progression. *BMJ Open* 11, e041479
106. Belli, R. *et al.* (2019) Metabolic reprogramming promotes myogenesis during aging. *Front. Physiol.* 10, 897
107. Molinari, F. *et al.* (2017) The mitochondrial metabolic reprogramming agent trimetazidine as an 'exercise mimetic' in cachectic C26-bearing mice. *J. Cachexia. Sarcopenia Muscle* 8, 954–973
108. Chandrashekhar, S. *et al.* (2022) Open-label pilot study of ranolazine for cramps in amyotrophic lateral sclerosis. *Muscle Nerve* 66, 71–75
109. Dupuis, L. *et al.* (2004) Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. *Proc. Natl. Acad. Sci. U. S. A.* 101, 11159–11164
110. Agarwal, S. *et al.* (2017) Peroxisome proliferator-activated receptors (PPARs) as therapeutic target in neurodegenerative disorders. *Biochem. Biophys. Res. Commun.* 483, 1166–1177
111. Dupuis, L. *et al.* (2012) A randomized, double blind, placebo-controlled trial of pioglitazone in combination with riluzole in amyotrophic lateral sclerosis. *PLoS One* 7, e37885