REVIEW

Journal of Cachexia, Sarcopenia and Muscle (2018)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12314

Iron deficiency as energetic insult to skeletal muscle in chronic diseases

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Abstract

Specific skeletal myopathy constitutes a common feature of heart failure, chronic obstructive pulmonary disease, and type 2 diabetes mellitus, where it can be characterized by the loss of skeletal muscle oxidative capacity. There is evidence from *in vitro* and animal studies that iron deficiency affects skeletal muscle functioning mainly in the context of its energetics by limiting oxidative metabolism in favour of glycolysis and by alterations in both carbohydrate and fat catabolic processing. In this review, we depict the possible molecular pathomechanisms of skeletal muscle energetic impairment and postulate iron deficiency as an important factor causally linked to loss of muscle oxidative capacity that contributes to skeletal myopathy seen in patients with heart failure, chronic obstructive pulmonary disease, and type 2 diabetes mellitus.

Keywords Iron deficiency; Skeletal muscle; Oxidative capacity; Heart failure; Chronic obstructive pulmonary disease; Type 2 diabetes mellitus

Received: 8 January 2018; Revised: 5 April 2018; Accepted: 22 April 2018
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Introduction

Specific skeletal myopathy represents an important pathophysiological feature of many chronic diseases and contributes to debilitating symptomatology. Indeed, derangements within skeletal muscle occur in such illnesses as rheumatoid arthritis, chronic kidney disease (CKD), chronic liver disease, heart failure (HF), chronic obstructive pulmonary disease (COPD), and type 2 diabetes mellitus (T2DM).[1–6] Pathophysiology of skeletal myopathy secondary to systemic disorders is multifactorial, being particularly complex in rheumatoid arthritis, CKD, and chronic liver disease where muscle structure and functioning may be influenced among others by a variety of circulating toxic metabolites, immune complexes, or enhanced muscle inflammatory signalling.[7–10] Instead, functional impairments of skeletal muscle seen in HF, COPD, and T2DM, such as decreased performance and decreased exercise capacity, seem to co-exist with similar histological abnormalities and to result from comparable molecular pathomechanisms, most of which concerns energetics and yields in loss of muscle oxidative capacity.[11]

There are premises that iron plays a crucial role in skeletal muscle functioning, especially in the context of energy metabolism. Cellular oxidative metabolism strongly relies on iron availability, which is indispensable for both sufficient oxygen supply and effective substrate catabolism.[12] It is worth noting that both iron overload and iron deficiency (ID) were proven to be detrimental for mitochondria that constitute cellular energy centres.[13] Iron overload leads to the excessive formation and accumulation of reactive oxygen species whose harmful effects have already been described.[14,15] On the other hand, although numerous deleterious effects of ID on skeletal muscle have been summarized (for a detailed review, see Stugiewicz *et al.*[16]), they have not been discussed in the

particular context of fuel selection and efficiency of specific catabolic routes for the energy production.

In this review, we aim to describe the possible molecular pathomechanisms of skeletal muscle energetic impairment, gathering evidence from *in vitro* and animal studies. Further, we postulate ID as an important causative factor of loss of muscle oxidative capacity that significantly contributes to skeletal myopathy seen in patients with HF, COPD, and T2DM and therefore may be considered as a co-target in a therapeutic process.

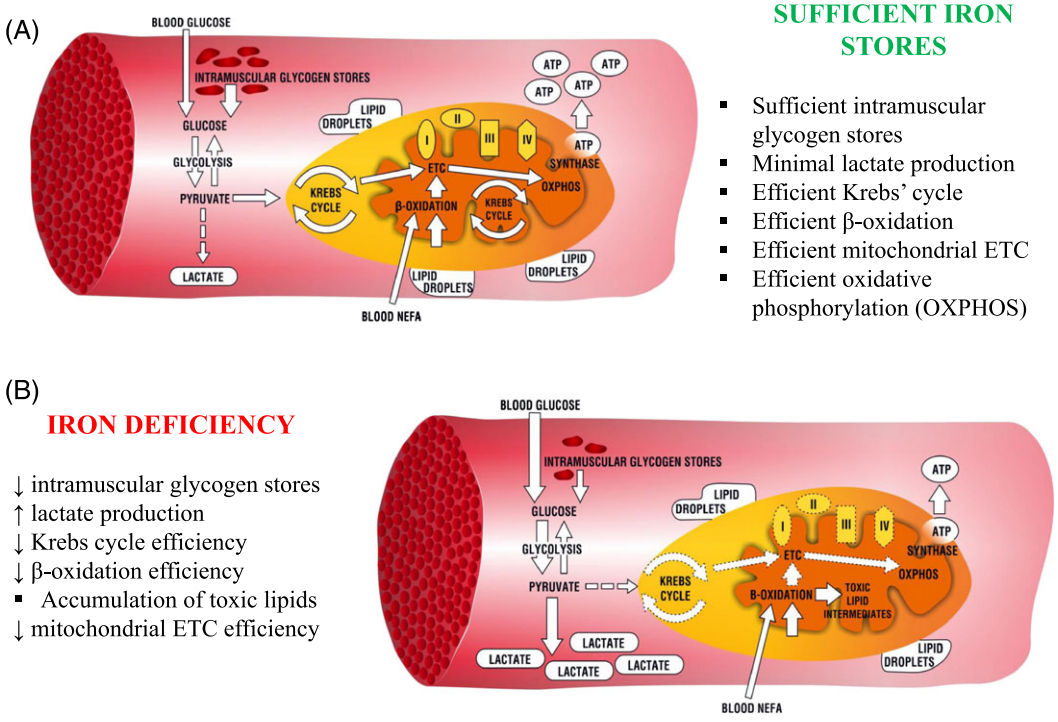
Paragraph 1. Skeletal muscle energy metabolism

Energy-consuming and multitasking skeletal muscle tissue possesses complex machinery, which integrates various pathways for the efficient adenosine triphosphate (ATP) production.[17–19] The flexibility of usage of different energy sources that can be metabolized along distinct metabolic routes is inevitable for skeletal muscle to adapt to dynamic changes in their energy demand. The total amount of ATP stored in human skeletal muscles accounts for approximately 80 g and needs to be continuously re-synthesized at the rate of its consumption.[20] Muscles can take advantage of three main groups of energy substrates such as high-energy phosphates (creatine phosphates), carbohydrates (glycogen and glucose), and lipids (triacylglycerol and free fatty acids).[21–24] Notably, endurance power of muscles is strongly related to their capacities to oxidize energy fuels in the process of mitochondrial oxidative phosphorylation (OXPHOS), which yields in ATP synthesis. Once oxygen flux to a muscle cell is not disturbed, OXPHOS can result in most efficient energy production, being fuelled by carbohydrate or fat as substrates.[20] Both carbohydrate and lipid pathways branch to form four parallel pathways that converge on mitochondria.[23] Thus, mitochondria integrate several metabolic routes, which result in the energy supply being essential for skeletal muscle functioning and capacity (*Figure* 1A).

Anaerobic vs. aerobic energy metabolism

Under limited oxygen availability, energy from carbohydrates in skeletal muscle is produced via anaerobic glycolysis, which results mostly in lactate production.[25] The process has a net yield of 2 molecules of ATP per molecule of glucose. Therefore, it is not sufficiently powered to provide muscle with energy for a prolonged submaximal exercise. As soon as myocytes receive sufficient oxygen, they switch towards a more advanced form of energy acquisition, or OXPHOS,

Figure 1 Energetic pathways in human skeletal myocytes (A) when iron stores are sufficient and (B) when changed upon iron deficiency. ETC, electron transport chain; ATP, adenosine triphosphate; I–IV, mitochondrial enzymatic complexes; NEFA, non-esterified fatty acids.



DOI: 10.1002/jcsm.12314

which is programmed as a natural continuation of glycolysis and is preceded by Krebs cycle.[20] OXPHOS is conditioned by enzymatic complexes (complexes I–IV) of mitochondrial electron transport chain (ETC) that enables the generation of electrochemical gradient across the mitochondrial membrane essential for the synthesis of about 30–36 molecules of ATP. On the other hand, the efficiency of oxidative consumption of fats is estimated at 14 molecules of ATP.[25]

Carbohydrate energy metabolism in skeletal muscle

Catabolic processing of carbohydrates in skeletal muscle relies on two substrate sources, namely, intramuscular glycogen and blood glucose,[22] which, depending on the oxygen availability, can be metabolized via anaerobic glycolysis in the cytoplasm or aerobic OXPHOS within mitochondrial enzymatic machinery. Notably, the substrates for mitochondrial oxidation at work intensities of around 80% of VO_2max are initially supplied from glycogen droplets inside the muscle cells with no more than 20–30% of the fuel acquired from the capillaries.[23,26] During prolonged exercise, as soon as glycogen stores are depleted, the contribution of blood glucose becomes more appreciable, reaching close to 100% of muscle carbohydrate metabolism.[22,27] There are three points at which muscle glucose acquisition can be regulated: glucose delivery to the muscle cells, transmembrane transportation, and flux through the intracellular metabolism.[22] The amount of glucose delivered to the muscular capillaries is usually referred as a resultant of blood flow and blood glucose concentration from which only the latter component has been proven to constitute a considerable limitation for glucose uptake during prolonged exercise.[22,28] Second rate-limiting step of glucose acquisition is the permeability of the muscle cell membrane, which can be influenced by either extracellular stimuli, like contraction or insulin, or internal cellular factors, including metabolic status and Ca^{2+} signalling. All of the factors mentioned earlier have been proposed to affect either abundance or activity of the muscle-specific glucose transporter (GLUT-4).[29–31] Finally, the final site of regulation of muscle glucose delivery is the flux of this monosaccharide through the metabolic routes, being mainly dependent on the activity of enzymes involved in glucose catabolism.

Lipid energy metabolism in skeletal muscle

Another two pathways for muscle energy metabolism rely on the lipid catabolism, which can be fuelled by intramuscular triglycerides or blood lipids. In general, in the main form of non-esterified fatty acids (NEFA), lipid substrates are released from their stores in skeletal muscle or adipose tissue and transport to muscle mitochondria to be metabolized in the β-oxidation process, which in turn yields in substrates for OXPHOS. The contribution of fatty acids to oxidative metabolism is essentially maximal at exercise intensities of 60% of VO_2max, while at higher intensities being decreased.[24,32] Similarly to the order of carbohydrate substrate utilization, muscles primarily take an advantage from the intracellular lipid droplets, which remain in direct contact with the outer mitochondrial membrane. It allows muscle cell to circumvent the transport problems because of the low solubility of NEFA in the cytosol. Notably, lipid droplets comprise mainly intramuscular triglyceride whose concentration can adaptively increase in response to endurance training,[23,33] but also, according to the experimental evidence from human studies, it can accumulate in pathological conditions, contributing to the development of skeletal muscle insulin resistance.[34–38]

Interactions between carbohydrate and lipid metabolism in skeletal muscle

Crosstalk between carbohydrate and lipid metabolic routes in skeletal muscle has been proposed decades ago by Randle *et al*. and has been referred as 'glucose-fatty acid cycle' or 'Randle cycle'.[39,40] The original hypothesis has evolved over the years and in its current form postulates that the products of NEFA catabolism inhibit rate-limiting enzymes of glycolysis, thus limiting glucose uptake and catabolism.[41,42] In general, Randle cycle should be considered as the biochemical mechanism that controls fuel selection, adjusting substrate supply and demand within skeletal muscle tissue, thus fine-tuning hormonal regulation of substrate concentrations in the blood.[42,43] However, under conditions of disturbed energy status, an activation of the major sensor of cellular energy demand in skeletal muscle, AMP-activated protein kinase, leads to abrogation of mechanisms of the glucose-fatty acid cycle. Then, NEFA oxidation no longer inhibits the glucose uptake itself, while it may limit carbohydrate oxidative metabolism.[44,45]

Paragraph 2. The importance of iron in the context of energy metabolism in skeletal muscle

Over recent years, there has been increasing interest in a role of iron metabolism in skeletal muscle functioning. Containing 10–15% of iron in the body, skeletal muscle mainly utilizes this micronutrient to build enzymes indispensable for oxidative metabolism, including myoglobin, which secures oxygen for a muscle cell as well as enzymes involved in substrate catabolism for OXPHOS.[46,47] Taking into consideration different extent of reliance on OXPHOS in a distinct type of muscle fibres, it should be noted that major amount of iron is

DOI: 10.1002/jcsm.12314

present in slow 'red' fibres in which the oxidative energy production prevails. Thus, iron is of particular importance for muscles rich in red fibres, such as dorsal muscles, lower extremity extensors, the diaphragm, and intercostal muscles.[48]

Involvement of iron in Krebs cycle in skeletal muscle

Skeletal myocytes, like other mammalian cells, are attributed with two central regulators of cellular adaptive response to ID: IRP1 and IRP2 (for a detailed review, see Anderson *et al*.[49] and Guo *et al*.[50]). Noteworthy, however, is that in a state of optimal or elevated intracellular iron, IRP1 switches from its transcriptional function towards enzymatic activity, being an important catalyst of Krebs cycle[51] or series of reactions that intermediate between glycolysis and OXPHOS in the oxidative metabolism. Therefore, in non-ID, environment IRP1 appears as a cytosolic isoform of aconitase that transforms citrate to isocitrate in Krebs cycle, which, in turn, constitutes a metabolic link between initial catabolism of either carbohydrate or fat and mitochondrial ETC, which leads to OXPHOS. Importantly, the second isoform of the aforementioned enzyme, which is referred as mitochondrial aconitase, is involved in Krebs cycle held in mitochondria. Because both cytosolic and mitochondrial aconitases contain iron–sulfur clusters (ISC), their activities decrease in a low iron state, because of either conversion to IRP1 in the case of cytosolic isoform[51] or inactivation in the case of the mitochondrial enzyme.[52]

Involvement of iron in oxidative phosphorylation in skeletal muscle

As mentioned before, the efficiency of OXPHOS is directly related to the activities of four mitochondrial enzymatic complexes. Being embedded in the mitochondrial inner membrane, together they form the mitochondrial ETC that enables generation of electrochemical gradient needed for the final ATP synthesis.[13,25] It is worth mentioning that each of these enzymatic complexes contains iron in its structure in the form of either haem, which builds haem proteins (cytochromes) present in complexes III and IV, or ISC, which are the parts of ISC proteins in the complexes I, II, and III.[13,25] Because of its ability to exist in two interchangeable oxidative states [the reduced ferrous (Fe 2+) and the oxidized ferric (Fe 3+) forms], iron plays a central role in oxidation–reduction reactions (redox) carried out within mitochondrial ETC.[13,25] Because none of those aforementioned enzymes can efficiently function without iron atoms, this micronutrient is indispensable for the effective oxidative catabolism of both carbohydrates and fats.

Involvement of iron in fat catabolism

Iron-containing prosthetic groups are not only present in the aforementioned enzymatic complexes but also account for the essential components of molecules that link initial catabolism of fatty acids to OXPHOS to enable the efficient energy acquisition in skeletal muscle. Indeed, an iron–sulfur enzyme, electron-transferring-flavoprotein dehydrogenase, was identified to be responsible for the transfer of products of fatty acids oxidation to the mitochondrial ETC.[53,54] Therefore, iron appears to be a microelement unique in its ubiquity in molecular systems of myocytes' energetics.

Possible importance of muscle-specific regulation of iron metabolism

Taking into consideration the apparent role of iron availability in the efficient energetics of skeletal muscle, one should consider more in-depth studies on the mechanisms orchestrating iron metabolism within myocytes. Although systemic iron homoeostasis has been extensively studied and can be reviewed elsewhere,[55–57] local iron metabolism in skeletal muscle and its crosstalk with fuel selection and metabolism are still poorly understood. Because the expression of two main regulatory peptides, namely, hepcidin and hemojuvelin, has been confirmed in skeletal muscle,[58,59] therefore, the possibility of involvement of muscle-specific regulation of iron metabolism in energy metabolism may worth to be discussed and further investigated.

Paragraph 3. Iron deficiency and metabolic alterations in skeletal muscle

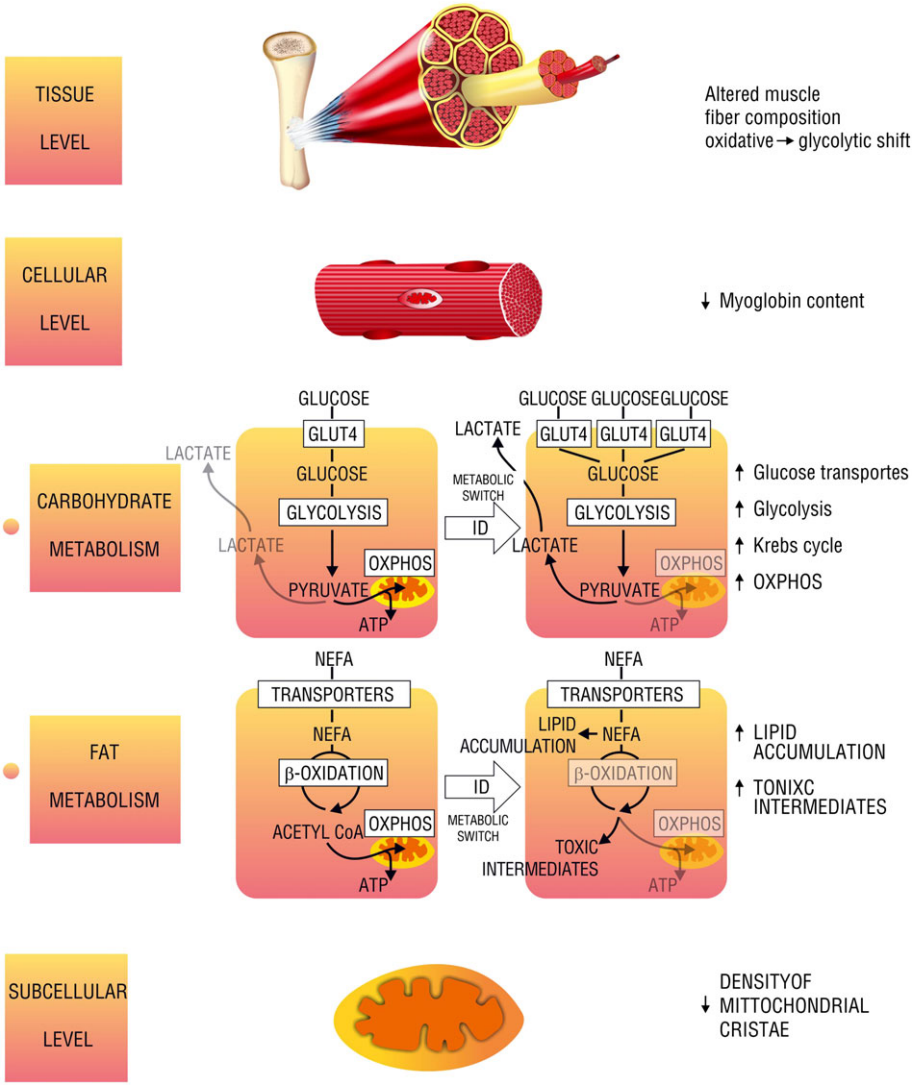
Manifold deleterious effects of ID on skeletal muscle include a deranged selection of energy substrates and altered catabolic pathways. Experimental data from *in vitro* and animal studies indicate that skeletal muscle network of pathways for energy production is hampered by ID at different points of the distinct metabolic routes (*Figure* 1B).

Alterations in oxidative metabolism: oxidative-to-glycolytic shift

Affecting oxidative metabolism on several sites, ID rearranges skeletal muscle energy metabolism, limiting the contribution of the oxidative pathway in favour of glycolysis (*Figure* 2). Firstly, ID affects the morphology of mitochondria as the density of cristae of the mitochondrial inner membrane is

DOI: 10.1002/jcsm.12314

Figure 2 Different levels of muscle energetic alterations caused by iron deficiency. GLUT4, glucose transporter; NEFA, non-esterified fatty acids; OXPHOS, oxidative phosphorylation; ID, iron deficiency; Acetyl-CoA, acetyl coenzyme A; ATP, adenosine triphosphate.



decreased.[60] Because these structures are responsible for binding of enzymes of mitochondrial ETC, such an alteration contributes to the mitochondrial oxidative inefficiency. Further, ID dramatically impairs OXPHOS, affecting both oxygen delivery and the final step of substrate catabolism within mitochondrial ETC. Notably, the concentration of myoglobin was decreased in predominantly slow- and mixed-fibre skeletal muscle from iron-deficient rats as compared with iron-replete controls.[61] ID also caused multifocal decoupling of mitochondrial ETC as the activities of I, II, and IV enzymatic complexes were decreased along with an inhibition of ISC protein maturation and decreased the concentration of cytochromes.[62–68] Furthermore, Graber *et al*. suggested that reduced amount of intracellular haem could affect myoglobin content, as a haem synthesis inhibitor was able to reduce also a myoglobin level by 40% in rat skeletal muscle cells.[69] Apart from derangements in OXPHOS, ID was reported to cause a decrease in level and activity of the key enzyme of Krebs cycle or mitochondrial aconitase, probably via post-translational regulation, thus limiting the conversion of acetyl coenzyme A for OXPHOS. Finally, Finch *et al*. described in rat skeletal muscle links between ID and excessive lactate production that could result from impaired OXPHOS and consequent accumulation of product of enhanced glycolysis.[70] All of these effects of ID may add to the general decrease in oxidative metabolism efficiency.

Alterations in carbohydrate metabolism

The influence of ID on muscle carbohydrate uptake and utilization is multifaceted. Most of all, experimental data

DOI: 10.1002/jcsm.12314

indicate an increased reliance on carbohydrate metabolism as reported for both mildly and severely iron-deficient rats.[71–74] Several studies investigated the effects of ID on the glucose transporters of skeletal muscle and yielded in partially inconsistent results. In general, ID was proven to increase the expression of muscle glucose transporters. However, skeletal muscle of iron-deficient rats demonstrated an increased expression of the muscle-specific GLUT-4,[75] while experimental data from *in vitro* studies on the myocytes suggested an increase in expression of ubiquitously distributed transporter GLUT-1. Concerning the intensity of carbohydrate metabolism, Barrientos *et al*. demonstrated that mice with skeletal muscle-specific transferrin receptor knockout, which was interpreted as muscle-specific ID, presented with an upregulation of genes involved in glycolysis along with an enhancement of gluconeogenesis in liver possibly due to increased muscle glucose demand.[76]

Alterations in fat metabolism

In general, ID is presumed to shift the skeletal muscle reliance from fat to glucose as the preferred metabolic substrate. Davis *et al*. have reported a significant decrease in the expression of several enzymes involved in the central pathway of muscle fat catabolism, β-oxidation. Notably, the same study demonstrated an increase in expression of lipogenic genes, which leads to lipid accumulation in skeletal muscle.[74] Indeed, an increased abundance of lipid droplets was reported in the skeletal muscles of ID rats.[51,77] Further, in transgenic mice lacking transferrin receptor, the β-oxidation of fatty acids was impaired, with an accumulation of potentially toxic intermediates.[76] It is worth noting that ID was also reported to increase lipid peroxidation in rats,[78] leading to the severe cell damage. Therefore, the accumulation mentioned earlier due to ID may yield in the intensified detrimental effects.

The possible mechanism of impaired fuel metabolism in iron-deficient skeletal muscle

Considering metabolic changes induced by ID in skeletal muscle, it can be concluded that low iron state increases non-anaerobic glucose metabolism, thus improving glucose uptake and insulin sensitivity in this tissue. Indeed, ID is reported to improve insulin sensitivity in peripheral tissues of iron-deficient animals[71,79–81] possibly through an enhanced expression of the glucose transporters,[75,82] but it also triggers less desirable metabolic adaptations, such as hyperglycaemia, hyperinsulinaemia, and hypertriglyceridaemia.[73,74,77,80,83,84] This phenomenon may result from the ID-induced deficiencies of mitochondrial ETC, which in turn lead to ineffective carbohydrate and fat oxidative metabolism combined with compensatory increased glucose demand.

Paragraph 4. Links between iron deficiency, loss of oxidative capacity, and functional capacity in patients with chronic diseases accompanied by skeletal myopathy

The decline in muscle strength and quality has emerged as a common pathophysiological feature of HF, COPD, and T2DM, significantly aggravating symptoms and outcomes.[1,3,85–90] Skeletal myopathy that accompanies these diseases has been linked to the loss of skeletal muscle oxidative capacity, defined by the ability to oxidize nutrients to obtain energy.[11] Macroscopically, structural changes that correlate with the decreased functional muscle capacity can be observed as a reduced muscle mass and volume measured in different body regions.[3,91–93] Among the skeletal muscle derangements occurred at various levels, from the macroscopic to subcellular, and reported in patients with HF, COPD, and T2DM, many may result from the loss of oxidative capacity.

Histological and ultrastructural alterations in skeletal muscle in chronic diseases

Histological examination of skeletal muscle in patients with HF reveals changes in fibre composition with an increased contribution of fast glycolytic fibres.[85,94] Because the fast muscle fibres rely mainly on anaerobic metabolism, this observation accounts for microscopic evidence on the decreased extent of OXPHOS within skeletal muscle, thus a shift in energy metabolism towards anaerobic route. Further, alterations in skeletal muscle seen at the cellular level involve mostly myocyte energetic centres, namely, mitochondria, and comprise not only a decreased total number and volume of these organelles but also diminished both mitochondrial volume density and surface density of mitochondrial cristae.[85,95] These structural modifications of cellular organelles may lead to severe limitation of oxidative ATP synthesis, which normally takes place exactly on mitochondria cristae. Indeed, the changes as mentioned earlier in mitochondria ultrastructure significantly correlate with decreased oxidative capacity of skeletal muscle,[85,95] suggesting a significant contribution of compromised muscle oxidative metabolism to exercise intolerance seen in patients with HF.

Analogous oxidative-to-glycolytic shifts within muscle fibres are observed in both patients with COPD[96] and patients with T2DM.[97] Skeletal muscle in COPD is characterized by a decreased mitochondrial content and decreased the fractional area of these organelles,[98] whereas in T2DM, because muscle mitochondria present with smaller mean size and narrowed cristae, they most likely contribute to skeletal muscle dysfunction seen in diabetic patients.[99–101]

DOI: 10.1002/jcsm.12314

Therefore, both in COPD and in T2DM, the molecular centres of oxidative energy production exhibit structural alterations that diminish their ability to bind the oxidative enzymes.

Alterations of oxidative metabolism in skeletal muscle in chronic diseases

In general, oxidative metabolism in skeletal muscle in HF is limited, and the anaerobic glycolysis is enhanced. Concerning oxidative energetics, the efficiency of Krebs cycle in skeletal muscle of patients with HF is decreased because the activities of rate-limiting enzymes, namely, citrate synthase (CS) and succinate dehydrogenase, are diminished.[102,103] These results suggest a limited substrate flux to OXPHOS and resultant inefficient ATP synthesis. Abnormal oxidative metabolism is coupled with a shift towards rapid energy sources such as high-energy phosphates or glycolysis, which leads to intracellular acidification.[85,104]

Abnormalities in oxidative metabolism of skeletal muscle have also been demonstrated in patients with COPD. The changes include a decrease in activity of CS of Krebs cycle[105] and a diminished activity of enzymatic complex IV of mitochondrial ETC.[106] Similarly, skeletal muscles in T2DM have decreased the activity of both CS and enzymatic complexes I and IV of mitochondrial ETC.[99,107] Importantly, in both COPD and T2DM, deranged oxidative metabolism coexists with increased activities of enzymes of anaerobic glycolysis.[107,108]

Alterations of carbohydrate and fat metabolism in skeletal muscle in chronic diseases

Apart from the general decline in oxidative metabolism, skeletal muscle in HF demonstrates significant changes in fuel selection and their catabolism. For example, the glycogen content is decreased in skeletal muscle of patients with HF.[2,94] This alteration may contribute to the limitation of muscle functional capacity taking into consideration that mitochondrial oxidation is predominantly supplied from intramuscular glycogen droplets.[23] On the other hand, fat catabolism is also compromised because skeletal myocytes in HF present with a diminished concentration of an essential enzyme mediating initial catabolism of fatty acids, 3-hydroxyacyl-coenzyme A-dehydrogenase.[94] Therefore, oxidative metabolism in skeletal muscle of patients with HF is disturbed not only because of abnormalities within mitochondria but also because of regarding inefficient initial catabolism of two main fuels, carbohydrates and fat. Also, Keith *et al*. reported that in patients with HF, plasma concentrations of lipid peroxidation products are increased,[109] which possibly may result from abnormal mitochondrial functioning, namely, inefficient oxygen reduction coupled with the large accumulation of lipid intermediates being not effectively catabolized in the oxidative pathway. Skeletal muscle in patients with COPD demonstrates similar alterations as the amount of intramuscular glycogen is decreased.[110] Furthermore, the accumulation of fat within skeletal muscle in COPD and the enhanced lipid peroxidation may suggest a deranged lipid oxidative metabolism.[111,112] Similarly, in T2DM, lipid accumulation occurs within skeletal muscle as a supposed consequence of impaired mitochondrial oxidative capacity and might contribute to the development of insulin resistance.[113–115]

The prevalence of iron deficiency in patients with chronic diseases

Iron deficiency has been recognized as a frequent comorbid condition in patients with HF with the prevalence estimated at 30–60% of those patients.[116–118] In an international pooled cohort of >1500 European patients with HF, ID affected 50% of subjects.[117,119] Previously, we have gathered available evidence on the correlation between ID and impaired functional capacity in patients with HF, as well as on beneficial effects of iron supplementation on physical performance in patients with HF and ID, regardless of the presence of anaemia.[16] Moreover, there is evidence on the improvement of myocardial function in patients with HF and ID after iron replacement therapy.[120–122] Indeed, Gaber *et al*. reported that intravenous (i.v.) iron administration improved diastolic and systolic function as assessed using echocardiographic parameters, such as S′-wave, E/E′ ratio, and peak systolic strain rate.[121] In another small trial, iron repletion caused a correction of left ventricular end-systolic dimension, left ventricular end-diastolic dimension, left ventricular end diastolic posterior wall dimension, interventricular septal end diastolic dimension thickness, left ventricular mass index and left ventricular end systolic volume.[120] Regarding COPD, several studies refer to the prevalence of ID. For example, among 113 patients with stable, moderately severe COPD, 18 were found to be iron deficient.[123] Data from the study mentioned earlier indicate that iron-deficient patients had more self-reported exacerbations as well as a trend towards worse exercise tolerance.[123] Notably, the higher severity of the disease has been correlated with the greater decline in lung function as assessed using FEV1%FVC.[124] In other study, Horadagoda *et al*.[125] detected ID in 38% of 94 consecutive patients with acute exacerbations of COPD. Further, ID has been linked to increased pulmonary artery pressure in a group of 75 non-anaemic outpatients with COPD (subjects with COPD—41%).[126] There are also data from the study of a prospective sample of 70 non-anaemic patients with COPD where iron-deficient subjects (48%) demonstrated lower pre-training aerobic capacity and reduced training-induced response in comparison with those with normal iron

DOI: 10.1002/jcsm.12314

status.[127] Concerning T2DM, there is a scarcity of data on the prevalence of ID. In general, a deranged iron metabolism seems to play an important role in the pathophysiology of diabetes.[128,129] Many studies have shown that iron overload contributes to diabetes mellitus,[130–132] but there are also data from a large cohort study indicating that ID is not protective against T2DM.[133] Furthermore, ID is highly prevalent (about 39%) in obese and overweight children and adolescents[134] as well as in adult men and women.[135–137] Indeed, ID is associated with the major risk factor for diabetes, obesity, which is causally related to the decrease in the ability of effective fat catabolism.[136,138,139] Further, ID has been proposed to participate in obesity-related inflammation.[129] Importantly, there is an ongoing randomized placebo-controlled clinical trial investigating the hypothesis that i.v. substitution with ferric carboxymaltose reduces HbA1c levels in patients with type 2 diabetes and ID, thereby improving metabolic status and quality of life.[140]

The mechanism of development of iron deficiency in patients with chronic diseases

The mechanism in which patients with chronic diseases develop ID is not fully understood. Regarding chronic illnesses assisted by inflammation, such as CKD, infections, cancer, and autoimmune diseases, the prevalent literature emphasizes the role of inflammatory-driven up-regulation of hepcidin, which presumably leads to functional ID or anaemia.[141–146] However, in case of HF, the mechanism seems to be different, because the level of hepcidin in patients with systolic HF is reported to be associated with low circulating pro-inflammatory markers, being related neither to the presence of anaemia nor to haemoglobin level.[147] Therefore, it has been proposed that in the initial phase of HF, hepcidin is high, which is probably related to its protective role against iron excess manifested by elevated serum ferritin.[147] However, the prolonged up-regulation of hepcidin inhibits iron absorption and release, thus leads to the development of ID with manifestation of its deleterious clinical consequences. In the end, ID represses hepcidin production to the bloodstream.[147] It is worth noting that although the aforementioned mechanism has been postulated, it has been tested neither in the context of other factors influencing hepcidin expression nor in terms of time course or risk factors of ID development. In case of COPD and T2DM, there is lack of data proposing mechanism and indicating the time course of ID development.

Iron deficiency as a potential cause of impaired skeletal muscle energetics in chronic diseases

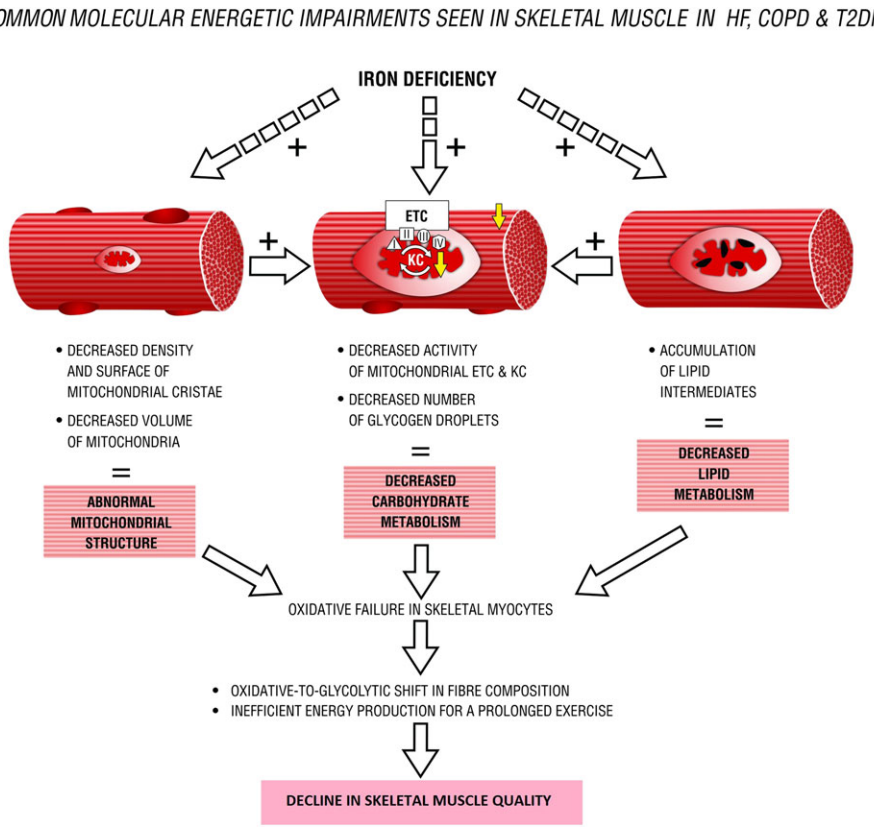
According to the so-called muscle hypothesis, abnormalities occurring in structure and functioning of skeletal muscles include significant metabolic derangements and are to be directly responsible for impaired exercise capacity in patients with HF.[148] Similar intrinsic metabolic alterations within skeletal muscle with possible important impact on exercise capacity are observed in COPD and T2DM [see above]. Physiologically, metaboreceptors (the kind of muscle afferents) are stimulated by products of skeletal muscle work, which in turn inform the brain stem on the level of muscle activity. The response to such metaboreflex involves sympathetic activation and consequent ventilatory, haemodynamic, and physiological adaptations to meet the muscle nutritional requirements.[149–151] Abnormally large metaboreceptor response, however, contributes to the experience of dyspnoea and leads to the disordered exercise physiology. Such phenomenon has already been demonstrated in HF,[152,153] and it has been postulated in COPD[154] where it needs further in-depth investigation. Although the excessive activation of ergoreceptors has not been evaluated in T2DM, its contribution to exercise intolerance may be hypothesized as skeletal muscle in diabetes has the oxidative capacity limited with the accumulation of anaerobic metabolites.

It is worth noting that ID has been postulated as an important causative factor that can significantly contribute to the loss of skeletal muscle oxidative capacity seen in patients with HF, COPD, or T2DM.[11] Therefore, it is possible that ID exerts its detrimental effects by limiting the oxidative metabolism and consequent accumulation of anaerobic metabolites, which in turn contributes to the exaggerated ergoreflex response, thus to exercise limitation. Skeletal myopathy that occurs in response to ID and resultant energetic impasse may constitute a potential pathophysiological link between disturbed iron status and diminished exercise capacity in patients with aforementioned chronic diseases. It is worth noting that ID predominantly damages skeletal muscle energetics, which is reported to be disturbed at similar points in certain chronic syndromes (*Figure* 3). However, there is still a lack of direct experimental or clinical evidence to support this hypothesis.

To date, mechanistic studies on ID and resultant decreased exercise performance have been performed predominantly in animal models, while data regarding the relationship between ID and skeletal muscle dysfunction in iron-deficient anaemic human subjects are limited and inconsistent (for a detailed review, see Stugiewicz *et al*.[16]). With regard to oxidative capacity, although there is lack of mechanistic studies investigating the effects of iron supplementation on skeletal muscle energetics, clinical findings show that iron administration to iron-deficient both untrained subjects and athletes improves muscle energetic efficiency.[155,156] Therefore, further studies are needed to establish the pathophysiological links between ID and skeletal muscle dysfunction observed in HF, COPD, and T2DM, to step forward in co-targeting of muscle abnormalities in a therapeutic process.

DOI: 10.1002/jcsm.12314

Figure 3 Common molecular energetic impairments seen in skeletal muscle in heart failure (HF), chronic obstructive pulmonary disease (COPD), and type 2 diabetes mellitus (T2DM). ETC, electron transport chain; KC, Krebs cycle; I–IV, mitochondrial enzymatic complexes.



Iron therapy in chronic diseases

It is worth noting that to date iron therapy has already been tested in anaemic and/or iron-deficient patients. Particularly, i.v. iron replacement, as compared with oral iron or inactive controls, is reported to be effective in improving both haemoglobin levels together with reduction in blood transfusion rates and quality of life in anaemic adults without CKD.[157]With regard to iron-deficient patients with HF, irrespective of concomitant anaemia, i.v. iron is associated with an improvement in exercise capacity, clinical status, quality of life, and significant reduction in the risk of hospitalizations for worsening HF.[158,159] Based on two clinical trials (FAIR-HF and CONFIRM-HF), i.v. ferric carboxymaltose has been recommended for treatment of ID in symptomatic patients with HF and left ventricular ejection fraction $<45\%$.[159–161] Importantly, in acutely decompensated HF, ID has been also recognized as a highly prevalent comorbidity that should be monitored (especially regarding not stationary character of iron status in those patients) and managed.[162] Considering other therapeutic approaches, because myocardium of HF patients has decreased iron content, which may significantly contribute to the existing mitochondrial dysfunction,[163] novel myocardial-targeted therapies should be designed and developed. In case of COPD, data on iron therapy are limited.[164] In a small retrospective study, i.v. iron together with erythropoiesis-stimulating agents has been reported to improve anaemia and ID and that has been associated with a significant improvement in self-assessed shortness of breath.[164] Regarding T2DM, in the ongoing clinical trial, i.v. iron is tested in the context of metabolic status and quality of life in iron-deficient patients with T2DM.[140] Apparently, iron therapy has been investigated more deeply in HF patients, and there is a need of more in-depth studies on iron replacement in other diseases, such as COPD or T2DM.

Of note, several current therapeutic strategies aim to target muscle mitochondrial energetics in order to enhance metabolic efficiency, and an optimal iron supply may play an important role in an adequate response to such attempts. For example, the utilization of trimetazidine as a metabolic modulator that acts by re-programming muscle metabolism towards the enhanced glucose oxidative catabolism has been tested in animal models.[165,166] Importantly, the aforementioned agent is reported to induce a fast-to-slow shift in fibre composition and to restore oxidative phenotype of muscle.[165,166] Similarly, another muscle-targeted compound, namely, acylated-ghrelin, is proposed to normalize mitochondrial oxidative capacity.[167] Thus, both

DOI: 10.1002/jcsm.12314

the two molecules mentioned earlier are meant to increase muscle oxidative capacity, which in turn is crucially dependent on optimal iron availability. In case of other experimental attempt, Inoue *et al*. has reported beneficial effects of exercise train on ageing mice skeletal muscle in the context of improvement metabolic and mitochondrial impairments.[168] Taking into consideration the fundamental role of iron in both exercise capacity[16] and mitochondrial functioning, it may be hypothesized that undisturbed iron metabolism may be of particular importance for the adequate response to the therapy.

Conclusions

Evidence gathered from animal and *in vitro* studies indicates that ID damages skeletal muscle energetics at different levels. Skeletal muscle dysfunction causally linked to the impaired cellular energy metabolism has been recognized as an important pathophysiological feature in chronic diseases, such as HF, COPD, and T2DM. Although the unfavourable influence of ID on the energy metabolism has been postulated in the syndromes mentioned earlier, the hypothesis of whether abnormal iron homoeostasis contributes to the skeletal muscle derangements still needs to be verified. Therefore, further studies are indispensable to investigate the clinical correlations between ID and skeletal muscle dysfunction in chronic diseases.

Acknowledgements

This research was financially supported by the National Science Centre (Kraków, Poland) grant allocated on the basis of the decision number DEC-2012/05/E/NZ5/00590. The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle.[169]

Conflict of interest

Wrocław Medical University received an unrestricted grant from Vifor Pharma outside the submitted work. M.K. reports financial support from Vifor Pharma for travel and accommodation for scientific meeting. W.B. reports personal fees from Vifor Pharma, outside the submitted work. P.P. reports personal fees from Vifor Pharma, personal fees from AMGEN, outside the submitted work. E.A.J. reports personal fees from Vifor Pharma and FRESENIUS, outside the submitted work. All the other authors report no conflict of interest related to the content of this manuscript.

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