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**Review**

## Drug-induced myopathies. An overview of the possible mechanisms

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**Abstract:**

Myopathy is usually a non-fatal muscle disease involving skeletal muscle weakness, tenderness and pain with the possibility of the plasma creatinine kinase elevation. There are many different types of myopathies, some of which are genetic, inflammatory, or related to endocrine dysfunction. Also, numerous drugs have been reported to possess myotoxic effect. Myopathy is included among the potential side-effects and toxicities associated with the lipid lowering agents, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. However, the precise mechanism of statin-induced muscle toxicity remains unclear. The muscle-related side-effects reported with lipid-lowering drugs are significant but quite rare (0.1%), when used in monotherapy; while the incidence of steroid-induced myopathy has varied from 7 to 60% and chronic alcoholic myopathy seems to be common complication of alcoholism affecting approximately 50% of patients, respectively.

This review focuses on the differential pathophysiological grounds of these muscular injuries induced by statins, fibrates, as well as some other agents: corticosteroids or alcohol. A wide spectrum of possible mechanisms and hypotheses including muscle enzyme defects, changes in mitochondrial function and intracellular metabolism, the influence on the cell membrane stability and drug interactions involving P-glycoprotein or cytochrome P 450 system have been presented.

**Key words:**

myopathy, mechanism, ethanol, corticosteroids, HMG-CoA reductase inhibitors

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Myopathy, usually a non-fatal muscle disease, involves skeletal muscle weakness, tenderness and pain with the possibility of the plasma creatinine kinase (CK) elevation. There are many different types of myopathies, some of which are genetic, inflammatory, or related to endocrine dysfunction. Also numerous drugs have been reported to possess myotoxic activity. Skeletal muscle accounting for around 45% of total body weight and characterized by high metabolic rate and blood flow, are highly exposed to circulating drugs (13–98% binding ability) [22]. Thus, cases of drug-induced myotoxicity may appear, usually as a consequence of high plasma drug concentration and their

direct toxic effect on skeletal muscles. These effects may be classified as muscle diseases caused by drugs and toxins affecting the muscle endplate and neuromuscular transmission, involving acute myopathy in the critically ill intensive care patients, as well as drug-induced chronic myopathy [74].

A lot of medications have been reported to affect neuromuscular transmission. D-penicillamine induces a variety of antibodies, especially anti-AchR (acetylcholine receptor) antibody which results in immune system-mediated complications including polymyositis, systemic lupus erythematosus, nephritis, scleroderma and iatrogenic myasthenia gravis [57, 76].

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Moreover, at high doses, it impairs neuromuscular transmission by inhibiting release of Ach and blocking calcium entry at the motor nerve terminal, especially if given parenterally. Magnesium may intensify the action of neuromuscular blocking agents too. Moreover, the impaired Ach release is described to be a pathogenic background of botulism. *Botulinum* toxin blocks Ach release at the presynaptic motor nerve terminals [15]. Another factor, chloroquine, widely used for the treatment of malaria as well as rheumatoid disorders, may be responsible for many neurological complications, such as peripheral neuropathy, myopathy and neuromuscular transmission disturbances. Additionally, chloroquine has been reported to reduce the muscle membrane excitability directly and induce autoimmune disorder. Its mechanism involves impairment of the miniature endplate potential amplitude at presynaptic level. Other medicaments, including aminoglycoside antibiotics, quinine, quinidine and high doses of corticosteroids may also exacerbate neuromuscular transmission impairment, including preexisting myasthenia gravis [74].

However, this review focuses on the muscular injuries classified as drug-induced myopathies, considering a spectrum of the possible mechanisms and indicating some similarities or differences between separate pathophysiological factors responsible for them.

### Alcoholic myopathies

Alcohol consumption is associated with injuries of many organs, including liver, lungs, heart as well as skeletal muscles [62], as a result of the numerous morphological, biochemical and functional changes in the above tissues. The extent and severity of the myotoxic symptoms tend to be proportional to the quantity of alcohol consumed.

Alcoholic skeletal muscle myopathy has been subdivided into two different forms. Acute alcoholic myopathy is a rare condition affecting approximately 1% of alcoholics and is characterized by myalgias, weakness, very high CK levels, frequent renal impairment with myoglobinuria and rhabdomyolysis implicating morbidity and mortality [38]. Muscle biopsy reveals acute muscle necrosis, varying degrees of inflammatory infiltrate and polymyositis affecting both red and white muscles fibers [34, 53]. However, it is worth noting that the above symptoms usually normalize after withdrawal and under general medical support.

On the contrary, chronic alcohol ingestion (> 100 g/d, > 10 y) occurs in approximately 45 to 75% of alcoholics [80, 81]. It leads to progressive proximal weakness and muscle atrophy involving legs and arms and is characterized by decreased muscle strength, normal or slightly elevated CK level. Chronic alcohol myopathy is not associated with extensive muscle necrosis. Moreover, it is worth noting that, opposite to acute myopathy, type II b fibers (anaerobic, glycolytic, fast-twitch) are mainly affected, whereas type I – aerobic, slow-twitch fibers are relatively resistant [35]. These effects of chronic alcohol intoxication appear to be long-term. Stabilization requires alcohol discontinuation or maintained low-dose “controlled drinking” condition [25], however, the muscle strength recovery may be incomplete [21].

The etiology of the alcoholic myopathy is multifactorial, including protein content disturbances related to the possible role of acetaldehyde, decreased both, amino acid availability and insulin-like growth factor (IGF-I) concentration, as well as free radical-induced protein membrane damage. Nearly one half of all proteins in the body can be found in skeletal muscle. About 70–80% of them, as myofibrillar and sarcoplasmic proteins constitute a part of the contractile apparatus, making possible mechanical and locomotor activity, as well as supporting the systemic metabolic requirements of the body. The tissue protein content is maintained by a dynamic balance of protein synthesis and degradation processes. It has been demonstrated that alcoholic myopathy, especially acute one, was related to significant decline of protein synthesis rate, even by 30–40%, affecting both types of muscle fibers (I and II) [52, 86, 103], as well as non-myofibrillar (sarcoplasmic) proteins [50]. Moreover, the decreased contribution to whole body protein synthesis (from 27 to 15%) in chronic alcoholics has been reported [80]. However, the mechanisms explaining the development of myopathy due to disturbances of the cell protein contents have still remained unresolved.

One of the hypotheses is based on the role of acetaldehyde-induced protein synthesis inhibition, as demonstrated in the myocardium model. It is worth noting that acetaldehyde has been shown to inhibit cardiac protein synthesis [94], in opposition to acetate, another ethanol metabolite released into the systemic circulation [53]. Similar studies have demonstrated that even low doses of acetaldehyde acutely reduced protein synthesis in skeletal muscles, too.

Moreover, it has been indicated that the above effect was independent of the ethanol inhibiting activity.

Potential mechanism may involve ethanol-related mitochondrial dysfunction with impairment of both oxygen consumption and ATP production process. As a result of this, there is a decrease in the myocyte energy charge [39] and this is supposed to be responsible for reduction of protein synthesis rate. These processes may lead to energy generation or utilization deficiencies, reduced fatty acid oxidation, enhanced accumulation of triglycerides [11] and contractile depression, respectively [77]. However, the definite role of acetaldehyde has not been confirmed; ultrastructural changes in cardiac mitochondria, observed following acute and chronic alcohol ingestion, have not corresponded with significant depression of myocardial oxygen consumption [39, 53]. Acetaldehyde may also form addition products with proteins [79], in the muscle membrane as well as subsarcolemmal regions of type I and II fibers [111]. These adducts are probably responsible for modifying the structure and conformation of cardiac proteins involved in polypeptide formation. However, any differences with respect to ATP or creatinine phosphate have not been detected in skeletal muscle, suggesting that acetaldehyde adducts have no influence on mitochondrial oxidative damage.

Ethanol-induced protein content disturbances are also supposed to be mediated by IGF-I factor. Insulin is a potent anabolic hormone, capable of stimulating protein synthesis in striated muscles. Thus, IGF-I, as a mediator and/or hormone stimulating synthesis of proteins, modulates striated muscle metabolism [112]. Moreover, IGF is believed to play antiapoptotic role in myocytes as well as trophic role during differentiation of myoblasts into myotubes [99]. Therefore, inhibition of IGF-I activity may result in several muscle dysfunctions and myopathic changes. Animal studies have confirmed this, *viz.* they have demonstrated significant ethanol-induced decline in IGF-I factor content in skeletal muscles (type II b). Additionally, the observed decrease appeared to be linearly proportional to the reduction of the IGF-I mRNA expression [50, 100], indicating that ethanol diminished IGF-I translation efficiency. However, the acute ethanol administration resulted in the decrease in muscle IGF-1 mRNA expression, while chronic exposure led to the reduced plasma peptide concentration, too [51].

The impairment of protein synthesis, resulting from acute and chronic ethanol intoxication, is also supposed to be associated with the increase in

IGFBPs (IGF binding proteins) level [28]. These proteins (phosphorylated or non-phosphorylated) inhibit IGF-I-induced protein synthesis, through IGF-I receptor, and prevent IGF-I-stimulated glucose uptake in myoblasts. However, the mechanisms linking ethanol consumption with the increased IGFBPs as well as IGF-I level have still remained unclear. One of the hypotheses underlines that ethanol increases the level of some cytokines: TNF- $\alpha$ , IL-1, IL-6, which have been described to antagonize IGF-1 factor and impair the muscle protein synthesis [18]. As mentioned above, insulin stimulates protein synthesis, that is why it is suggested to be taken into account as a factor contributing to ethanol-induced myopathy. However, the performed studies have not demonstrated the decrease in insulin plasma level after both acute and chronic ethanol administration. Other authors suppose that acute alcohol intoxication may produce insulin resistance in skeletal muscle *via* the insulin signal transduction pathway impairment [101, 112]. This may explain the role of insulin in protein synthesis disturbances and myopathy.

Amino acids play an important role in modulating muscle protein balance, for example, leucine stimulates peptide-chain initiation. Disturbances of glutamine as well as leucine are supposed to be related to pathogenesis of corticosteroid-induced myopathy. However, the plasma level of total amino acids as well as leucine, glutamine or branched-chain amino acids have not been decreased by ethanol intoxication [1], indicating that amino acid availability does not appear to limit muscle protein synthesis.

Another possible pathogenetic pathway implicated in alcohol intoxication involves free radical-mediated muscle damage [78]. Reactive oxygen species (ROS) have been supposed to be associated with the decrease in cardiac CK activity in acute ethanol intoxication. On the other hand, excitation-coupling changes [37], as well as conformational changes of contractile cardiac proteins [88], are linked to free radicals-induced reduction of calcium uptake rate in sarcoplasmic reticulum (SR). It is supposed that free radicals may influence changes in skeletal muscles, too. As a direct evidence of oxidative stress, the increased protein carbonyl group concentration or formation of malondialdehyde (MDA) protein adducts have been shown to induce myopathic changes in myocytes, especially of type II fibers [47, 68].

Also, as a consequence of oxidative stress, alcohol has been demonstrated to increase the concentration of the membrane-bound hydroperoxides:  $7\alpha$ -hydroper-

oxycholest-5-en-3 $\beta$ -ol (7 $\alpha$ -OOH) and 7 $\beta$ -hydroperoxycholest-5-en-3 $\beta$ -ol (7 $\beta$ -OOH). This may be related to perturbations in membrane lipids, such as defective functional activity of sarcolemma, significant increase in C18:2 fatty acids and concomitant decrease in non essential/essential fatty acid ratio [2]. Also disturbances of the myocyte membrane-associated muscle proteins have been supposed to influence the ethanol-induced myotoxicity. One of them, sarcolemmal protein dystrophin, has been decreased as a possible free radical-mediated response to ethanol intoxication. The impact of free radicals confirms that antioxidant status may also play an important role in the development of myopathic changes. For example, reduced activity of serum carnosinase, the enzyme which catalyzes the hydrolysis of an important antioxidant, carnosine, has been detected in myopathic alcoholics [19]. Additionally, it has been indicated that the inverse relationship between the concentrations of muscle antioxidants (i.e.  $\alpha$ -tocopherol) [77, 109] and the degree of susceptibility to ethanol might exist. Conversely, other studies have demonstrated that both, serum and skeletal muscle levels of  $\alpha$ -tocopherol had no influence on the presence of skeletal myopathy in chronic alcoholic patients [26]. Moreover,  $\alpha$ -tocopherol supplementation produced no improvement in myopathic injuries [93]. Thus, estimation of significance of the antioxidant status in ethanol-induced myopathy still requires further findings.

Alcohol-induced muscle membrane disturbances may also involve electrolyte homeostasis impairment. Membranes from alcohol-exposed muscle have shown impaired calcium uptake and release [16, 67], and also Na<sup>+</sup>/K<sup>+</sup> ATPase activities were defective [54].

Another important factor in pathogenic background of myopathic changes is Ca<sup>2+</sup>-mediated signaling. Ca<sup>2+</sup> plays a signaling role in such cellular functions as contractions, secretion, fertilization, proliferation or metabolism and regulates excitation-contraction coupling in skeletal muscle fibers. The prolonged elevation of Ca<sup>2+</sup> is deleterious to a cell; Ca<sup>2+</sup> precipitates phosphates and organic acids at high concentration. Moreover, it may activate apoptosis by triggering the opening of mitochondrial permeability transition pores, which destroys the energy balance of the cell. This has been confirmed to be connected with the release of cytochrome C, a proapoptotic protein, that activates cellular proteases (i.e. caspases) [31]. Key proteins in the regulation of muscle Ca<sup>2+</sup> form the voltage-dependent dihydropyridine sensi-

tive, slow or L-type Ca<sup>2+</sup> channels (DHPRs) and Ca<sup>2+</sup> release channels in SR (ryanodine receptors – RyRs) that elevate sarcoplasmic Ca<sup>2+</sup>. Others, particularly Ca<sup>2+</sup>ATPases (SERCAs), return sarcoplasmic Ca<sup>2+</sup> to SR, while plasma membrane Ca<sup>2+</sup> ATPases (PMCA), Na<sup>+</sup>/Ca<sup>2+</sup> exchange eject Ca<sup>2+</sup> from the cell [9]. In the cardiac muscle, SERCA activity is regulated by phospholamban, while in skeletal muscles, it is controlled by sarcopilin. Calmodulin, acidic phospholipids and phosphorylation regulate PMCA activity [10] and calsequestrin, and calreticulin provide a buffer for Ca<sup>2+</sup> stored in SR [56]. The impaired function of the Ca<sup>2+</sup> signaling has already been associated with several muscle diseases, including genetic disorders. Abnormalities in the skeletal muscle Ca<sup>2+</sup> release channel – RyR1, play a key role in halothane-induced malignant hyperthermia. Also central core disease and skeletal myopathy may develop from anesthetic-induced Ca<sup>2+</sup> elevation *via* RyR1 [56, 85, 113]. Additionally, abnormalities in DHPR1 are linked to malignant hyperthermia; impaired phospholamban function may contribute to cardiac contractility disturbances and possibly cardiomyopathies, similarly to calsequestrin [63, 69].

The decrease in Ca<sup>2+</sup>ATP-ase activity or protein level is associated with many different conditions, such as ischemia [106], heart failure [95], exhausting exercise [61], skeletal muscle denervation [90]. Moreover, the increased Ca<sup>2+</sup> release from SR results from doxorubicin intoxication and also leads to skeletal or cardiac muscle cytotoxicity [44]. Similarly, the elevated cytosolic Ca<sup>2+</sup> concentration resulting from the decreased luminal Ca<sup>2+</sup> ATPase activity (SERCA1) is supposed to be responsible for statin-induced skeletal myopathies [5]. Also, the reduced plasma membrane Ca<sup>2+</sup>ATPase activity due to ethanol intoxication has been observed in hepatocytes, erythrocytes and neutrophils [4, 72]. On the contrary, similar changes have not been detected in skeletal muscles [70]. It is also supposed that the increase in SERCA1 activity in chronic ethanol ingestion may result from the specific process of tolerance or adaptation. Similarly, it would explain no leakage of the muscle CK related to chronic ethanol intoxication in contrast to acute one [70].

### Corticosteroid myopathy

High dose of glucocorticoids may induce significant myopathy, with loss of the thick myofilament from

the muscle. The incidence of steroid myopathy has varied from 7 to 60% and oppositely to alcohol intoxication, no relationship between the duration or dose and occurrence of myopathy has been observed [6]. Short-term high-dose steroid administration (e.g. in exacerbation in asthmatics) may lead to the development of acute steroid myopathy. Similarly to acute ethanol intoxication, pathological features include diffuse muscle weakness, generalized fiber atrophy or focal/diffuse necrosis, with CK elevation and rhabdomyolysis [32, 89]. The respiratory muscle may also be affected. Recovery appears to be a long-term process [46, 107]. Chronic treatment with glucocorticoid produces a classic pattern of skeletal muscle injury called "steroid myopathy", with proximal weakness, atrophy and myalgia. Similarly to chronic alcohol myopathy, normal or slightly increased serum muscle enzymes, with CK level and predominant part of type II fibers affected (high glycolytic and low oxidative activity) [24, 89]. Muscle biopsy tends to reveal non-specific histological changes including variation of the fiber size and centralization of the nuclei without, evidence of inflammation and occasional random necrosis, possible in alcohol myopathy. The management of steroid myopathy also includes discontinuation of steroid administration. The recovery may take weeks or months [24]. Steroid myopathy usually develops from more potent fluorinated steroids (dexamethasone, betamethasone, triamcinolone), however, the cases of non-fluorinated steroid (prednisolone, hydrocortisone)-induced myopathy have also been observed [24].

The studies conducted so far have indicated that also steroid myopathies are characterized by multifactorial pathogenetic background, which mainly involves protein content disturbances and glycogen accumulation. Glucocorticosteroids inhibit protein synthesis, primarily in type II muscle fibers, as demonstrated in ethanol myopathies, too [43]. The main inhibitory mechanism includes the impaired regulation of the activity of factors involved in peptide initiation. It is worth noting that also alcohol may impair protein synthesis by reducing the translational efficiency, especially the initiation process. This is associated with the decrease in the level of the cap binding protein, an eukaryotic initiation factor eIF4E which controls the binding of mRNA to the 43 S pre-initiation complex [51]. The ethanol-induced protein disturbances, may result from the decrease in protein synthesis *via* inhibition of IGF-I activity. Also, steroids are supposed to inhibit antiapoptotic effects of

IGF-I by reducing its expression [29, 99]. This pathway could be one of the mechanisms of toxic steroid myopathy, especially because additive or synergistic effects of IGF-I inhibition due to multiple metabolic stressors contribute to severe protein catabolism and muscle apoptosis observed in acute myopathy [98].

Moreover, glucocorticosteroids increase the cytoplasmic protease activity in muscles, leading to myofibrillar destruction. However, the enhancement of intracellular proteolysis, as well as disturbances in amino acid contents due to ethanol intoxication are still discussed. Paradoxically, studies in myopathic alcoholics have demonstrated the decreased level of an urinary marker of contractile protein degradation, suggesting that alcohol might inhibit proteases [53].

It is supposed that glutamine synthetase activity plays a key role in the development of steroid-induced muscle atrophy. Glutamine synthetase is a key enzyme in the mechanism by which skeletal muscle requires the systemic demand for amino acid carbon. It catalyzes the formation of glutamine from glutamate and ammonia [40]. Under catabolic conditions, glutamine and other amino acids are liberated from skeletal muscles. The amino acid carbon, *via* tricarboxylic acid cycle intermediates, is then used to synthesize glucose in the liver, whereas in other tissues, including small intestine and kidney, glutamine is used directly to provide energy [40]. The excess of circulating glucocorticoids results in the decrease in muscle protein synthesis with the reduced intramuscular glutamine level. This leads to the enhanced glutamine synthetase activity in skeletal muscles which releases glutamine at high rate [60], resulting from the intensified proteolysis process [23, 92]. The pathogenic role of glutamine synthetase has also been confirmed in studies showing that glutamine supplementation antagonized effectively the glucocorticoid-mediated muscle atrophy [40]. Moreover, previous studies have demonstrated that, under catabolic condition, the steroid-enhanced glutamine synthetase activity in skeletal myocytes was decreased by IGF-I factor, [73].

Additionally, in steroid myopathy, a significant decrease in the glycogen phosphorylase activities has been observed and this effect was more prominent in type II fibers [24]. The elevated muscle glycogen concentration is supposed to be associated with muscular atrophy and weakness. However, no correlation between muscle glycogen metabolism and histological, myopathic changes have been confirmed, thus, it is

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still unclear if this is a reason or biochemical consequence of steroid myopathy [24].

### Lipid lowering drug-associated myopathy

(HMG-CoA) reductase inhibitor-associated muscle toxicity is a quite rare (0.1%) but serious adverse event, including myotoxic effects with the variety of symptoms and severity. The most frequent adverse reaction is myalgia accounting for up to 25% of all adverse reactions, it demonstrates diffuse muscle pain, tenderness and weakness, with a normal CK level. Muscle biopsies tend to reveal mitochondrial dysfunction, increased lipid storage and ragged red muscle fibers [5, 22, 102].

Typical statin-induced myopathy is characterized by muscle pain, tenderness, weakness with an elevated (> 10 times) CK level. The above symptoms predominantly involve proximal muscles. Muscle biopsy demonstrates inflammatory cell infiltration and immunological cell activity. It is worth noting that the incidences of statin-associated myopathy have also been described in patients with a normal CK level. Thus, it has recently been suggested that serum CK level may be an adequate test for this type of myotoxicity [75].

Similarly to ethanol- or steroid-induced acute myopathy, the incidence of rhabdomyolysis (2–5% muscular adverse events), with severe muscle destruction, myoglobinuria, resulting, if untreated, in electrolyte disturbances, acidosis, acute renal failure, arrhythmias, cardiac failure and death. Histopathological findings demonstrated then characteristic changes in muscle cells: loss of cross-striations and nuclei, partial regeneration, but without inflammatory cell infiltration [102].

Several mechanisms are supposed to contribute to pathogenesis of statin-induced muscle injuries, and inhibition of (HMG-CoA) reductase pathway seems to be one of them. Impairment of protein synthesis, a crucial factor for the development of steroid- or ethanol-induced myopathy, is also supposed to contribute to statin myotoxic effect. This effect probably results from the blockade of farnesyl pyrophosphate production, geranylgeranyl pyrophosphate and their metabolites, but not inhibition of squalene or cholesterol synthesis pathway. The above hypothesis has been confirmed in studies demonstrating that inhibition of protein synthesis and loss of differentiated myotubes in neonatal rat skeletal muscle was reversed after far-

nesol and geranylgeraniol but not squalene supplementation [27]. This may be explained by farnesol and geranylgeraniol contribution to activating regulatory proteins: small GTP-binding proteins (i.e. Ras, Rac, Rho) which promote cell maintenance and growth, attenuating apoptosis process [55, 71]. As a result, statin-induced (HMG-CoA) reductase inhibition is supposed to trigger skeletal myocyte apoptosis and myopathy development. Conversely, the dose-dependent increase in apoptosis due to statin therapy is observed in vascular smooth muscle cells (VSMCs), showing pleiotropic activity of statins [33]. Thus, it is possible that the same mechanism is involved in inhibition of VSMCs proliferation and apoptotic cell death in muscle fibers [59].

It has been suggested that coenzyme Q10, an essential cofactor of the electron transport, as well as important antioxidant in mitochondria and lipid membranes, may also contribute to the pathogenic background of statin-associated myopathy. Studies performed *in vitro* have confirmed that statin-induced apoptosis has been inhibited by coenzyme Q10 [42]. Also, the efficacy of the coenzyme Q10 supplementation in ameliorating the clinical symptoms of statin-associated myopathy has been described [13]. Some laboratory investigations revealed the decrease in muscle as well as serum coenzyme Q10 concentration after statin therapy [5]. The other ones, paradoxically have demonstrated the increase in coenzyme Q10 concentration after treatment with (HMG-CoA) reductase inhibitors [48]. Thus, the exact relationship between long-term statin therapy and secondary ubiquinone deficiency seems to require further investigations.

Similarly to ethanol intoxication, statin therapy may impair the stability of the skeletal muscle cell membrane leading to the decrease in the cell proliferation [64, 102]. This is associated with reduction of cholesterol synthesis, while ethanol tends to induce oxidative stress with formation of cholesterol-derived hydroperoxides. The statin-induced reduction in myocyte cholesterol may account for up to 60% of total content [64].

Also, similarly to ethanol, statins have been reported to affect skeletal muscle membrane physiology impairing  $\text{Na}^+/\text{K}^+$  ATPase,  $\text{Na}^+/\text{Ca}^{2+}$ , as well as  $\text{Na}^+/\text{Ca}^{2+}$  ATPase pump activity, which may also result in development of myotoxicity [66]. Lovastatin, through mechanism unrelated to membrane cholesterol, decreases sarcolemmal  $\text{Na}^+/\text{K}^+$  ATPase pump

density in skeletal and cardiac muscle, leading to increased sarcoplasmic  $\text{Na}^+$  concentration, which possibly could invoke  $\text{Ca}^{2+}$  influx *via*  $\text{Na}^+/\text{Ca}^{2+}$  antiport and, finally, the increase in sarcoplasmic  $\text{Ca}^{2+}$  concentration [30]. Similarly, simvastatin may inhibit the  $\text{Na}^+/\text{H}^+$  antiport [45], which induces extracellular  $\text{Ca}^{2+}$  influx. Another possible mechanism, responsible for the elevated sarcoplasmic  $\text{Ca}^{2+}$  concentration and myofibre necrosis/apoptosis, may involve an increase in SR  $\text{Ca}^{2+}$  release or decrease in SR  $\text{Ca}^{2+}$  ATPase (SERCA) activity. However, the exact correlation between SERCA activity and statin-induced myopathy has not yet been estimated. Conversely, it has been reported that significant increase in cytosolic  $\text{Ca}^{2+}$  concentration may also result from simvastatin-mediated reduction of the mechanical threshold of rat skeletal muscles, due to their dose-dependent action on resting potential [5]. Moreover, it was supposed that simvastatin decreased chloride conductance, destabilizing membrane electrical potential and increasing susceptibility to myotonic afterdepolarizations, which may also result in elevation of cytoplasmic  $\text{Ca}^{2+}$  concentration. It is important to underline that the above mechanisms are independent of statin HMG-CoA reductase inhibitory activity, and neither mevalonic acid nor cholesterol supplementation could abolish these effects. However, further studies assessing the pathogenic role of the impaired cell conductance and statin-related myopathy are needed.

The risk of statin-induced myotoxicity increases significantly in combination therapy. Such drug interactions have been attributed to inhibition of cytochrome P-450 system. It has been well documented that the risk of myopathy could increase with concomitant administration of other medicaments inhibiting CYP3A4 of cytochrome P-450 (i.e. macrolide antibiotics, azole antifungals, cyclosporine), resulting in the elevated concentration of statins metabolized *via* this isoenzyme (i.e. lovastatin, atorvastatin and simvastatin) [41]. Additionally, the mechanisms other than CYP3A4 inhibition may be responsible for adverse reactions developing due to statin-drug interactions. Passage through the muscle cell depends on the statin solubility. Lipophilic statins are transported by passive diffusion, however, hydrophilic HMG-CoA reductase inhibitors (i.e. pravastatin) tend to require such proteins as the multidrug resistance protein 2 (MRP2). Thus, the elevated hydrophilic statin serum level associated with the increased risk of myopathy is supposed to result from treatment with MRP2 inhi-

bition [102]. The above mechanism may contribute to muscle injury developing as a result of interaction between CYP 3A4 inhibitor cyclosporine and pravastatin, a hydrophilic agent, which is not metabolized *via* P450 system [7, 8]. Recently, other glycoprotein P inhibitors: itraconazole, diltiazem and mibefradil, have been shown to trigger the statin-associated myotoxicity [7].

Pathogenic background of statin- and other drug-induced myopathy has also been suggested to involve the inhibition of glucuronidation pathway. Glucuronidation constitutes a common metabolic pathway for statin biotransformation, in addition to other pathways including P-450-mediated oxidation or  $\beta$ -oxidation processes [83, 84]. It plays an important role in mediating the process of statin lactonization [83]. The statin acids are supposed to be metabolized to unstable acyl glucuronide intermediates, which subsequently are rapidly and spontaneously converted to the corresponding inactive lactones [83]. It is worth noting that the above process may be taken into account in assessing gemfibrozil-statin interaction. Gemfibrozil has been suggested to increase the risk of muscle disorders resulting from the elevated active statin acid form by inhibiting the above described glucuronidation pathway [91, 108]. Another gemfibrozil-mediated pathway, contributing to an increase in both statin concentrations and risk of skeletal muscle injury, involves the inhibition of CYP2C8 activity [108]. This isoenzyme participates in the metabolism of cerivastatin and this seems to explain more significant gemfibrozil-induced elevation of cerivastatin than simvastatin concentration [83]. Other fibrates, such as fenofibrate, have been demonstrated to possess little effect on the glucuronidation process, and poor potential to inhibit CYP3A4 isoenzyme [82]. Thus, interaction between statin and other fibrates is suggested to be pharmacodynamic, especially as fibrates also have been reported to induce skeletal muscle myopathy. The mechanism of fibrate-induced skeletal muscle injuries involves the activation of pyruvate dehydrogenase kinase 4 (PDK4). As a result, bezafibrate, clofibrate and ciprofibrate inactivate pyruvate dehydrogenase complex (PDC) which catalyzes irreversible decarboxylation of pyruvate to acetyl-CoA. It limits oxidation of glucose and three-carbon compounds and enhances fatty acid oxidation. Thus, PDK4 activation which is marked in the liver as well as skeletal muscle tissue, leads to enhanced fatty acid utilization [65]. The fibrate-associated decrease in availability of triglycerides and fatty acids may re-

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sult in the elevated usage of amino acids from proteins as an energy source and elevated protein degradation. The above process is probably responsible for subsequent myopathy, as well as rhabdomyolysis [59, 110].

### Zidovudine-induced myopathy

It has recently been reported that also zidovudine (ZDV), more commonly known as 3-azido-3'-deoxythymidine (AZT), the principal anti-retroviral agent used in the treatment of HIV-positive patients, was associated with skeletal and cardiac muscle pathologies. Some ZDV-treated AIDS patients, particularly those on long-term ZDV therapy, complained of proximal muscle weakness, fatigue, myalgia and experienced elevated blood levels of creatine phosphokinase, a response indicative of muscle overuse or damage [20, 87, 104]. The amelioration of these symptoms tended to coincide with removal of ZDV therapy [12, 17, 36, 104, 105]. Biopsies usually reveal the presence of ragged red fibers with structurally abnormal mitochondria [17, 49, 87].

The *in vitro* studies have demonstrated that the possible mechanism of ZDV-associated myopathy may involve the impairment of skeletal muscle mitochondria *via* a mechanism similar to its anti-retroviral effect. AZT, as a substrate for DNA polymerase gamma, is responsible for catalyzing the replication of mitochondrial DNA (mtDNA), disturbances of which may be related to drug myotoxicity [97]. However, the precise nature of the ZDV-associated myopathy has not been well defined yet. There is no clear relationship between the duration of ZDV therapy [3], the dose given, and the severity of the myopathy [17]. The present findings have shown two mechanisms of AZT-induced mitochondrial damage. A short-term mechanism involves impairments of respiratory chain, while long-term treatment leads to mitochondrial protein synthesis disturbances, crucial for development of alcohol- or steroid-induced myopathies [58]. Also, the pathogenic background may involve cytochrome C oxidase deficiency [14]. It is worth noting that there have been difficulties in separating the effects of the disease process on skeletal muscle *vs.* those effects due to drug treatment in HIV patients. Thus, it has also been concluded that the myotoxicity was due to HIV rather than ZDV or that ZDV may exaggerate the overt expression of inflammatory-type myopathies [17, 96]. Animal studies have confirmed

this hypothesis, that ZDV-related myopathies observed in AIDS patients might be due to interactions between the drug and complications associated with HIV infection. No ultrastructural abnormalities in animal cardiac or skeletal muscle developed after chronic AZT treatment. Additionally, animal data have shown the significant increase in cytochrome oxidase activity in ZDV group [20]. Moreover, the incidents of statin- and ZDV-related rhabdomyolysis have been reported, but the precise nature of these drug-drug interactions has also not been well defined.

In conclusion, drug-related myopathies constitute a serious part of muscle disorders. A lot of medications may induce or trigger myotoxicity, especially if used concomitantly. Moreover, the differential pathophysiological background should be taken into account. A wide spectrum of the possible mechanisms involves enzyme defects, changes in mitochondrial function and intracellular metabolism, including protein or glycogen disturbances, the influence on the cell membrane stability and drug interactions involving P-glycoprotein or cytochrome P-450 system. However, despite this, the pathogenic nature of the described drug-induced myopathies has not been estimated yet. Moreover, recent studies have still resulted in new insight into existing mechanisms and pathways.

In the light of the above findings, the drug-associated myopathies become an important adverse effect of the medical treatment, especially, if the risk of drug-drug interactions is increased.

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