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Review

Safety issues and harmful pharmacological interactions of nutritional supplements in Duchenne muscular dystrophy: considerations for Standard of Care and emerging virus outbreaks



Brigida Boccanegra^{a,1}, Ingrid E.C. Verhaart^{b,c,1}, Ornella Cappellari^a, Elizabeth Vroom^{c,d}, Annamaria De Luca^{a,*}

^a Unit of Pharmacology, Department of Pharmacy and Drug Sciences, University of Bari Aldo Moro, Bari, Italy

^b Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

^c Duchenne Parent Project, the Netherlands

^d World Duchenne Organisation (UPPMD), the Netherlands

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ABSTRACT

At the moment, little treatment options are available for Duchenne muscular dystrophy (DMD). The absence of the dystrophin protein leads to a complex cascade of pathogenic events in myofibres, including chronic inflammation and oxidative stress as well as altered metabolism. The attention towards dietary supplements in DMD is rapidly increasing, with the aim to counteract pathology-related alteration in nutrient intake, the consequences of catabolic distress or to enhance the immunological response of patients as nowadays for the COVID-19 pandemic emergency. By definition, supplements do not exert therapeutic actions, although a great confusion may arise in daily life by the improper distinction between supplements and therapeutic compounds. For most supplements, little research has been done and little evidence is available concerning their effects in DMD as well as their preventing actions against infections. Often these are not prescribed by clinicians and patients/caregivers do not discuss the use with their clinical team. Then, little is known about the real extent of supplement use in DMD patients. It is mistakenly assumed that, since compounds are of natural origin, if a supplement is not effective, it will also do no harm. However, supplements can have serious side effects and also have harmful interactions, in terms of reducing efficacy or leading to toxicity, with other therapies. It is therefore pivotal to shed light on this unclear scenario for the sake of patients. This review discusses the supplements mostly used by DMD patients, focusing on their potential toxicity, due to a variety of mechanisms including pharmacodynamic or pharmacokinetic interactions and contaminations, as well as on reports of adverse events. This overview underlines the need for caution in uncontrolled use of dietary supplements in fragile populations such as DMD patients. A culture of appropriate use has to be implemented between clinicians and patients' groups.

1. Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive muscle wasting disorders affecting around 1 in 5 000 newborn boys. First symptoms arise around two to three years of age, after which a progressive loss of muscle tissue leads to wheelchair dependency,

usually in the early teens. Hereafter respiratory and cardiac failure occur, which are often the cause of death before the age of thirty [1]. It is caused by mutations in the *DMD* gene, located on Xp21, which encodes for the dystrophin protein, leading to its absence [2,3]. A less severe form is Becker muscular dystrophy (BMD), which a short yet partly functional dystrophin protein is expressed [2,3]. Dystrophin

Abbreviations: ADME, administration distribution, metabolism and elimination; ADR, adverse drug reaction; ASO, antisense oligonucleotide; BCAA, branched-chain amino acid; CoQ₁₀, Coenzyme Q₁₀; CYP, cytochrome P450; DMD, Duchenne muscular dystrophy; EAA, essential amino acid; EGCG, Epigallocatechin-3-gallate; EMA, European Medicines Agency; EMS, Eosinophilia-Myalgia Syndrome; FDA, Food and Drug Administration; GTE, green tea extract; NAC, N-acetyl cysteine; NO, nitric oxide; NSAID, nonsteroidal anti-inflammatory drug; PD, pharmacodynamics; PK, pharmacokinetics; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species

* Corresponding author.

E-mail address: annamaria.deluca@uniba.it (A. De Luca).

¹ Both authors equally contributing to the manuscript.

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provides stability to the muscle fibres by linking the cytoskeletal actin to the extracellular matrix. In its absence, muscle cells get damaged easily, which leads to chronic inflammation, continuous cycles of degeneration and regeneration and eventually replacement of muscle tissue by adipose and fibrotic tissue [4]. Corticosteroids are at the moment the main pharmacological treatment for DMD. Furthermore, treatment of, among others, respiratory and cardiac failure belongs to the standard care for DMD [5–7].

Recently three therapies that target the primary effect, have received marketing authorization. In Europe, the European Medicines Agency (EMA) has approved ataluren, applicable to patients carrying premature stop codons [8], and in the United States, the Food and Drug Administration (FDA) has licensed eteplirsen and golodirsen, relevant for patients amenable for exon 51 and 53 skipping, respectively [9,10]. The research in the field is intense and in the last few years, EMA and FDA granted the orphan designation to several drugs with various mechanism of actions like, among the other, monoamine oxidase inhibitors (rasagiline), ion transporters blockers (rimeporide) and histone deacetylase inhibitors (givinostat) and at different level of clinical investigation. Lists of designated orphan drugs and trials ongoing in DMD and BMD are available and accessible online (<https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>; https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a; <https://clinicaltrials.gov/>).

Other potential primary therapies, like gene therapy using microdystrophins and exon skipping of other exons are investigated [11]. These therapies have so far shown moderate improvements and most of them are not applicable to all patients, targeting the secondary effects of the lack of dystrophin could be an alternative approach. Furthermore, it could serve as an additional treatment to enhance the effects of primary medicines [11]. With the aim to facilitate the research process, EMA and FDA released guidelines for the development of medicinal products for the treatment of Duchenne or Becker muscular dystrophy [12] (<https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy>; <https://www.fda.gov/media/92233/download>).

Disturbances of the metabolic system are one of the secondary consequences of the absence of dystrophin [13]. Changes in insulin signalling and mitochondrial function have been observed in animal models and patients [14–18]. DMD patients show alterations in body composition and energy expenditure [19–21]. In glucocorticoid-naïve boys at young age up to 50 % of patients is overweight [22,23,24]. Effects are exacerbated using corticosteroids, which is now the main treatment for DMD. These can lead to weight gain, cushingoid features, hyperglycaemia and growth restrictions [25]. Older patients, however, are at risk of underweight and malnutrition, amongst others due to increasing difficulties with eating [22,26,27]. Therefore, the importance of nutritional management becomes more and more recognized [28,29]. Knowledge is, however, lacking what are the best recommendations for DMD patients of different ages. The current guidelines only give general recommendations in the field of nutrition [5].

One of the aspects of nutrition is the use of dietary supplements. At the moment, only the use of vitamin D if the serum level of 25hydroxyvitamin D is below 30 ng/mL, and calcium if intake is low, is recommended [5]. It is advised to follow the dietary reference intakes for the general population [30]. It is known that many patients use other nutritional supplements without prescription, but information on the magnitude and the exact supplements used is lacking. This is also influenced by geographical and cultural differences, which increases the uncertainty in this field for the DMD community. Similarly, extraordinary emergencies, like those related by COVID-19 by the outbreak of SARS-CoV-2 virus, may reinforce the idea that implementation of diet with vitamins and other supplements can enhance the immune response, thus protecting fragile patients such as DMD as well as BMD patients. This can lead to further fragmentation of the situations

worldwide, that are in turn poorly controlled by health specialists.

The aim of this review is to briefly review the long list of dietary supplements commonly used by DMD patients and easily available without medical prescription. Other than briefly mention the presumed mechanism of their claimed beneficial action, the present work mainly focuses to underline that their use needs to be carefully balanced with the limited information about proper dosing and different pathological phases to observe the efficacy and the high risk of toxicity related to the uncontrolled use. Also, a better distinction has to be made between “dietary supplements” and “natural active principles” as the rationale for their use is markedly different along with doses, benefit/safety ratio and experimental settings for validation.

2. Complex therapeutic regimens and risk of adverse drug reactions (ADR)

Complex and chronic pathologies in the paediatric population, such as DMD, are at high risk of adverse drug reactions (ADR), due to the combination of factors. These include the little information available about drug safety in children, the altered pharmacokinetic (PK) and pharmacodynamic (PD) process due to both body development and pathology progression, and mostly for the possible interactions between drugs. In fact, according to the pathology phase, DMD patients are exposed to multiple therapies: standards of care prescribe the early start of treatment with steroids, with various other medications added on the top, e.g. to prevent and control cardiovascular complication (e.g. ACE inhibitors, beta-blockers) or other pathology processes, or new drugs when patients take part in clinical trials [5–7,31]. Polytherapy should also take into account supplements, such as the above-mentioned vitamin D to delay steroid-induced osteoporosis.

A careful post-marketing monitoring of ADR is crucial for assessing the risk/ benefit ratio of drugs and complex therapeutic protocols in the real world conditions [32].

2.1. Mechanisms of drug-to-drug and drug-to-supplement interactions

Drug-to-drug (D-D) and drug-to-supplement (D-S) interactions can occur at both the PD and the PK level. Biological effects of any sort of bioactive compounds, of either natural, chemical or biosynthetic source, are due to high-affinity interaction with molecular targets with intensity of effect and risk/benefit ratio being also related to dosing. Two compounds acting on the same target, or on its cellular path, may lead to synergistic or antagonistic PD interaction with the result of enhancing effects, disclosing potential ADR or reducing therapeutic efficacy. Importantly, the inability to reach the therapeutic effect, due to inadequate target engagement is by itself an ADR [33,34].

Clinically relevant D-D and D-S interactions can also occur during each of the four distinct phases (ADME) of PK (Fig. 1). Consequently, this may profoundly affect the reciprocal level of a drug or its metabolite in the body, including main target or off-sites, and consequently therapeutic action and toxicity. Interactions at the level of the enzymes of phase I and phase II metabolic reactions are key ones. Many compounds can act as enzyme inducers or inhibitors which would result in either reduced or enhanced exposure of another therapeutic, respectively. Similarly, synergistic or antagonistic interaction can occur at any other level, from drug absorption to distribution (i.e. competition for plasma protein binding) and elimination, also via specific interaction with transporters and other targets. According to these considerations novel approaches for predicting ADME interactions, i.e. by in silico studies, are ongoing [35,36].

3. General aspects in safety control by law of dietary supplements

Dietary supplements include one or more ingredients labelled to enrich diet, including vitamins, minerals, herbs, amino acids, whey protein, essential fatty acids and other components, formulated for oral

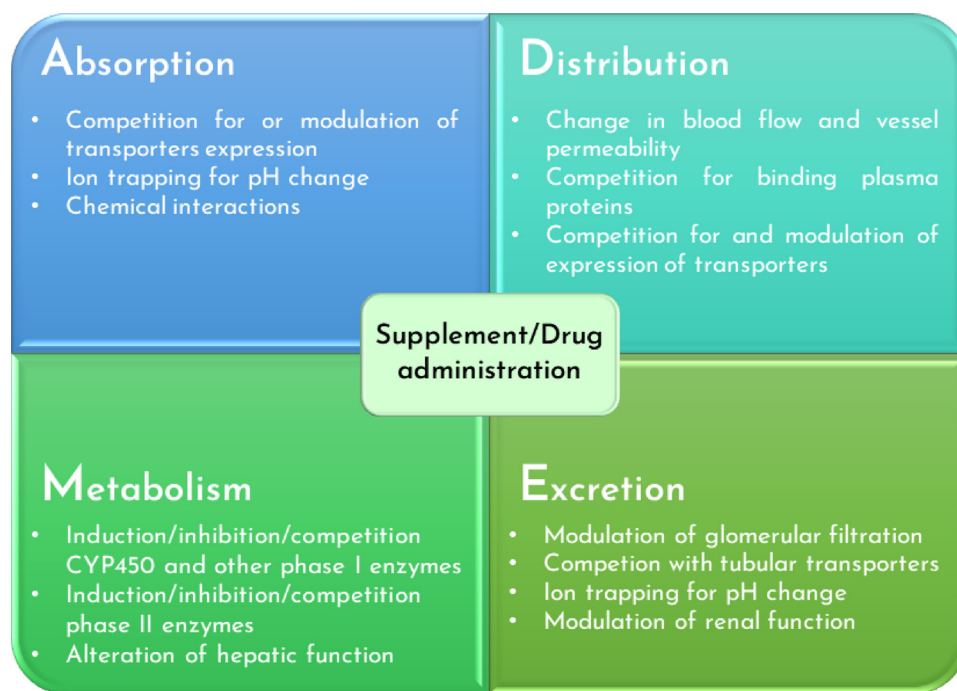


Fig. 1. Phases of ADME and primary mechanisms involved in drug-to-supplement interactions.

use as pills, tablets, syrups, etc.

In USA and EU-countries, dietary supplements are regulated as food, and no prove of safety nor formal approval is required before their commercialization; however, due to the intense and global interest toward these products, there is an increasing attention by regulators with respect to safety issues [37,38]. For instance, for a new dietary ingredient, the manufacturer must provide information about the reasonable evidence for safe human use of the product.

Legally, dietary supplements cannot be claimed to exert any action towards pathology, either for diagnosis, prevention or treatment. Rather, the health claim for a dietary supplement is for correcting nutritional deficiencies that increase the risk of a health-related condition. In parallel, nutrient content claims and structure/function claims are related to the amount of the nutrient and how this has an impact on physiological functions. As described by the Office of Dietary Supplements of NIH (<https://ods.od.nih.gov/>), although structure/function claims do not require FDA approval, the label should clearly indicate that the product has not been approved by FDA nor intends to have any drug-related action [37–39].

Regulators, such as FDA and European Commission (through the European Food Safety Authority; EFSA, <https://www.efsa.europa.eu/en/topics/topic/food-supplements>) are active in post-marketing safety surveillance and in providing specific guidance to evaluate sources, and establishing limits for ingredients and contaminants. Consumers, health professionals and industry members can report unwanted reactions to dietary supplements and regulators can take actions to protect the public from unsafe products, including withdrawal due to proven or suspected harmful effects and toxicity. Reasons for recalls include contamination by microbiological species, pesticides, and heavy metals as well as abnormal presence of dietary ingredients with respect to what claimed in the label, including absence, reduction or excess, or the presence of other active principles [40]. In fact, many supplements contain ingredients that have strong biological effects, and such products may not be safe in all people, especially if an underlying pathology or an acute viral or bacterial infection requires concomitant use of other drugs, increasing the risk of potential harmful interactions (see Directive 2002/46/EC [41]).

It should be underlined that food and dietary supplements are also

freely available on the web, which increases the risk of consumers being exposed to products of limited quality in terms of content of active principles and contaminants.

4. The reason for attention to supplements and nutraceuticals in DMD

A great interest has been raised toward dietary supplements in DMD [42]. One of the main reasons resides in the possibility to get adjuvant control of secondary pathogenic events, possibly related to altered metabolism, diet intake or dietary requirements, and based on their claimed mechanism of action. Then, supplements and nutraceuticals can potentially control inflammation and oxidative stress, provide a clue to overcome impaired protein synthesis/proteolysis related to acute necrosis or act as energizer or metabolic booster at skeletal muscle level [42]. The actions of some supplements in DMD have been supported by well-designed preclinical studies, while for many others the action is elusive, and more evidence is needed [28]. Based on what is stated in paragraph 3, any reference to a “therapeutic” action of food supplements without a clear link to dietary deficiency or metabolic requirement, would be misleading. Some of the nutritional supplements could be important in case of a clear nutritional deficit, as may occur in specific phases of the pathology. In this respect, if a dietary deficiency is corrected with a supplement, then an adjuvant therapeutic-like action can be expected. It is anticipated that this would, in any case, be the most reasonable use of any dietary supplement although not always easy to proof preclinically in animal models [37]. The dark side of nutritional supplementation is related to the wrong assumption that these compounds, because of natural origin and normally present in diet, are safe and pivotal to maintain the wellbeing state and potentially help to prevent other pathological conditions, as those related to infections as in case of pandemic COVID-19. This holistic view is totally misleading, since the basis for the action of these exogenous compounds, especially at the high doses chronically used as supplements, follows the same mechanisms that underlie efficacy and safety issues of regular drugs. As anticipated supplements may contain natural active principles that have drug-like effects, like steroids present in a Chinese supplement with claimed beneficial effects in DMD boys [43], or statins

present in red yeast rice [44]. In this case, an active principle of natural origin can have therapeutic action, *i.e.* impact on pathology-related events, and act as a disease modifier. However, the active principle should be considered *per se* as a drug, with no specific reference to dietary requirement and follow the same rule and experimental validation needed for pharmaceutical compounds [34]. For most natural compounds the boundary is very narrow, with doses and underlying rationale making the big differences. Consumers and patients need to be properly informed.

Other than being wrong, the assumption of natural-being-safe is dangerous, because caregivers can decide in an autonomous way and without medical prescription or suggestion to implement a supplement in the diet of a DMD boy with the idea that this is without danger and can only help. To increase the level of complexity, legislation can differ in various countries worldwide, with some preparations being considered somewhere “dietary supplements” and “pharmaceutical products” elsewhere. In a global world, as that of rare disease, this can increase confusion and misuse [37]. Unfortunately, this attitude exposes patients to high risk of ADR, may delay or counteract the effect of other therapeutics, and also adds economic burden to families, due to both the high costs of this class of compounds and the poor control of pathology progression.

5. Effects of the most used dietary supplements in DMD: side effects, mechanisms of toxicity and interactions

A wide range of dietary supplements is used by DMD patients. The present review is not aimed at entering into the specific rationale of their use; however, in Fig. 2 their main site of action is indicated, while concepts about the mechanism of action and an overview of the pre-clinical and clinical studies performed in DMD is given in Table 1. As general considerations, a variety of both preclinical and clinical experimental approaches have been used and many contradictory results have been obtained over the years. Variables including age, stage of the disease, dosage, route of administration, time of exposure and readouts, have to be considered when reviewing efficacy data of these compounds or when designing preclinical and clinical studies. Importantly, the scientific community increasingly recognizes the need of properly conducting preclinical studies in this field, also for de-risking the possible clinical assessment of supplement need in DMD patients [45], similarly to the standardization in drug preclinical studies [46]. When testing dietary supplements different nutritional requirements between species should also be considered and accurately balanced with the more limited information about doses/levels needed to correct an alteration, so to reach the proper amount in target tissues and have a biological impact, further complicating the general picture. Based on the above consideration, we will presently focus on the main mechanisms that can account for possible safety concerns or harmful interactions for the most used dietary supplements in DMD (Table 1) as well as describing specific cases of reported toxicity by pharmacovigilance monitoring in the wide population (Table 2).

5.1. Branched-chain amino acids

The anabolic effect of branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) on animal and human muscles has been well described in several studies [47,48] and is primarily due to BCAAs' capability to affect pathways involved in protein synthesis (mTOR, S6K1). BCAAs are considered essential amino acids (EAAs) for humans, and, like the other six EAAs, they need to be necessarily introduced through the diet. However, recently, doubts were raised about the real ability of BCAAs to stimulate muscle anabolism, occurring when the rate of muscle protein synthesis exceeds the muscle protein breakdown and depends on the presence of an adequate amount of intracellular EAAs. The intake of BCAAs alone cannot prevent, in the post-absorptive state, the protein breakdown required for the production of the

remaining six EAAs, making it impossible to create an anabolic state [49].

In addition, contradictory outcomes have been described in clinical studies [50,51], reinforcing the need for proper preclinical assessment in animal models in order to obtain more consistent and reliable results that may be useful for translational research on BCAA effects.

5.1.1. Side effects, mechanism of toxicity and interactions

The most common side effects revealed during the aforementioned trials were gastrointestinal: decreased appetite, anorexia, nausea, and general stomach discomfort [51].

The potential anabolic effect of BCAAs is a costly process that requires a proper availability of energetic substrates: in fact, leucine administration promotes glucose uptake in skeletal muscle and enhances insulin response [52]. Consequently, it must be taken into account that BCAAs have a complex interaction with glucose metabolism. Supplementation might lower blood glucose levels (see Table 2), and this may have additive effects in DMD patients treated with antidiabetic drugs [53]. On the other hand, elevated BCAA can be prognostic of insulin resistance [54]; also, this aspect can be harmful in steroid treated DMD patients that already experience insulin resistance (*v.* Fig. 3). Another hypothesis to consider is the expression of BCAA transporters in skeletal muscle of dystrophic patients. In fact, muscle mass reduction could re-address the distribution of BCAAs towards other tissues, with changes in the amino acid flow. So far, no data seem to be available concerning BCAA levels in DMD patients.

The work of Carunchio et al. in 2010 [55] also suggested that excessive use of BCAAs (with a BCAA-enriched diet, 2.5 % valine, isoleucine and leucine in 1:1:1 ratio) in sport athletes caused a major increase in the risk of amyotrophic lateral sclerosis (ALS) due to enhanced hyperexcitability of cortical neurons and excitotoxicity (see commentary by Manuel & Heckman, 2011 [56]). A risk to alter calcium homeostasis by BCAA has also been proposed, which would be dangerous in DMD subjects.

BCAAs are also important for the ammonia detoxification in skeletal muscle, promoting the synthesis of glutamate, which acts as a substrate for glutamine production. On the other hand, an excess of BCAAs supplementation and, consequently, of glutamine synthesis, may increase glutamine breakdown and the production of ammonia in the intestine and kidneys. This condition might lead to the development of hepatic encephalopathy. For these reasons, attention should be given to the dose of BCAAs administrated [57].

5.1.2. Contaminants

A study of 2004 [58] revealed the presence of dehydroepiandrosterone (DHEA) and 4androstenedione not indicated on the label of BCAA supplements. The abuse of anabolic steroids might cause relevant side effects and alters the normal hormonal production in the body [59], especially in DMD patients already under steroid therapy (*v.* Fig. 3).

5.2. L-arginine and L-citrulline

Another proposed approach to counteract muscle wasting in DMD is enhancing utrophin expression, a protein sharing 80 % homology with dystrophin. Utrophin has a similar function in the maintenance of the dystrophin-glycoprotein complex (DGC) integrity and myofibre structure. A widespread strategy to improve utrophin expression was to enhance the activity of the muscular isoform of nitric oxide synthase (NOS- μ) and NO synthesis by means of NO-donors administration, like L-arginine (or its precursor, L-citrulline [60,61]). NO is also critical to support mitochondrial function and biogenesis [62,63]. Interestingly, a recent study also showed that the levels of L-arginine and its precursor L-citrulline were significantly lower in *mdx* muscles with respect to wild type ones [64]. A recent study showed that L-homoarginine (one of the direct products of L-Arg metabolism in human) serum levels were

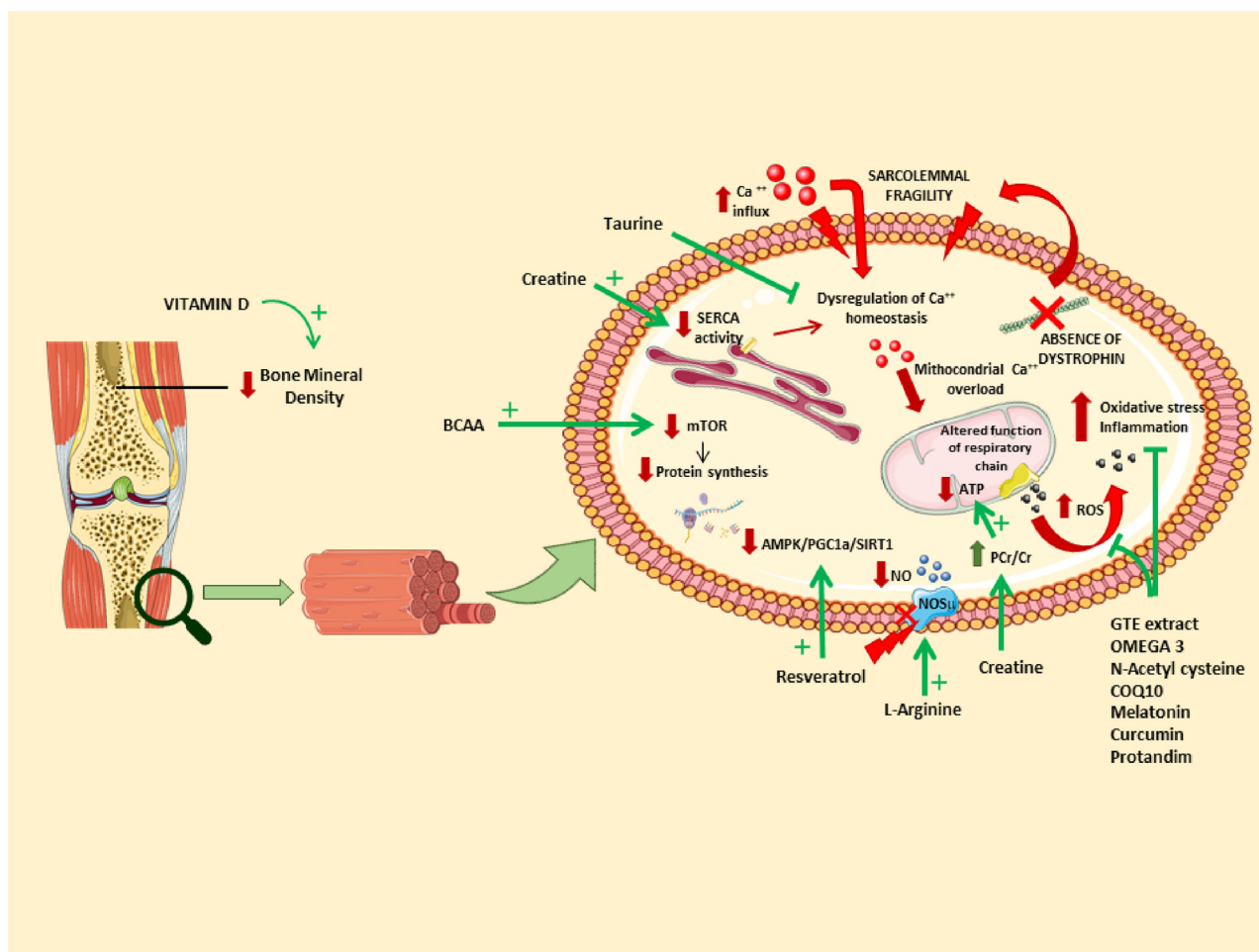


Fig. 2. Targets of dietary supplements. The absence of dystrophin affects both mainly, but not exclusively, skeletal muscle. Many signalling pathways in myofibers are disturbed (in red). Nutraceuticals and dietary supplements can act on different parts of the pathology (in green). This figure was modified from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License; <http://smart.servier.com/>. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

significantly lower in Becker muscular dystrophy patients [61]. This evidence, if confirmed in DMD patients, might give more support to the requirement of L-arginine and L-citrulline supplementation through diet.

Although no other clinical trials with L-arginine administration alone or in combination with different drugs in DMD boys are currently published, a wide range of evidence in healthy and unhealthy subjects have been collected [65,66] (Table 1). L-arginine was administered alone or in combination with multiple active ingredients, in various dosage forms and with varying duration of treatment. This marked heterogeneity in experimental procedures makes it difficult to establish the upper level of intake of L-arginine and the accurate evaluation of its safety and real effect.

5.2.1. Side effects, mechanism of toxicity and interactions

The absence of serious adverse effects related to L-arginine or L-citrulline administration in human trials confirms the safety profile of these amino acids. However, the most common side effects reported were nausea and mild diarrhoea [67,68]. This is probably due to the increase of local NO synthesis by means of stimulation of intestinal NO synthase (NOS-1) activity, promoted by L-arginine ingestion. As it is well known, NO is strictly related to intestinal function at different levels, including motility, water retention and electrolyte transport. The excess of local NO synthesis might generate an imbalance in the equilibrium between intestinal absorption and secretion, promoting abnormal water loss and, consequently, nutrient depletion [69].

L-arginine contributes to the regulation of hemodynamic. In fact, animal and human studies demonstrated a hypotensive effect of L-arginine administration, not only related to the increase of NO synthesis but also to the enhanced endothelial cell function and the decreased resistance of peripheral blood vessels [70–72]. L-arginine also induced hyperkalaemia in animals and humans [73]. A recent study suggested that L-arginine and other dibasic amino acids increased plasma potassium levels, promoting the metal ion efflux from liver and pancreas to the extracellular aqueous environment [74].

L-arginine supplementation downregulates the expression, in liver and ileum, of cationic transporter-1 (CAT-1) that is also able to transport other basic and essential amino acids, like lysine and histidine, with a consequent reduction of EAAs plasma levels. This condition should be avoided in DMD patients. Furthermore, it was demonstrated that L-arginine affected the expression of enzymes involved in its metabolism, as such as arginase I, reducing its own bioavailability [75].

Considering these effects on vascular homeostasis and electrolytes balance, uncontrolled administration of L-arginine, particularly in unhealthy subjects, should be avoided. While an improvement of peripheral blood flow may contrast functional ischemia in DMD patients [76], L-arginine might cause excessive low blood pressure in DMD patients under treatment with antihypertensive drugs and could have a synergistic effect with agents that increase potassium levels, such as beta- and alpha-blockers. In accordance with this assertion, three cases of palpitations, irregular heartbeat, tachycardia and syncope were reported in healthy subjects after taking arginine supplementation [77]

Table 1
Mechanisms of action and outcome readouts for efficacy in preclinical and/or clinical studies, for dietary supplements most commonly used in DMD.

Compound	Claimed mechanism of action	Preclinical studies in <i>mdx</i> mice: assessed endpoints	Evidences from clinical trials in DMD patients
Branched-chain amino acids	Increase protein synthesis	Modulation of vascular function	↓ Protein degradation [50]
L-arginine	Enhance utrophin expression	Myofibre phenotype Motor function [206] Utrophin expression [62,63] Necrosis [63] Respiratory function [63]	No improvements [51] In combination with metformin (AMPK activator) [60]: ↑ Activity of mitochondrial electron transport chain ↓ Oxidative stress ↑ Clinical scores ↑ Insulin secretion [83] ↓ Protein degradation [82] No effect on muscle function or strength [80,81]
Glutamine	Antioxidant activity	Oxidative stress Protein breakdown [207]	↑ (PCr)/inorganic phosphate (Pi) ratio [90] ↑ Muscle strength [90,91,92,93] ↓ Markers of bone breakdown [92] ↑ Fat free mass [92]
Creatine	Enhance metabolism ↑ Ca ²⁺ -ATPase (SERCA2) content	Necrosis [86,87] Energy metabolism [86,88] Muscle force [87,88,89]	↑ (PCr)/inorganic phosphate (Pi) ratio [90] ↑ Muscle strength [90,91,92,93] ↓ Markers of bone breakdown [92] ↑ Fat free mass [92]
Taurine	Antioxidant and anti-inflammatory activity; restoration of Ca ²⁺ homeostasis	Muscle damage [103] Oxidative stress [103] Muscle function [89] Membrane conductivity [89] Cardiac function [104] Muscle strength (in combination with prednisolone) [105]	
Green tea extract	Antioxidant and anti-inflammatory activity	Muscle damage and CK plasma levels [110,111] Necrosis [111,112,113] Regeneration [110] Oxidative stress [111,112,113] [208], Muscle force [111,113] Oxidative stress markers [114]	Clinical trial ended but data not available
Protandim	Antioxidant and anti-inflammatory activity	Oxidative stress markers [114]	↓ Insulin resistance Trend towards a decrease of muscle loss [135]
Omega-3 fatty acids	Anti-inflammatory activity	Necrosis [133] Inflammation [133,134]	In combination with calcium-rich diet [210]:
Vitamin D	Restored insufficient 25-hydroxyvitamin D serum levels in DMD boys	Muscle force	↑ Bone mineral density ↑ Bone mineral content
Resveratrol	Anti-inflammatory activity	Muscle damage (CK/LDH plasma levels) [103] Oxidative stress [103,150,151] Inflammation [211] Autophagy/mitophagy [150,212] Muscle force [103] Utrophin expression [211]	
Curcumin	Anti-inflammatory activity	Muscle strength [152,153] Muscle damage [152,153] Inflammation markers [152,153] NF-kappaB activity [152,153]	
N-Acetyl cysteine	Antioxidant activity	Muscle damage (CK plasma levels) [168,169] Necrosis [168,169] Inflammation [169,170] Oxidative stress [169,170] βdystroglycan and utrophin expression [172]	
Coenzyme Q₁₀	Antioxidant activity		↑ Muscle strength [179] No effect on echocardiographic parameters [182]
Melatonin	Antioxidant activity	Muscle damage (CK plasma levels) Oxidative stress Muscle force [186]	↓ Oxidative stress [187] ↓ Plasma pro-inflammatory cytokines [187] ↓ Hyperoxidative status in erythrocytes [213]

(see Table 2).

5.2.2. Contaminants

No relevant contaminations have been reported for L-arginine. In 2014, an investigation by the FDA discovered N-acetyl-L-leucine instead of L-citrulline in lots of these supplements with subsequent evidence of hyperammonaemia and related health hazards in patients

[68].

5.3. Glutamine

Dystrophic muscles show a low glutamine concentration and DMD boys exhibit a significant decrease of glutamine bioavailability in the post-absorptive state, with the result that this amino acid should be

Table 2
Adverse events reports. Selection of adverse drug reactions reported for the different compounds.

Product	Patient	Country	Year	Adverse reaction	Possible interaction with other drugs/supplements	
Mix of BCAA	Multiple reports Female; 70 years	UK	2015–2018	Vomiting; dyspnoea; diarrhoea; dehydration	–	
		Canada	2012	Asthenia; cold sweat; diarrhoea; feeling abnormal; vomiting	–	
	Female; 23 years	Canada	2015	Abdominal pain; cheilitis; diarrhoea; disorientation; dyspnoea; feeling abnormal; gait disturbance; gingival pain; hypersensitivity; ocular hyperaemia; palpitations; paraesthesia; peripheral swelling; swelling face; throat tightness	–	
		Canada	2016	Blood glucose decreased	insulin	
	Male; 29 years	Canada	2015	Abdominal pain; anxiety; blood pressure increased; chest pain; dehydration; diarrhoea; disorientation; dyskinesia; gait disturbance; heart rate increased; hyperhidrosis; hyperventilation; hypokinesia; muscle spasms; pain in extremity; respiratory rate increased; seizure; tongue discoloration; toxicity to various agents; yellow skin	ibuprofen; nadolol	
		Canada	2013	Rhabdomyolysis	energy drink + creatine	
	Male; 19 years	Canada	2013	Blood pressure fluctuation	–	
		Canada	2017	Vitamin B6 increased; pain in extremity; neuropathy peripheral; hypoaesthesia	–	
	Leucine	Female; 80 years	USA	2010	Asthenia; burning sensation; Chest discomfort; Daydreaming; Disability; Dizziness; Feeling of body temperature change; Fine motor skill dysfunction; Heart rate increased; Movement disorder; Musculoskeletal stiffness; Palpitations	–
		Female; 31 years	Canada	2009	Diarrhoea; myocardial infarction; nausea	–
Mix of arginine, others amino acids and caffeine	Male; 64 years	Canada	2012	Chromaturia; flank pain; haematuria	carvedilol; atorvastatin; furosemide; warfarin	
	Male; 12 years	Canada	2015	Palpitations; heart rate increased	clonidine	
	Male; 69 years	USA	2014	Neutrophil and monocyte percentage increase; lymphocyte percentage decrease; hyponatraemia; hypertension; hyperkalaemia; heart rate irregular; haematocrit decreased; fatigue; dizziness; discomfort; blood urea increased; blood sodium, calcium and chloride decreased; blood albumin decreased; atrioventricular block complete; alanine aminotransferase increased	–	
	Female; 86 years	USA	2016	Supraventricular arrhythmias; malaise; neutropenia	–	
		USA	2006–2015	Cardiac and gastrointestinal disorders, hypotension	–	
	Multiple reports Female; 48 years	UK	2006–2015	Ear disorder; headache; hypoacusis; pruritus; rectal haemorrhage; vomiting	ginseng	
		Europe	2019	Psychomotor hyperactivity; panic attack; nervousness; heart rate increased; disturbance in attention; discomfort; confusional state; cerebrovascular accident	–	
	Female 40 years	Canada	2002	Vomiting; nausea; jaundice; hepatic enzyme increased; hepatic enzyme increased; chills; body temperature increased; blood bilirubin increased; abdominal pain	–	
		USA	2014	Syncope; nausea; dizziness; blood pressure decreased	–	
	L-glutamine	Female 27 years	USA	2014	Vomiting; vision blurred; paraesthesia; neurological symptom; nausea; insomnia; hypoaesthesia; dysarthria; dizziness; depression; confusional state; balance disorder; anxiety; amnesia	–
Female 65 years		USA	2015	Blood creatine increased; chest pain; renal failure; thrombosis	–	
Creatine	Not specified	USA	2017	Hyperhidrosis; nausea; vomiting	–	
	Male; 16 years	Canada	2008	Muscle spasms; blood creatine phosphokinase increased	–	
	Male; 34 years	Canada	2006	Acute renal failure; iatrogenic injury; blood thyroid stimulating hormone decreased; blood creatine increased	–	
	Male; 28 years	USA	2014	Arrhythmia; dry mouth; rash; skin discoloration; speech disorder; tongue oedema; tremor	–	
Taurine	Male; 25 years	USA	2014	Renal pain; micturition urgency; back pain	–	
	Male; 14 years)	Canada	2007	Vomiting; pyrexia; nausea; hospitalisation; hepatic pain; headache; abdominal pain upper	–	
	Male; 41 years	USA	2016	Diarrhoea; vomiting; headache; dyspnoea; flushing	–	
	Not specified	USA	2017		–	
Multiple reports	UK	2014–2018		–		

(continued on next page)

Table 2 (continued)

Product	Patient	Country	Year	Adverse reaction	Possible interaction with other drugs/supplements
Green tea	Female; 63 years	Canada	2008	Constipation ; dizziness; fatigue; phlebitis superficial	turmeric; aspirin
	Male; 63 years	Canada	2015	Haemorrhagic stroke	-
	Female; 17 years	Canada	2016	Abdominal distension; atelectasis; blood creatinine increased; chest pain; hepatic failure; hepatitis acute; hepatomegaly; malaise; nausea; pain; pleural effusion; renal failure; renal tubular necrosis; transaminases increased; urine output decreased; vomiting; weight increased	ethinyl estradiol; norgestimate; ibuprofen
	Female; 23 years	Canada	2014	Liver function test abnormal; hepatitis acute; hepatic enzyme increased; blood bilirubin increased; blood alkaline phosphatase increased; aspartate aminotransferase increased	-
	Female; 66 years	USA	2014	Hepatitis; fatigue; dyspnoea; diarrhoea; chromaturia	-
	Male; 70 years	USA	2014	Heart rate irregular	-
	Female; 46 years	Canada	2005	Arrhythmia; dizziness; lethargy; palpitations; pruritus; rash papular; urticaria	-
	Female; 65 years	Canada	2010	Rash macular; rash pruritic	-
	Female; 57 years	Canada	2010	Pruritus; rash; skin disorder	-
	Male; 38 years	Canada	2012	Blood mercury abnormal	-
Omega 3-6-9 Fish Oil	Female; 58 years	Canada	2012	Abdominal pain; arthralgia; asthma; chest discomfort; cough; fall; flushing; gallbladder disorder; hair texture abnormal; headache; joint swelling; lymphadenopathy; muscle spasms; nausea; neck pain; nephrolithiasis; neuropathy peripheral; oesophageal pain; pain in extremity; peripheral swelling; skull fracture; spider vein;	salbutamol; imatinib; allopurinol
	Male; 88 years	Canada	2018	Bedridden; drug ineffective; drug interaction; fall; hypoacusis; movement disorder; nocturia; vision blurred	calcium; vitamin D 400 I.U.; mirabegron
	Male; 58 years	USA	2014	Thrombosis; respiratory tract congestion; liver function test abnormal; fatigue; dyspnoea	-
	Not specified	USA	2014	Diarrhoea; abdominal pain upper	-
	Female; 57 years	USA	2015	Rash pruritic; rash erythematous	-
	Female; 64 years	USA	2015	Low density lipoprotein increased; high density lipoprotein increased	-
	Multiple reports	UK	2003–2018	Thrombocytopenia; nausea; diarrhoea; arthralgia; pain in extremity; rash	-
	Multiple reports	Europe	2019	Abnormal clotting factors, thrombocytopenia, gastrointestinal disorders, musculoskeletal stiffness, myalgia, blood arsenic increased, blood and urine mercury abnormal	-
	Female; 57 years	USA	2014	Palpitations; hypotension; heart rate increased; headache	-
	Female; 53 years	USA	2014	Nephrolithiasis	calcium carbonate
Vitamin D	2 months	USA	2015	Vitamin D increased; failure to thrive; blood calcium increased	-
	Female; 78 years	Canada	2010	Angioedema; lip blister; lip swelling; oral candidiasis; pharyngeal oedema; rash generalized	atenolol; prednisone; ranitidine
	Female	Canada	2016	Transient ischaemic attack	calcium; ibuprofen
	Male; 4 years	Canada	2017	Creatinine urine increased; nephrolithiasis; red blood cells urine positive	-
	Multiple reports	UK	2000–2018	Nausea; vomiting; diarrhoea; abdominal pain upper; hypercalcaemia; dehydration; myalgia; pruritus	-
	Male; 79 years	New Zealand	2004	Oedema peripheral	colecalfiferol oral (suspect); prednisone oral (concomitant)
	Female; 64 years	New Zealand	2014	Angina pectoris; arthralgia; chest pain; dysgeusia; headache	alendronic acid; colecalciferol oral (suspect)
	Multiple reports	Europe	2019	Gastrointestinal disorders; osteomalacia	-
	Not specified	USA	2016	Transient ischaemic attack; blood pressure increased	-
	Not specified	USA	2016	Atrial fibrillation	-
Resveratrol	Not specified	USA	2017	Sensation of pressure; paraesthesia; heart rate decreased; blood pressure increased	Omega Q
	Not specified	USA	2018	Palpitations; heart rate irregular; heart rate increased; atrial fibrillation	-

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Table 2 (continued)

Product	Patient	Country	Year	Adverse reaction	Possible interaction with other drugs/supplements
Curcumin	Male 66 years	Canada	2014	Urine arsenic increased	-
	Multiple reports	UK	2015–2019	Gastrointestinal disorders, headaches	-
	Female, 75 years	USA	2014	Vomiting, pain, nausea, headache, dizziness, deafness	-
	Not specified	USA	2015	Sinus congestion, nausea, headache	-
	Female, 57 years	USA	2015	Vomiting, ultrasound kidney abnormal, renal failure, nausea, hypophosphataemia, hypokalaemia, haematocrit decreased, blood creatinine increased.	-
N-acetyl cysteine	Female; 70 years	USA	2016	Speech disorder; migraine without aura; headache; convulsion; confusional state; blood pressure increased; aphasia; amnesia	-
	Male; 80 years	Canada	2002	Asthma; chills; diarrhoea; dizziness; hypotension; myocardial infarction; nausea; rash; renal failure; serum sickness; skin exfoliation; vomiting	-
	Female; 16 years	New Zealand	2016	Angioedema; bronchospasm; rash; vomiting	acetylcysteine injection (suspect); paracetamol oral (concomitant)
	Multiple reports	Europe	2019	Gastrointestinal disorders, chest pain, asthma, respiration abnormal	-
	Male; 70 years	Canada	2005	Drug interaction; prothrombin level increased	fluticasone; atorvastatin; warfarin
CoQ₁₀	Male; 80 years	USA	2014	Pruiritis; paraesthesia; hypertension; feeling hot; burning sensation	-
	Female; 58 years	USA	2015	Flatulence; diarrhoea; abdominal distension	-
	Female; 64 years	USA	2015	Pain; myopathy; muscular weakness; hepatic enzyme increased; gait disturbance; fatigue; dysstasia; cataract; asthenia; arthralgia	red yeast rice
	Male; 72 years	USA	2015	Palpitations; blood pressure systolic increased	-
	Female; 74 years	USA	2014	Insomnia; heart rate increased; dyspnoea; blood pressure increased	-
Melatonin	Female; 64 years	USA	2014	Wheezing; hypertension; dyspnoea; cough; chest discomfort	-
	Male; 61 years	USA	2005	Blood glucose increased	-
	Female; 59 years	USA	2008	Thrombocytopenia; platelet count decreased; hypersensitivity; ecchymosis; contusion	-
	Multiple reports	UK	2014–2018	Thrombocytopenia; tachycardia; muscle twitching; nausea	-
	Female; 69 years	Canada	2012	Muscle twitching	-
	Female; 63 years	Canada	2012	Blood pressure increased; confusional state; dizziness; dyskinesia; dysphagia; dyspnoea; heart rate increased; nausea; pain in jaw; palpitations; tremor	-
	Female; 18 years	Canada	2014	Headache; nervous system disorder; palpitations; tachycardia; vomiting	-
	Multiple reports	Europe	2019	Gastrointestinal disorders, agitation, confusional state, amnesia, insomnia, panic disorder	-

Retrieved from: Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database/medeffect-canada-aveat-privacy-statement-interpretation-data-search-canada-vigilance-adverse-reaction-online-database.html>.
 New Zealand: <https://medsafe.govt.nz/Projects/B1/ADRSearch.asp>.
 UK: <https://yellowcard.mhra.gov.uk/IDAP/>.
 USA: <https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers#files>.
 Europe: http://www.adrreports.eu/en/search_subst.html.

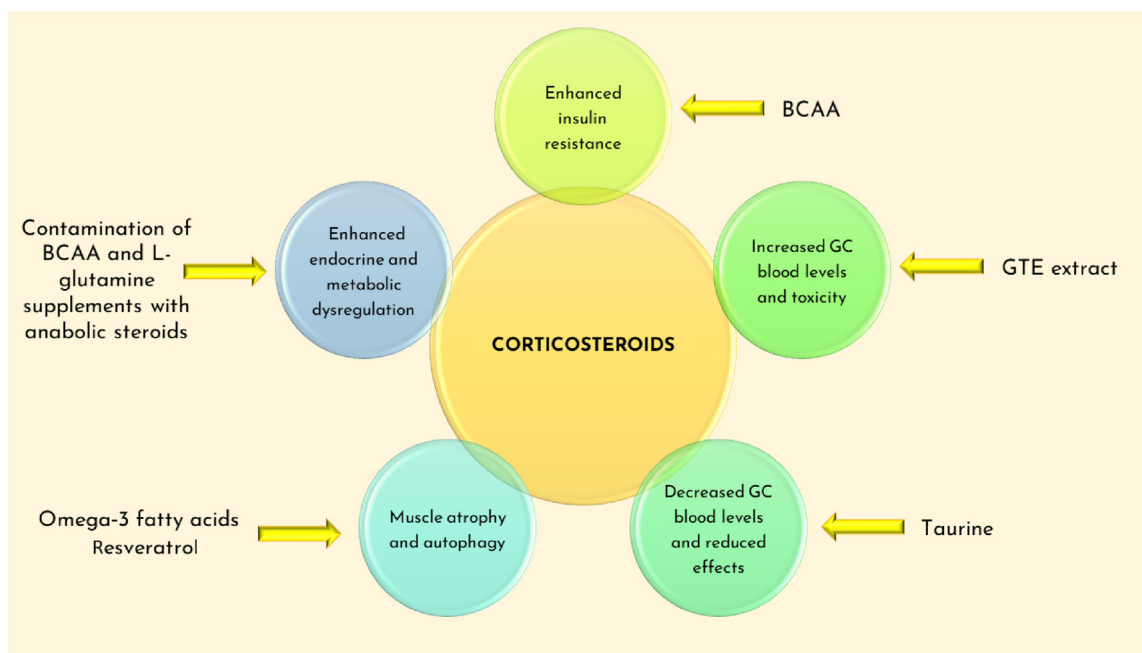


Fig. 3. Main effects of supplements interactions with glucocorticoids (GC) used to treat DMD (deflazacort and α -methylprednisolone). BCAA might enhance the insulin resistance caused by the chronic use of GC. Induction (GTE extract) or inhibition (Taurine) of CYP3A4 and P-gp (Gte extract) could influence the GC blood levels, with potential toxic effects or reduced bioavailability. Omega-3 fatty acids, resveratrol and GC might activate common pathways involved in muscle atrophy. Supplements contaminations with anabolic steroids could interfere with GC mechanisms of action and alter endocrine balance. Mechanisms are described in the text.

considered “conditionally essential” for DMD patients [78]. Skeletal muscle plays a crucial role in the stock, metabolism and release of glutamine, maintaining approximately 80 % of the entire body amino acid content [79]. According to this point, it is conceivable that the muscle-wasting condition would account for glutamine deficiency, paving the way for a proper rationale to proceed with glutamine supplementation in several muscle pathologies, including DMD.

Nonetheless, clinical trials in DMD patients revealed a lack of functional benefits of glutamine supplementation compared to placebo [80,81], despite the encouraging results obtained on the reduction of whole-body protein degradation [82].

5.3.1. Side effects, mechanism of toxicity and interactions

A vast number of studies in human subjects that investigated the safety profile of glutamine have been published. No evidence of adverse effects appeared, supporting the harmless of glutamine supplementation [67]. The two most common adverse effects reported after L-glutamine consumption are nausea and vomiting (see Table 2).

Interestingly, a recent study investigated the effect of glutamine on glucose metabolism in DMD boys [83]. Glutamine, in fact, is involved in gluconeogenesis as a source of carbon skeletons *via* the tricarboxylic acid cycle (TCA) cycle. After 5 h of glutamine infusion, a rapid and transient increase of insulin plasma levels, and a prompt return to normal values when blood glutamine concentration was maintained at basal level were observed. For this reason, DMD patients under insulin therapy should avoid glutamine co-administration.

5.3.2. Contaminants

Also, in glutamine supplements contaminations with anabolic steroids (4-estren3,17-dion, 4-androsten3,17-dion) were found (v. Fig. 3) [84].

5.4. Creatine

In the last decades, creatine (Cr) has become the most popular dietary supplementation among athletes, both professionals and amateurs. The reason for this widespread popularity of Cr is attributable to

the benefits on muscle performance globally observed in the sports field, not only at competitive level. Cr elicits various effects on muscle metabolism, managing energy resources in skeletal muscle cells. Cr and its phosphorylated form phosphocreatine (PCr) are responsible for the ATP shuttling between mitochondria and cytosol. In this way, during physical activity, myofibres have access to a dynamic reserve of energetic substrates, which remains locked within the cell, also thanks to the negative charge of PCr. Moreover, Cr is involved in the increase of muscle fibre size that might be related to an improvement of protein synthesis or a decrease of protein breakdown [85].

Muscles of DMD patients and *mdx* mice show a marked depletion of Cr and PCr concentration [86]. The administration of creatine in animal models demonstrated an enhancement of muscle strength and oxidative capacity of skeletal muscle cells with a reduction of myofibres necrosis [86–89]. These beneficial effects arose from an essential property of Cr to reduce the chronic Ca^{2+} -overload, a major feature in DMD myofibres. Importantly, it must be taken into account that the effects of Cr supplementation might be strictly related to the disease phase [90–93]. Despite these promising results, long-term studies would be necessary to assess benefits and potential side effects of Cr, particularly analysing interaction with corticosteroids.

5.4.1. Side effects, mechanism of toxicity and interactions

Aside from anecdotal cases of gastrointestinal distress and muscle cramps, a side effect that potentially represents a serious hazard for DMD patients is the weight gain observed after Cr supplementation, becoming more significant with prolonged use of the compound [94]. The increase of body mass is mainly due to water retention and this effect might represent a relevant issue for patients with reduced mobility, and cardiac and hemodynamic sufferance, like DMD boys.

In literature, high variability in responsiveness to creatine supplementation was described. This variance primarily depends on the muscular content of Cr, that is higher in fast-twitch type II fibres. In accordance with this evidence, muscles consisting mainly of type fibres II are more susceptible to Cr supplementation. As is well known, in dystrophic muscles the fibre type mainly affected by pathology is the fast one and a progressive replacement of type II myofibres with fibrotic

tissue is observed. Due to these reasons, a lack of responsiveness to Cr supplementation in DMD patients might be expected [95].

There are serious concerns about the renal safety of Cr. In detail, literature review and adverse events reports (see Table 2) mentioned cases of renal dysfunction in subjects with kidney disease history but also in healthy people taking Cr, even at the recommended dose [96,97]. Furthermore, there are no studies investigating the effect of Cr long-term administration in children/adolescent. Similarly, no clear evidence is available about the interaction of Cr with drugs potentially harmful for the kidney or mainly excreted *via* kidney, and possibly used on demand in DMD patients, including antibiotics, antivirals, hydroxychloroquine and other drugs of potential help in viral infections as COVID-19 [98–100].

5.4.2. Contaminants

It must be considered that Cr supplements most commonly traded in supermarkets, drugstores and also on internet, is a synthetic product derived from the reaction between sarcosine and cyanamide. Possible contaminants produced during this process are creatinine, arsenic, dicyandiamide and dihydrotriazines; all compounds potentially hazardous for human health [85]. For this reason, careful attention should be paid to the source of the product, rather relying on brands prescribed by clinicians, which ensure the traceability of ingredients and which are subject to inspections that guarantee the respect of the good laboratory practices.

5.5. Taurine

One of the supplements with the most multitasking potential is certainly taurine, an amino acid found free in mammalian tissues and particularly abundant in excitable ones. In the human body, taurine exerts various actions, ranging from the antioxidant and the anti-inflammatory effect to the regulation of ion channels functions. This plethora of actions explains the potential use of taurine in the adjuvant therapy of some disorders that affect the muscular system, like myotonia, sarcopenia and disuse muscle atrophy [101]. This is particularly true in conditions characterized by altered tissue amount of taurine as it occurs at different extent in the various phases of dystrophic pathology [89,102]. Preclinical studies in *mdx* mice showed amelioration of functional parameters and markers of necrosis, oxidative stress and inflammation, being more effective than creatine [89,101,103,104]. Accordingly, taurine appears to be most effective in early phases of muscle and cardiac pathology, and synergic effect effects with glucocorticoids have been described [105]. This profile may envisage the potential usefulness in chronic use.

5.5.1. Side effects, mechanism of toxicity and interactions

Taurine supplementation might interfere with hemodynamic: a study in male rats demonstrated that acute injection of taurine induced hypotension and vasodilatation whereas a long-term supplementation in drinking water had hypertensive effect [106]. However, a possible interaction with drugs for blood pressure should be considered.

Taurine also modulates the induction of cytochrome P450 (CYP) 3A [107]. For this reason, a possible interaction with CYP3A4 inducers such as glucocorticoids might decrease blood levels of steroids and other drugs in DMD patients (v. Fig. 3). Furthermore, taurine levels in the body are also controlled by its renal transport, a sodium and chloride dependent mechanism. Then taurine may influence diuresis; in turn, altered kidney function may alter taurine equilibrium in the body [101,108]. Then, the previous considerations raised for creatine about interaction with drugs at kidney level, also apply to taurine.

Adolescent and children consumption of energy drinks with caffeine and taurine is raising globally. Some studies observed an increase in systolic blood pressure and heart rate after consumption. In Table 2 was also reported a case of a young subject who shown symptoms like diarrhoea, tremors and speech disorders after energy drinks

consumption. Taurine also induced an increase of left ventricular stroke volume by suppressing sympathetic nervous stimulation and influencing calcium uptake in cardiac muscle cells and a long-term exposure may cause hypoglycaemia [109].

5.5.2. Contaminants

None described.

5.6. Green tea extract

Green tea extract (GTE), derived from *Camellia sinensis* leaves, contains flavonoids catechins (epigallocatechin-3-gallate (EGCG), epicatechin gallate, epicatechins, gallic acid) that have claimed antioxidant properties. For this reason, GTE supplementation was tested in *mdx* mice to counteract the oxidative stress in dystrophic muscle cells. Preclinical studies demonstrated that GTE improved muscle function and reduced necrosis in muscle tissues of treated animals. Even though encouraging results are available, there is still a lack of consistency among different studies [110–113].

EGCG is the principal polyphenol antioxidant present in green tea and has main potency in preclinical tests. EGCG was also tested in DMD patients (<https://www.clinicaltrials.gov/ct2/show/NCT01183767>) but, currently, there are no results available.

GTE extract is also a component of Protandim® (LifeVantage Corp., San Diego, CA), an over-the-counter supplement with antioxidant activity [114]. Other herbal components of this supplement are, in detail, *Bacopa monniera* extract (45 % bacosides), *Silybum marianum* extract (70 %–80 % silymarin), *Withania somnifera* (Indian ginseng) powder, and curcumin (95 %) from *Curcuma longa*. Protandim was firstly tested on healthy human subjects and a reduction of oxidative stress markers was observed. 6-months administration of Protandim in *mdx* mice confirmed the positive results with reduction of oxidative damage and profibrotic factors. However, no relevant effects on muscle histology and functional parameters were described.

5.6.1. Side effects, mechanism of toxicity and interactions

The most frequent side effects are due to the presence of caffeine in GTE extracts, and are headache, nervousness, sleep problems, vomiting, diarrhoea, irritability, irregular heartbeat, tremor, heartburn, dizziness, ringing in the ears, convulsions, and confusion [115] (see also Table 2). Caffeine has also a diuretic effect [116] and this may exacerbate the urinary calcium loss in DMD patients.

Excessive GTE consumption induced iron deficiency anaemia (case report) [117]. High dose of GTE has hepatic adverse effects: in animal models, EGCG induced hepatotoxicity and several case reports showed hepatic adverse events in humans, associated with an increase of liver enzymes [118,119] (see Table 2).

GTE has an inhibitory effect on drug-metabolizing enzymes: CYP1A2, 2C9, 2D6, and 3A4 [120]. The concomitant administration of GTE and drugs metabolized by the aforementioned cytochromes should be avoided, including steroids (v. Fig. 3), antibiotics and anti-viral drugs.

In addition, EGCG is a competitive inhibitor of the proton-coupled folate transporter (PCFT) that mediates the intestinal absorption of folic acid. Green tea intake could, therefore, interfere with the transport of folate across the small intestine and decrease the bioavailability of this essential vitamin [121]. The lack of folate absorption alters cysteine metabolism, inducing hyperhomocysteinemia (HHcy) [122]. HHcy is involved in skeletal muscle malfunction and could exacerbate the muscle degeneration in DMD.

The number of GTE-cardiovascular drug interactions reported in humans increased in the last years and now include simvastatin, rosuvastatin, nadolol, sildenafil, tacrolimus and warfarin. However, the list might be longer, as suggested by the results of animal experiments with diltiazem, verapamil and nicardipine. GTE may, on one hand, increase the exposure to some drugs (simvastatin, tacrolimus), and, on the other

hand, reduce the exposure to others (rosuvastatin, nadolol) [123]. Green tea consumption might also impair the correct gastrointestinal absorption of antibiotics (*i.e.* amoxicillin [124]) and also inhibits P-glycoprotein (P-gp) activity, a transporter that promotes the cellular efflux of a large variety of drugs including steroids and antiretroviral, increasing their potential toxicity (*v.* Fig. 3) [125,126]. Importantly, glucuronidation is the most important reaction of phase II metabolism of catechins, catalysed by UDP-glucuronosyltransferase (UGT) isoenzymes (1A3, 1A8, 1A9) [127]. DMD patients treated with drugs or other phenol-based nutraceuticals metabolized by UGT may, therefore, incur in unwanted interactions with GTE [128]. For instance, UGT1A9 is also the major enzyme that metabolizes ataluren, a novel drug recently approved for DMD to promote ribosomal read-through for patients with premature stop codon mutations [31,129]. Its metabolism could be delayed or impaired by GTE, with potential toxic effects.

Focusing on Protandim, most common adverse effects are related to allergic reactions to one or more herbal components of the product. (<https://www.tandfonline.com/doi/full/10.3109/21678421.2015.1088707>).

5.6.2. Contaminants

Thirty-two per cent of Chinese tea exceeded the national maximum permissible concentration for Pb [130]. Sources of green tea contamination are: pesticides (HCH and DDTs), environmental contaminants (Polycyclic aromatic hydrocarbons (PAHs)), mycotoxins and microorganisms (Aspergillum, Penicillium, Fusarium), toxic elements (mercury (Hg), lead (Pb), arsenic (As), cadmium (Cd), aluminium (Al), chromium (Cr), and nickel (Ni)), radioactive contaminants (in plantations near areas like Chernobyl and Fukushima), and plant growth regulators [131]. Pb is more bioavailable to tea plants growing in highly acidic soils: Japanese tea had the highest Pb contamination whereas Indian teas had the highest percentage of Cd leaching [132].

On 2012, LifeVantage Corporation announces voluntary recall for lots of Protandim due to contamination with small metal fragments in final products. (https://www.in.gov/isdh/files/LifeVantage_Corporation_Recall.pdf)

5.7. Omega-3 fatty acids

Inflammation is a hallmark of dystrophic muscles: for this reason, omega-3 fatty acids (ω 3FAs) that are claimed to have anti-inflammatory effects, were tested in dystrophic animals. Supplementation with the omega-3 fatty acid eicosapentaenoic acid (EPA) in *mdx* mice induced a decrease of inflammation, creatine kinase and improved muscle regeneration [133,134].

Omega-3 long-chain polyunsaturated fatty acids (Ω 3LCPUFA; 2.9 g/day) intake for 6 months reduced insulin resistance in boys with DMD and showed trends towards slowing the progression of muscle loss and decreasing the fat mass [135].

5.7.1. Side effects, mechanism of toxicity and interactions

A few side effects have been reported in subjects using ω 3FA supplements. Some of these include fishy breath, upset stomach, diarrhoea, and nausea [136].

PUFA are metabolized and often bio-activated by at least four families of CYP, leading to possible PK interaction with a large number of drugs metabolized by CYP enzymes [137].

In addition, PUFA can lead to several PD interactions with drugs acting as anticoagulants and modulating blood homeostasis. An increment of the International Normalized Ratio (INR) in a patient on therapy with warfarin has been reported. It is important to recall that heparins are used empirically in COVID-19 and risk of bleeding in association with omega 3 should be considered. The patient referred to take a high dose of fish oil (2000 mg/d) daily. PUFA, in fact, might interfere with platelet aggregation, with an additive anticoagulant effect [138]. Accordingly, PUFA may have interactions with NSAIDs.

A recent study [139] demonstrated that omega-3 fatty acids are capable of increasing the activity of the ubiquitin-proteasome system (UPS). UPS is a protein network responsible for inducing muscle atrophy and, if not inhibited, promotes protein breakdown. Long-term administration of GC inhibits IGF-1/PI-3 K/Akt/mTOR pathway that normally suppresses the UPS activity. For this reason, the co-administration of omega-3 fatty acids and GC might enhance the pro-atrophic effects of steroids in skeletal muscle.

The excessive consumption of fish oil may also cause hypervitaminosis (vitamin D and A) [136].

5.7.2. Contaminants

ω 3FA sources (fish and fish oils) are often exposed to environmental contaminants/toxins like mercury, polychlorinated biphenyls and dioxins [140]. A case report of 2012 shown an abnormal mercury blood level in a 38 years old man in Canada (see Table 2). Fish oil is also susceptible to oxidation and this process contributes to the rancid conversion of the compound, producing the typical “fishy” smell and aftertaste. This issue suggests an inadequate purification of the product by the manufacturer [140].

Fish oils taken as dietary supplements may contribute significantly to daily intakes of organochlorine contaminants due to the presence of pesticides in marine environments [141]. Most common non-animal sources of ω 3FA are flaxseed, walnut, echium and algal oil. Other potential plant sources are soybean and canola that were genetically modified to contain higher quantity of ω 3FA. However, as no indication about the use and safety of these oils are spread from the food agencies, the consumption of OGM products should be careful [142].

5.8. Vitamin D

Insufficient 25hydroxyvitamin D (25(OH)D) serum levels are seen in DMD boys. This is mainly due to the chronic corticosteroid use by DMD boys. In addition, reduced sun exposure due to little outdoor activities can play a role. Lowered levels of 25(OH)D contribute to reducing bone mineral density with an increasing probability of fractures of long bones and vertebrae. Vitamin D supplementation is a widespread strategy adopted in DMD boys to counteract corticosteroid-induced osteoporosis and is recommended by the standards of care [5,143]. Considering that vitamin D insufficiency may have detrimental role in the immune system, its supplementation in DMD patients should not be interrupted during viral pandemic emergencies, such as COVID-19 [144]. However, caution should be taken according to what described in 5.8.1 and for contaminants (see below).

5.8.1. Side effects, mechanism of toxicity and interactions

Vitamin D is generally considered safe when taken in appropriate amounts but can cause side effects when taken chronically in high doses. Side effects of vitamin D include weakness, fatigue, dizziness, nausea, vomiting, headache, anorexia, and others. Vitamin D assumption can further increase hypercalcemia as frequently reported *i.e.* in the UK (Table 2) and consequently, calcium supplementation needs to be monitored and balanced [145,146]. Excess vitamin D is also associated with symptoms related to hypercalcemia, such as hypertension, anorexia, nausea, and possible kidney damage [30].

25-hydroxylation of vitamin D₃ is the first step to produce the most common form of circulating vitamin D and occurs in the liver by means of a reaction catalysed by several CYP enzymes, such as CYP27A1 and CYP3A4 [147]. Literature reports occasional cases of drug-drug interactions with drugs metabolized by the same CYP (*e.g.*, anticonvulsants), with an accelerated degradation of vitamin D and consequent osteomalacia [148].

Vitamin D intake is associated with improved absorption of essential inorganic elements (calcium (Ca), magnesium (Mg), copper (Cu), zinc (Zn), iron (Fe), and selenium(Se)) but has also been linked to enhanced uptake of toxic elements such as aluminium (Al), cadmium (ca), cobalt

(Co), and lead (Pb) as well as radioactive isotopes including caesium (Cs) and radioactive strontium (Sr). In children, elevated 25(OH)D₃ levels are associated with an increase in blood lead levels [149]. Bioaccumulation of toxic metals, in turn, counteracts the renal synthesis of vitamin D active form.

5.8.2. Contaminants

In 2017, FDA released a warning letter about a potential contamination of batches of liquid Vitamin D products with bacteria *Burkholderia cepacia* (<https://www.fda.gov/news-events/press-announcements/fda-warns-potential-contamination-multiple-brands-drugs-dietary-supplements>). This bacterium causes severe respiratory infections, particularly resistant to antibiotics treatment. Accordingly, contamination with *B. cepacia* could be dangerous for subjects with respiratory distress and for children with immature immune system, like DMD boys.

5.9. Resveratrol and curcumin

Resveratrol supplementation has been associated with a variety of health benefits in skeletal muscle, such as increased oxidative capacity, decreased protein degradation, and decreased activation and inflammation. For this reason, this compound was tested in dystrophic animals and preclinical studies suggested that resveratrol supplementation may exert amelioration of muscle function and maturation of skeletal muscle cells by reducing oxidative stress [103,150,151].

The mechanism of NF- κ B inhibition is proper of another compound already tested on *mdx* mice: curcumin. This curcuminoid, produced by *Curcuma longa*, was administered i.p. in *mdx* mice for 10 days [152]. Treated mice showed an amelioration in muscle function and a mitigation of dystrophic symptoms. Nevertheless, a previous study [153], demonstrated that NF- κ B activity of *mdx* mice of three different ages (10 days; 4 and 8 weeks) was resistant to inhibition by oral curcumin supplementation, suggesting that the route of administration might heavily influence the bioavailability of the compound.

5.9.1. Side effects, mechanism of toxicity and interactions

In vitro studies, [154] showed that resveratrol is an irreversible inhibitor for CYP3A4 and a non-competitive reversible inhibitor for CYP2E1. CYP3A4 activity is important for the metabolism of calcium channel antagonists (e.g. felodipine, nicardipine), immunosuppressants (e.g. cyclosporine, tacrolimus), antihistamines (terfenadine), sildenafil, antiretrovirals; therefore, a possible interaction with drugs should be considered [155–157]. In addition, resveratrol is metabolized by liver and intestinal UGTs and may cause, like catechins, unwanted interactions with drugs metabolized by the same enzymes [127].

Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition [158]. Since glucocorticoids inhibit mTOR activity [159], possible additive effects should be taken into account [160] (v. Fig. 3).

Curcumin is generally considered as safe [161]. Studies in human subjects have shown only moderate adverse effects, like bloating, diarrhoea, headache and nausea [162,163].

5.9.2. Contaminants

None reported. However, careful attention of production chain for commercial resveratrol is advised, like pesticides, heavy metals and other contaminants can be present in grapes, soy, *Polygonon cuspidatum* and other resveratrol sources [164].

Analyses on curcumin supplements revealed contamination with metanil yellow (C₁₈H₁₄N₃NaO₃S), a toxic colorant used to adulterate *Curcuma longa* powder [165]. Furthermore, other compounds commonly used as adulterants are pigments containing lead, with serious concerns about the safety of these products [166,167].

5.10. N-Acetylcysteine

Because muscles in dystrophic individuals may produce more reactive oxygen species (ROS) and are thought to be more susceptible to oxidative damage, antioxidant supplementation may serve as an adjunct therapy that can be easily incorporated into treatment plans. N-acetylcysteine (NAC) is a potent antioxidant and has been studied as a potential DMD treatment in *mdx* mice [168–170]. In detail, NAC is a precursor of the amino acid cysteine that can itself function directly as an antioxidant, and indirectly through glutathione synthesis. Cysteine is also a precursor of taurine synthesis and the increase in muscle taurine content contributes to the amelioration of strength and function of *mdx* muscle, both *in vivo* and *ex vivo* [171,172]. Importantly, although it has no direct anti-viral actions, NAC has been claimed to have protective effects against pulmonary damages during viral infections in both pre-clinical and clinical studies due to its antioxidant and mucolytic activities [173–175]. Then safety issues of NAC as supplement deserve attention, also for the focus it may have in the media, as occurring during the COVID-19 emergency.

5.10.1. Side effects, mechanism of toxicity and interactions

A clinical trial in cancer patients revealed mostly gastrointestinal side effects, including nausea, vomiting, bloating and diarrhoea [176] (Table 2).

Paradoxically, long-term administration of NAC in humans increases oxidative stress after an acute muscle injury induced by eccentric exercise, with higher blood levels of markers of inflammation [177].

A preclinical study in *mdx* mice showed that NAC significantly impaired body weight gain in young growing mice (both *mdx* and wild type), and reduced liver weight in C57 mice and muscle weight in *mdx* mice [178].

5.10.2. Contaminants

None described.

5.11. Coenzyme Q₁₀

Coenzyme Q₁₀ (CoQ₁₀) is a naturally occurring compound that plays a fundamental role in cell bioenergetics as a cofactor in the mitochondrial electron transport chain. CoQ₁₀ is also a potent antioxidant and may counteract the excessive ROS production in dystrophic myofibres. The compound was tested in different clinical trials in DMD patients with encouraging results: CoQ₁₀ supplementation ameliorated the impaired myocardial function and physical performance [179–181], although no significant improvement in echocardiographic parameters was revealed [182]. Interestingly, idebenone, a synthetic analogue of CoQ₁₀ sharing its antioxidant profile, is at an advanced stage of development for treating cardiorespiratory dysfunction of DMD patients [182–184].

5.11.1. Side effects, mechanism of toxicity and interactions

There are no serious adverse events reported. One patient developed a headache of moderate intensity associated with high blood levels of CoQ₁₀. The event resolved with a decrease of the dose [179].

CoQ₁₀ supplementation may result in a reduction of diastolic blood pressure and might increase the effect of medication with anti-hypertensive activity [185].

5.11.2. Contaminants

None described. Sources (animal tissues and extracts and whole grains) have to be ensured for quality and purity.

5.12. Melatonin

Several studies corroborate the view that melatonin might protect

many tissues, including skeletal muscle, from oxidative stress, due to the antioxidant properties of this compound and its metabolites. In *mdx* mice, muscle of treated animals showed an amelioration of the contractile function of dystrophic myofibres, accompanied by a decrease of CK plasma levels [186].

In DMD patients, melatonin treatment normalizes plasma pro-inflammatory cytokines and nitrosative/oxidative stress, with a reduction of inflammation and muscle wasting [187].

Recently, interest has been raised around melatonin for its anti-inflammatory, immunomodulatory and sedative actions, that may foresee the use of melatonin as adjuvant to contrast the exaggerated immune response finally leading to acute lung injury and acute respiratory distress syndrome in critical care patients with COVID-19 [188]. These may further increase the use of melatonin as supplements by DMD patients as adjuvant in seasonal viral pandemics.

5.12.1. Side effects, mechanism of toxicity and interactions

Oral melatonin reduces blood coagulation activity with a dose-response relationship [189]. It has been reported that the evening administration of melatonin in hypertensive patients taking the calcium antagonist nifedipine, interfered with the mechanism of cardiovascular regulation, inducing an increase in blood pressure [190]. Melatonin seems to interfere with calcium signalling *via* calmodulin. This suggests caution should be taken in uncontrolled use of melatonin in hypertensive patients as well as possible interference with antihypertensive drugs.

Lastly, it should be underlined that the actual safety of melatonin was not properly assessed, in paediatric population. Doubts were raised over the potential harmful effect of melatonin supplementation on endocrine and reproductive systems in children and adolescents [191]. Further enquiries are needed to evaluate the effects of melatonin in young subjects.

5.12.2. Contaminations

A recent study demonstrated that a quarter of melatonin products sold in one city in Canada contained serotonin, some at potentially significant doses [192,193]. An increment of serotonin levels might cause symptoms like tachycardia, palpitations and hypertension as observed in some cases reported in Table 2. Reports indicated that the eosinophilia-myalgia syndrome (EMS) was triggered by the consumption of a contaminated batch of the dietary supplement L-tryptophan (L-Trp). Because melatonin is structurally like to L-Trp (both compounds contain the indole ring functionality), a study investigated the nature of the contaminants in commercial preparations of melatonin. Several contaminants in commercial preparations of melatonin were found (formaldehyde-melatonin condensation product and two structural isomers of hydroxymelatonin). Of interest, an EMS-related contaminant in L-Trp referred to as "peak C" has been proposed as a 5-hydroxytryptophan isomer. These findings should raise serious questions about the consequences of long-term ingestion of melatonin preparations containing such impurities [194].

6. Potential interaction between dietary supplements and advanced therapies: an unexplored world

Increasing efforts in DMD are devoted toward therapies able to counteract the absence of dystrophin by means of innovative approaches, such as antisense oligonucleotides (ASO) for skipping mutated exons and restoring reading frame, gene editing such as CRISPR/Cas9, transfer of microdystrophin gene and cell therapies. Two ASOs, eteplirsen and golodirsen, have been recently approved by FDA and others are currently in clinical trials, as well as gene and cell therapies. Little or no data are present about the possible interaction of those innovative therapies with classical drugs and even more with dietary supplements. Below an attempt to underline the main points of interaction susceptibility of these innovative approaches.

6.1. Antisense oligonucleotides

ASOs approved for DMD are phosphorodiamidate morpholino oligomers (PMO), very stable molecules in biological systems, administered in weekly regimens and mostly eliminated as such by renal excretion. Then approved ASOs do not undergo main metabolism *via* hepatic microsomes nor are they substrates of main transporters in the body. So, it is generally believed that the level of interaction with drug, food and dietary supplements is low. Both eteplirsen and golodirsen have little if any activity as inhibitor or inducer of cytochromes [195,196], golodirsen being a weak inducer of CYP1A2. This cytochrome is involved in the metabolism of various commonly used drugs and also involved in the biotransformation of PUFA; then interaction cannot be excluded.

Although the available information does not support major harmful interactions, these compounds have potential toxicity at kidney and liver level, suggesting that these tissues could be a possible site of harmful interactions. Moreover, since they are not very well absorbed at cellular level and they are excreted very fast *via* the kidney, supplements increasing renal clearance could interfere with their efficacy. Other ASOs under development may have different profiles and specific interaction can occur. Patients in clinical trials should then avoid using dietary supplements without medical control.

6.2. Cell therapy

Cell therapy represents another innovative approach for many diseases, including DMD. Various muscle progenitor cells have attracted interest, with some of them, such as mesangioblasts, tested in clinical settings, due to their ability to cross vessel wall in order to reach the site of the damage [197,198]. Although very little is known about possible interaction with drugs or with dietary supplements, it is intuitive to predict they may occur at various stages of cell therapy. In fact, muscle precursors are highly proliferating cells which are known to critically depend, for proliferation, fusion and adhesion, on nutrients, such as glucose and amino acids, *via* high expression of specific transporters such as CD98hc [199,200]. Also, extravasation may need a concerted action of cytokines and molecules involved in oxidative stress signalling and endothelial permeability, which may also be modulated by either drug or supplements. Another point of interaction can be related to a massive immune response that may be induced by the administration of high amounts of cells, which can also be influenced by supplements such as BCAA [201]. Then, although not easy to decipher, interaction with complex outcome may occur between cell therapies and dietary supplements.

6.3. Gene therapy

The idea behind gene therapy is to treat the pathology by substituting the defective gene(s) or at least one copy of it. For what it concerns muscular dystrophy, considering the size of dystrophin protein (usually not fitting in an adeno-associated virus (AAV)-vector), the transfer of microdystrophin is under clinical assessment [202]. One of the main points of interaction relates to the need to control the immune reaction to viral vectors and the new protein, then immunosuppressive drugs can be required. Accordingly, supplements able to modulate PD or PK profile of immunosuppressive drugs should be used with caution.

Another promising approach for DMD is nowadays offered by genome editing using the CRISPR/CAS9 technique. For this approach, important concern can be raised for off-target actions and gene mismatch [203,204], which can modify key organ functions for drug and supplement mechanism and clearance.

Basically, each of these new therapies presents a peculiar mechanism of action, also because they use different cell machinery and they act at different levels (DNA/RNA/protein). For this reason, it will be pivotal to fully understand and not rule out possible interactions

with supplements.

7. Discussion

During the last years, the interest in natural, dietary supplements is increasing in the DMD field as adjuvant approaches in controlling both dietary requirement and pathological events. The recent emergency due to the outbreak of SARS-CoV-2 further increased the interest toward dietary supplements, among the population worldwide. A recent report of New York Times on March 23, 2020, underlined the increase of sales of supplements with claimed action on cold and flu with respect to the same period of 2019, with specific peaks for so called immune boosters, among which vitamin C, zinc, and others, for the hope to prevent or better manage the Sars-CoV-2 infection by reinforcing natural defences (<https://www.nytimes.com/2020/03/23/well/live/coronavirus-supplements-herbs-vitamins-colds-flu.html>). Similarly, a Google search of “dietary supplements” and “COVID-19” on March 31st, 2020 led to more than 12 million of results, underlying the great interest on this topic from different stakeholders.

It is therefore understandable, and even more justified by the fragility of the population, that such interest also arises from DMD community. This for the hope to improve standard of care as well as to get protection in case of an unexpected health emergency, as dramatically arose for COVID-19 recently emerged from World Duchenne Organization (<https://www.worldduchenne.org/news/live-covid-19-coronavirus-and-duchenne-becker-muscular-dystrophy/>).

Many caregivers/patients may mistakenly assume these supplements are safe. They think that if a supplement will not be beneficial then it will also not be harmful, so it does not hurt to try. This can be amplified by media and internet, also in relation to economic interests. Consequently, the risks of dietary supplements are seriously underestimated and often their use is not discussed with experts (either medical specialists, practitioners or pharmacists), nor related to any proven nutritional deficits. In fact, most of the dietary supplements discussed herein and even those with claimed effect on the immune system, such as vitamin C, are present in food, especially fresh fruits and vegetables. Then, a proper diet, healthy and varied, is the first aid to supply necessary essential elements, amino acids and vitamins. Supplements can, on the other hand, exert unwanted effects related to the use of excessive doses or interact with other medicines patients are using, either inhibiting or enhancing their efficiency and cause serious health risks. There is often no solid proof of dietary supplements effectiveness, while many side effects have been reported, including the complication or the ineffectiveness of outcome of other therapies (see Table 2). Then, prolonged use of supplements may cause several adverse effects, that often lead to emergency department visits and, in severe cases, hospitalization. In United States alone, approximately 23 000 emergency department visits and 2154 hospitalizations are connected every year to side effects related to dietary supplement [205].

For DMD and also for BMD patients these interactions can be of particular relevance as they can occur with drugs used for standard care or with innovative therapies during clinical trials. A similar situation also applies in emergency cases, as in the current pandemic by Sars-CoV-2. In fact the treatment of symptomatic COVID-19 patients is still a largely empirical approach with a wide variety of drugs according to the phase of the disease and ranging from antiviral and antibiotics, repurposed old drugs, such as chloroquine and hydroxychloroquine, to immunosuppressants, monoclonal antibodies and low-molecular weight-heparins. All these class of therapeutics have either a low therapeutic index or can per se at high risk of ADR events which may increase with uncontrolled D-D and D-S associations. In addition, more than 1200 clinical trials are currently ongoing on COVID-19 worldwide (clinicaltrials.gov) which reinforce the need for caution in uncontrolled use of supplements.

Another issue is that the quality check of these supplements is not always as rigid as it should be and they can be contaminated, certainly

when they are retrieved from less controlled sources, like *via* the internet.

Awareness of the risks of uncontrolled use should be raised amongst caregivers and patients. They should be encouraged to always first discuss with their clinicians and pharmacists before starting supplement use and only retrieve them from certified sources, like their pharmacy.

Supplement use can also be a confounder in clinical studies and thereby influence the results. Unexplored interactions may reduce the efficacy of innovative therapies in clinical trials or cause unexpected toxicity. A database about the use of food supplements in DMD and BMD population, also in relation to geographical distribution, would be important, also with the aim to carry on properly conducted clinical studies. In parallel, it is important to consider that there is an increasing awareness to focus on dietary requirement in DMD patients. Then a reinforcement of active surveillance may help to detect ADR by dietary supplements, while patients' registries can be of support for better understanding supplements use in relation to geographic and cultural aspects. Accordingly, it is pivotal to reinforce translational research in the field of supplements, considering the different nutritional requirements in different species used for preclinical studies [28,29].

8. Conclusions

This review underlines that supplements may represent an important support in nutritional deficit occurring in DMD patients, although dosage and efficacy need to be better established with controlled studies [28]. Safety is a main concern, based on the concept of “*primum non nocere*” (first, do no harm). Caution has to be taken in properly discussing with experts before deciding to start using supplements. Also, supplements from unknown sources or acquired *via* the web or outside pharmacy or other authorized retailers should always be avoided. In this respect, the active role by regulators and health professionals helps to provide correct information, in order to avoid direct use of products that escape the normal paths of distribution or do not provide the possibility to check quality control or surveillance [37]. The uncontrolled use of dietary supplements may, in fact, represent an important confounding factor during the development of new therapies or during studies aimed at repurposing drugs in DMD. The pandemic emergency of COVID-19 provided further evidence of this critical issue, as seen by the greater demand for dietary supplements. Patients and caregivers aim to be protected, especially for the evident difficulties to put in place effective social distance for proper assistance of fragile patients. However, also in these conditions, the best prevention resides in efforts in maintaining proper food, hygiene and individual protection devices for patients and/or caregivers. Although specifically focused on DMD, the considerations raised in the present review can also apply to BMD and to other neuromuscular and non-neuromuscular rare patients, that share similar fragility, complexity and uncertainties.

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Declaration of Competing Interest

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