THE RISKS OF NUTRITIONAL SUPPLEMENTS
The main principle in health care is “primum non nocere” (first, do no harm). This means that the benefits should always outweigh the risks and safety comes first. This does not only apply to medical and drug therapies, but more widely to all activities and compounds used that affect your health/wellbeing. Therefore, knowledge about the risks of using nutritional supplements is very important. In this document the main concerns and the benefits/risks of the most commonly used supplements are discussed.

Treatment interactions
Most DMD patients are using a cocktail of different medicines. Next to the widely used corticosteroids (i.e. prednisone or dexamethasone), patients often use cardiac medicines, participate in clinical trials and/or use vitamin D or calcium supplements. If treatment regimens are complex (i.e. consist of multiple medicines) there is a chance of drugs interacting with each other. This can lead to them being less effective or potentially harmful. Because of this, before starting with (new) medications, they should be carefully checked for safety and constantly monitored. This risk does not only apply to (prescribed) medicines, but also to nutritional supplements (nutraceuticals) taken over-the-counter. You should always, at every visit, tell your doctor and, even more importantly, your pharmacist what you are/your child is using and if there have been any changes since your last visit. Pharmacists have the most knowledge about the working mechanisms of medicines and supplements, and their interactions. If you have any questions, they are the first point of contact.

Main concerns of nutritional supplements
Nutraceuticals are widely used, not only for DMD. Their use is based on their claimed health benefits; however, for the majority of them, solid evidence is lacking. A large misconception is that they are safe to be used, since they are of natural origin and widely available. Nonetheless, their use can be dangerous, have many side effects and cause discomfort. The same efficacy and safety principles apply as for regular medicines. First of all, the concentrations in the supplements are far higher than you will get by normal food intake. Secondly, some compounds contain active elements also found in regular medicines. Most importantly, often regulations are lacking and supplements can be contaminated with other substances (i.e. of which the effects are unknown). The risk of this is even higher if supplements are bought via the internet, where the origin is often unclear.
Nutritional supplement use in DMD

There are only two supplements, vitamin D and calcium, that are recommended by the standards of care (updated version published in 2018) for use in DMD if natural intake and blood levels are too low. They should only be used when prescribed by your doctor. Other supplements may be prescribed in case of a clear nutritional deficit, as may occur in specific phases of the disease. Since most patients use supplements on their own initiative, the magnitude of and exact supplements used is unknown. Here we discuss the most widely used nutraceuticals, bearing in mind that these are NOT recommended for general use in the standards of care.

Leucine, isoleucine, and valine

Leucine, isoleucine, and valine (so called 'branched-chain amino acids (BCAA)') may counteract muscle wasting, but only few studies have been performed in DMD patients. Two studies from the eighties show mixed results. One study indicated a positive effect of leucine on muscle protein quantity; however, in a well-controlled, large study no improvement of muscle function was seen.

The main side effects are related to the stomach/intestines (i.e. nausea, decreased appetite and anorexia). Furthermore, they can have an effect on glucose and insulin metabolism. They can be contaminated with anabolic steroids, which influence the hormonal system.

L-arginine

L-arginine might improve the energy system of the cells, which could increase their viability. Only one small study in five DMD boys has been done, combining L-arginine with metformin (another compound that may improve energy metabolism). Some functional improvement was seen, but this study was far too small to draw reliable conclusions.

Studies in healthy persons and other disease groups indicated that the use of L-arginine is generally safe, but it can cause nausea and diarrhoea. Another concern is that L-arginine also has effects on other systems, which can result in low blood pressure. Especially in patients using antihypertensive drugs this could lead to serious cardiac problems.

Glutamine
Glutamine levels are low within dystrophic muscle and the total amount of glutamine available is lowered in DMD. Glutamine is important for muscle and may therefore be essential in DMD. Nonetheless in DMD patients no beneficial effects have been seen.

In many non-DMD studies glutamine has proven relatively safe, but it affects insulin levels and should therefore be avoided in diabetic patients using insulin. Also, glutamine supplements can be contaminated with anabolic steroids.

Taurine
Taurine has many effects in the body (e.g. antioxidant and anti-inflammatory), whereby it can be a potential additional therapy for some disorder; however, it also increases the risk of interaction with other medicines. Taurine has never been tested in DMD patients, only in DMD animal models; effects have been seen, indicating potential efficacy in early phases of muscle and cardiac pathology.

Risks of taurine are that it may induce hypotension in the short-term (low blood pressure), but in the long-term it induces hypertension (high blood pressure). Therefore, special caution is needed when drugs for blood pressure are used in parallel. It could also lead to higher levels of steroids if they are used together. Taurine is also present in energy drinks as Red Bull. This drink should also be avoided.

N-Acetyl cysteine
N-Acetyl cysteine can directly function both as an anti-oxidant (counteracting the oxidative stress on muscle cells, seen in DMD) and as a precursor of taurine. Also, N-Acetyl cysteine has never been tested in DMD patients, and amelioration of strength and muscle function has only been seen in animal studies.

During a trial in cancer patients, patients experienced nausea, bloating and diarrhoea. In mice, also DMD mice, impaired body weight gain during growth and reduced muscle weight were seen.

Green tea extracts
Green tea extract (GTE), e.g. Chinese tea, and its major compounds (epigallocatechin gallate (EGCG), epicatechin gallate, epicatechins and gallic acid) are one of the most used supplements by DMD patients. Their active ingredients may have antioxidant properties and have been shown to protect the muscle cells against oxidative stress in DMD mice. It must be noted that in these studies the dose used is far higher than can be used safely in humans. Several clinical trials have been conducted in DMD or BMD patients, but no results have been published yet.

GTE can have many unwanted effects. An important source
of side effects is caffeine present in GTE (e.g. headache, vomiting, diarrhoea, heart problems, sleep problems). Importantly it may also have diuretic effects, leading to an additional loss of calcium via the urine (calcium is important for bone health, especially in DMD patients using corticosteroids). GTE could also lead to anaemia and liver toxicity. Furthermore, there are multiple reports of interactions with cardiovascular drugs. One third of Chinese tea contains too much lead. GTE can also be contaminated with other heavy metals and pesticides.

**Omega-3 fatty acids**
Omega-3 fatty acids (e.g. present in fish oil) have anti-inflammatory effects (inflammation is a hallmark of dystrophic muscle). Only one study has tested its effect in DMD and saw some improvements in muscle function as well as reduced insulin resistance.

Reported side effects are nausea and diarrhoea. Excessive use can also lead to too high levels of vitamins A and D. Fish oil is often impure and may contain toxins and/or pesticides.

**Resveratrol**
Resveratrol supplementation has been associated with a variety of health benefits in skeletal muscle and indeed mouse studies suggest it may have beneficial effects. This has, however, not been confirmed in patients.

Preclinical studies indicate possible interactions with other drugs. Most importantly, it also inhibits a protein, called mTOR, which has been associated with severe muscle breakdown.

**Coenzyme Q10**
Coenzyme Q10 can improve the energy metabolism and act as an antioxidant. Studies in DMD patients indeed showed an improvement in energy status and physical performance, but no improvement in cardiac function.

In these trials no serious side effects were seen, only some headache, but it may reduce blood pressure. Therefore, extra caution is needed when antihypertensive medicines are also used.

**Melatonin**
Melatonin may protect many tissues, due to its anti-oxidative effects. A single, small study has been performed in DMD, in which normalization of plasma levels of several markers for inflammation and oxidative stress was seen. The study, however, did not look at any functional effects.

In patients suffering from hypertension being treated with a calcium inhibitor (nifedipine), there was interaction between melatonin and nifedipine, whereby melatonin counteracted the effect of nifedipine and lead to increased blood pressure. Some melatonin products have been found to be contaminated with...
significant doses of serotonin, which has psychological effects and is used, among others, in antidepressants. Also, other contaminants have been found and many commercial preparations contain impurities. This raises serious concerns for their long-term use.

Laxatives
Laxatives are also available over the counter, but you should always first discuss with your clinician and your pharmacist which laxatives are most appropriate for you and how long you should take them.

Many DMD patients suffer from constipation, due to reduced function of the intestines (dystrophin is also present in these muscle fibres), diet and/or decreased activity. Laxatives haven proven to be beneficial in DMD and are used by many, especially older, patients. Laxatives and other medicines can be helpful and certainly have more benefits than risks, if they are used properly. Many different types of laxatives exist. Some of these can be very dangerous for patients with cardiomyopathy and/or using cardiac medication. Ask your primary care provider or neuromuscular team which laxatives are most appropriate for you and how long you should take them. Improper use can lead to (serious) side effects, which may lead to emergency department visits, or even hospitalisation. Most common adverse events are cardiac related. Other common side effects are diarrhoea and abdominal pain.

Main points
For most nutritional supplements little evidence supporting there use for DMD, exists. Using unprescribed nutritional supplements can be dangerous and lower the working of your regularly prescribed medicines. You should always first discuss with your doctor and pharmacist before using any over-the-counter supplement. If thereafter is decided to use a supplement always obtain them from established suppliers and never buy anything via the internet.

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