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EFFECTIVENESS OF DIETARY SUPPLEMENTATION WITH UBIQUINONE, IN USE OF STATINS, IN THE PREVENTION OF MYOPATHIES

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Abstract: HMG-CoA reductase inhibitors or statins act on the mevalonate pathway, preventing the formation of GPP (geranyl pyrophosphate) and consequently the formation of isoprenoids such as dolichols and ubiquinone, which are used in mitochondrial metabolism to produce ATP (adenosine triphosphate). and its lack leads to the development of statin-related muscle symptoms (SMRE). The entire theoretical reference of the research was taken from the PubMed, Google Scholar and Scielo databases, over the last 5 years, in Portuguese, English and Spanish, the Boolean operator used was "AND", 49 articles were found, from which we selected -se 10. Studies have demonstrated the effectiveness of ubiquinone in the treatment of SMRE, as by acting directly on the pathophysiology that involves the decrease in ATP and the impairment of muscle function, it promotes a quantifiable improvement in fatigue, pain and other muscle symptoms. While some studies reported doubt regarding the efficiency of CoQ10, others expressly denied the beneficial effects of ubiquinone supplementation. During the research, factors were found that limited further investigation into the subject, which were the scarcity of studies that followed supplementation with ubiquinone over a prolonged period, the failure to establish an effective dosage for the use of CoQ10 to prevent ERMS, in addition to the little attention to the comorbidities and lifestyle habits that were related to the pathology of the patients studied. The supplementary use of CoQ10 showed positive results when used individually. In this way, it proved to be a highly viable option to prevent ERMS, even though there is not yet the diversity of studies necessary to establish medical management.

Keywords: Ubiquinone. Statins. Myopathy. Hydroxymethylglutaryl-CoA Reductase Inhibitors. Dietary supplements**.**

INTRODUCTION

It is known that statins are drugs prescribed for different etiologies that are associated or not with dyslipidemia, in addition, their pleiotropic action can be highlighted, which is highly favorable to their users (Attardo 2022). There is a wide variety of these drugs on the market with a similar mechanism of action, but they differ into two groups in terms of affinity to water or lipids, as expressed in the table below:

Lipophilic Statins	Hydrophilic statins
Atorvastatin	Rosuvastatin
Fluvastatin	Pravastatin
Simvastatin	
Pitavastatin	
Lovastatin	

Table 1- Statin subtypes

Source: ATTARDO, 2022

It is generally known that the most effective prophylactic therapy for atherosclerotic disease are HMG-coenzyme A reductase inhibitor drugs, which is why such drugs are the most prescribed in the United States (RAIZNER 2019).

Statins inhibit HMG-CoA reductase, acting on the mevalonate pathway, an essential component in the biosynthesis of endogenous cholesterol, limiting its formation, especially low-density lipoproteins (LDL), however, this restriction on the mevalonate pathway also inhibits the production of GPP (geranyl pyrophosphate) which would be converted into FPP (farnesyl pyrophosphate), then to GGPP (geranyl geranyl pyrophosphate) and finally into isoprenoids, such as dolichols and ubiquinone, affecting muscle mitochondrial function.

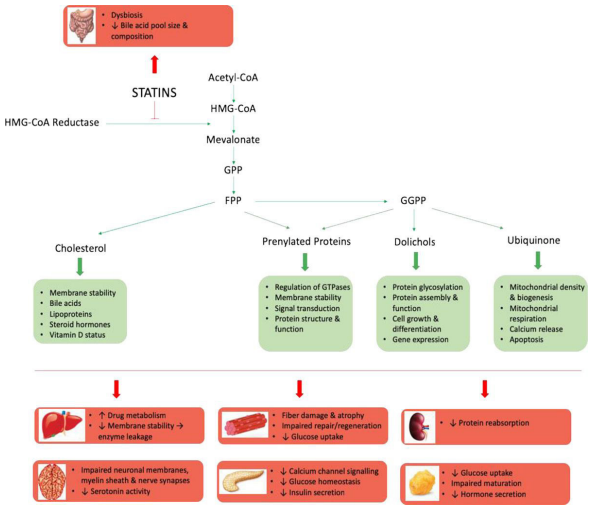

Figure 1- Potential mechanisms for the development of statin toxicity

Source: WARD, 2019.

Non-steroidal isoprenoid cholesterol is of great importance in gene expression, cytoskeleton construction, protein glycosylation, intracellular signaling and even cell differentiation and growth (WARD 2019).

The decrease in ubiquinone levels compromises the mitochondrial capacity to generate energy, resulting in the appearance of SMRE (muscle symptoms associated with statins), as it is related to the generation of ATP (Adenosine Triphosphate), in addition to being an important enzymatic cofactor and antioxidant. According to Hua (2018), "the reduction in coenzyme Q10 could be associated with myopathy in patients treated with statins". Therefore, SMRE have a wide range of presentations, ranging from myalgia, myopathies associated with an increase in creatine kinase (CK), which can cause rhabdomyolysis, its most serious consequence, culminating in acute renal failure and/or death. Look at the table below:

ADR	Myalgia (n=2,870)		Myopathy (n=233)		Rhabdomyolysis (n=613)	
Statin	≤60 years (n=1,174)	>60 years (n=1696)	≤60 years (n=88)	>60 years (n=145)	≤60 years (n=159)	>60 years (n=454)
Simvastatin (n=1,191)	369 (41.2%)	526 (58.8%)	31 (40.8%)	45 (59.2%)	51 (23.2%)	169 (76.8%)
Atorvastatin (n=1,784)	554 (40.6%)	812 (59.4%)	41 (36.3%)	72 (63.7%)	86 (28.2%)	219 (71.8%)
Rosuvastatin (n=741)	251 (41.2%)	358 (58.8%)	16 (36.4%)	28 (63.6%)	22 (25.0%)	66 (75.0%)

p>0.05

Table 2 - Distribution of reports of ADRs of myalgia, myopathy and rhabdomyolysis with statins according to age (n=3,716)

ADR (Adverse drug reactions), EU (European Union)Fonte: IÑESTA apud EudraVigilance Data Analysis System, 2019

The table above shows the relationship between the class of statins, represented by three drugs, with muscular symptoms such as myalgia, myopathy and rhabdomyolysis in groups of people up to 60 years of age and groups over 60 years of age (IÑESTA apud EudraVigilance Data Analysis System , 2019). In the meantime, attention should be paid to the proven relationship between the use of statins and the appearance of ERMS, as well as a higher prevalence in the elderly.

Therefore, supplemental CoQ10 appears as a highly suitable option for preventing these symptoms, as it restores the shortage of ubiquinone to the mitochondria of the muscles, especially the cardiac and skeletal striatum, as these tissues require a greater supply of adenosine triphosphate. (ATP) for your activities.

METHODOLOGY

The selection of data sources was carried out through a search in the databases: PubMed, Google Scholar and Scielo, to identify relevant studies published in the last 5 years (2018-2023). The search terms used included "Ubiquinone", "statins", "myopathy", "Hydroxymethylglutaryl-CoA Reductase

Inhibitors", "Dietary supplements" and related variations, the Boolean operator chosen was "AND". The search was restricted to studies in English, Portuguese, Spanish and carried out only on human beings.

Included were studies that investigated the effectiveness of coenzyme Q10 supplementation in preventing statin-induced myopathy. Studies that reported objective measures of myopathy, incidence of clinically diagnosed myopathy, or the presence of clinical symptoms of myopathy were considered.

The articles were then surveyed, carefully read and selected according to the inclusion criteria already mentioned above. Exclusion criteria were considered, as follows: Studies that were not among the three chosen languages that deviated from the proposed topic, that addressed another type of supplementation along with ubiquinone, that were limited to discussing other non-myopathic adverse effects, which explained exclusively on adverse effects unrelated to statins were also waived.

RESULTS AND DISCUSSION

49 articles were found, 45 on Google Scholar, five on Pubmed and none on Scielo. Of the 45 found on Google Scholar, 41 were in English and four in Portuguese, on Pubmed all five were in English, no articles were found in Spanish. Of these 49, 36 were excluded because they did not meet the inclusion criteria and/or met the exclusion criteria, in addition, two others that had restricted access were excluded. Finally, the number of articles selected was 10.

According to an analysis carried out using an established theoretical framework, ubiquinone was partially demonstrated to be effective both in the treatment of statin-associated muscle symptoms (SMRE) and in their prevention. Since ubiquinone depletion and the resulting mitochondrial dysfunction are the main pathophysiological cause of ERMS, through a decrease in ATP production compromising the capacity for muscle contraction and recovery, which leads to the process of early muscle fatigue.

However, other studies still demonstrate some doubt regarding CoQ10 and its real effect, such as KENNEDY (2020) "A significant reduction in muscle pain in the group treated with CoQ10 compared to placebo was reported in two studies, while the remaining six studies did not find a significant reduction in the pain score", others have demonstrated a certain ambiguity in their results, as expressed by CHEN (2022) "Several randomized controlled trials (RCTs) have tested the effectiveness of CoQ10 in the treatment of SMRE, but the interpretation is not clear because some of the CoQ10 RCTs found significant benefits, but others did not."

While other articles denied the beneficial effects of using CoQ10, such as WARD (2018) "Only 36% of patients had reproducible myalgia and, in these, CoQ10 did not improve symptoms, muscle strength or maximum oxygen consumption during the period of 8-week treatment."

It is worth mentioning that, a restrictive factor is the scarcity of randomized studies that favor a longer period of treatment with ubiquinone in individuals who present muscular symptoms related to statin or that consider the comorbidities of each patient, their lifestyle habits, diet and their level of sedentary lifestyle. So that it is understood which types of patients will benefit from the use of ubiquinone and those who may not demonstrate any benefit.

Another limiting factor is related to the failure to establish an effective dosage of ubiquinone supplementation in the prevention and/or treatment of ERMS. Furthermore, it is not known for certain which statins, in long-term use, would be mandatory or highly The

association with CoQ10 is recommended to prevent SMRE.

Therefore, it is suggested to carry out research that seeks to establish an effective therapeutic dose of ubiquinone in randomized groups with the presence of individuals who do not use statins, comparing it to a group in continuous use of statins, specifying the statin, the dose used and the duration of use, in addition, paying attention to the comorbidity of patients.

CONCLUSION

Therefore, CoQ10 supplementation, according to much of the theoretical framework, demonstrated results when used individually, taking into account the severity of the patient's dyslipidemia and the dose of statin used for treatment. Thus, CoQ10 becomes a highly suitable option for preventing these symptoms, however there is still no consensus among researchers regarding the effectiveness of ubiquinone both in preventing and treating symptoms related to statin use, in addition, there is no satisfactory diversity of studies to establish therapeutic, preventive and/or associative medical management between CoQ10 and statins.

REFERENCES

ATTARDO, Silvia et al. Statins neuromuscular adverse effects. **International journal of molecular sciences**, v. 23, n. 15, p. 8364, 2022.

BALAKRISHNAN, Angarika et al. Analeptic Properties of Rosuvastatin and CQ10 Combination. 2021.

BANSAL, Agam B.; CASSAGNOL, Manouchkathe. HMG-CoA reductase inhibitors. 2019.

CERDÁ, Judith. Pharmacogenetics in statin use. 2019.

CHEN, Wilson et al. Coenzyme Q10 supplementation for the treatment of statin-associated muscle symptoms. **Future Cardiology**, v. 18, n. 6, p. 461-470, 2022.

KAKLAN, Hilal et al. Dysfunctional endocannabinoid CB1 receptor expression and signaling contribute to skeletal muscle cell toxicity induced by simvastatin. **Cell Death & Disease**, v. 14, n. 8, p. 544, 2023

RAIZNER, Albert E. Coenzyme Q10. **Methodist DeBakey cardiovascular journal**, v. 15, n. 3, p. 185, 2019.

KENNEDY, Cormac; KOELLER, Yasmin; SURKOVA, Elena. Effect of Coenzyme Q10 on statin-associated myalgia and adherence to statin therapy: A systematic review and meta-analysis. **Atherosclerosis**, v. 299, p. 1-8, 2020.

QU, Hua et al. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. **Journal of the American Heart Association**, v. 7, n. 19, p. e009835, 2018.

WARD, Natalie C. et al. Nutraceuticals in the management of patients with statin-associated muscle symptoms, with a note on real-world experience. **Clinical cardiology**, v. 41, n. 1, p. 159-165, 2018.

WARD, Natalie C.; WATTS, Gerald F.; ECKEL, Robert H. Statin toxicity: mechanistic insights and clinical implications. **Circulation research**, v. 124, n. 2, p. 328-350, 2019.