U.PORTO

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2023/2024

Micaela Maria Crespo Croce

# CPTII deficiency: a therapeutical approach

JULHO, 2024

Micaela Maria Crespo Croce

# CPTII deficiency: a therapeutical approach

Mestrado Integrado em Medicina

Área: Ciências Médicas e da Saúde - Medicina Básica

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Professora Doutora Maria De Fátima Moreira Martel

Trabalho organizado de acordo com as normas da revista:
Journal of Clinical Lipidology

**JULHO, 2024**

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

**UC Dissertação - DECLARAÇÃO DE INTEGRIDADE**

Eu, MICAELA MARIA CRESPO CROCE, abaixo assinado, nº mecanográfico 201304078, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração do meu trabalho de Dissertação ou Monografia.

Neste sentido, confirmo que **NÃO** incorri em plágio (acto pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 01/07/2024

Assinatura conforme cartão de identificação:
Micaela Maria Crespo Croce

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

**UC Dissertação – DECLARAÇÃO DE REPRODUÇÃO**

NOME

MICAELA MARIA CRESPO CROCE

NÚMERO DE ESTUDANTE | E-MAIL

201304078 | MICAELACROCE310@GMAIL.COM

DESIGNAÇÃO DA ÁREA DO PROJECTO

CIÊNCIAS MÉDICAS E DA SAÚDE - MEDICINA BÁSICA

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

CPT II DEFICIENCY: A THERAPEUTICAL APPROACH

ORIENTADOR

MARIA DE FÁTIMA MOREIRA MARTEL

COORIENTADOR (se aplicável)

———

ASSINALE APENAS UMA DAS OPÇÕES:

| | |
|---|---|
| É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE. | ☐ |
| É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE. | ☐ |
| DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO. | ☒ |

Faculdade de Medicina da Universidade do Porto, 01/07/2024

Assinatura conforme cartão de identificação: Micaela Maria Crespo Croce

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

**UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS**

Eu, MICAELA MARIA CRESPO CROCE, abaixo assinado, nº mecanográfico 201304078, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 01/07/2024

Assinatura conforme cartão de identificação:
Micaela Maria Crespo Croce

## Abstract:

Fatty acid oxidation is a major metabolic pathway for maintaining energy homeostasis. It is especially important during fasting, but also supports the extra energy required in strenuous conditions such as prolonged exercise, exposure to extreme temperatures, fever, illness, and even emotional stress.

Long-chain fatty acids (LCFA) are the most abundant fatty acids in the human diet and in body stores and so their metabolism is of critical importance. Oxidation of fatty acids, including LCFA, takes place predominantly in the mitochondria. While short and medium-chain fatty acids can freely diffuse from the cytoplasm into the mitochondria, LCFA need a transport system. Known as the carnitine shuttle, it is comprised of three enzymes: carnitine palmitoyltransferase I and II (CPT I and II), and carnitine acylcarnitine translocase (CACT). Pathogenic mutations in the genes encoding for these enzymes result in an impaired LCFA transportation and so in a LCFA oxidation disorder in which the energy homeostasis is compromised.

Among the rare LCFA oxidation defects, CPT II deficiency is the most common inherited disorder. Signs and symptoms can manifest as early as a few hours after birth, but may also only appear during adulthood, with a great variation in clinical severity between patients. The three clinical presentations are lethal neonatal form, severe infantile hepatocardiomuscular form, and myopathic form. While the first two are severe multisystemic diseases characterized by liver failure with hypoketotic hypoglycemia, cardiomyopathy, seizures, and early death, the latter is characterized by exercise-induced muscle pain and weakness, sometimes associated with myoglobinuria.

Classically, management of this disorder is based upon a high-carbohydrate/low-fat regimen, supplemented with medium-chain triglycerides (MCT) and carnitine, as well as avoidance of fasting and/or exercise.

The aim of this review is to contextualize the rationale behind the classic treatment for CPTII deficiency, to bring focus on new treatments currently being proposed and implemented, and to explore future research possibilities for treatment of this disease.

## Keywords:

Long-chain fatty acids; carnitine shuttle; carnitine palmitoyltransferase II deficiency; treatment

# INTRODUCTION

## Fatty Acids (FA) as a source of energy

Fatty acid oxidation (FAO) is a key metabolic pathway in preserving energy homeostasis.
It is especially important during fasting when glucose and glycogen stores are low. Indeed, in this situation, triglycerides are hydrolyzed in the adipose tissue and free fatty acids are released into the blood circulation and become available for other tissues. Under this condition, fatty acid oxidation becomes a significant source of energy provision in the form of adenosine triphosphate (ATP) [1, 2].

Other than in fasting, fatty acid oxidation also supports the extra energy required in strenuous conditions such as prolonged exercise, exposure to extreme temperatures, fever, illness, and even emotional stress [3, 4].

Fatty acids are particularly important sources of energy for the heart, liver, and muscles [1, 2, 5].
Skeletal muscle turns to FAO during prolonged exercise [5]. The heart mostly depends on FAO (60–90%) for its energy expenditure, even at rest or when glucose levels are high [5, 6]. In contrast, the brain mostly relies on the oxidation of glucose, but may also resort to ketone bodies [1].
In situations of glucose depletion, the liver oxidizes fatty acids to produce ketone bodies that serve as a replacement for this sugar in the brain, as well as in other tissues. This mechanism ensures the maintenance of a stable content of glucose in the blood. In addition, this supplementation with ketone bodies through the oxidation of fatty acids prevents the breakdown of muscle protein for the purpose of gluconeogenesis [5, 7].

## Oxidation of Long-Chain Fatty Acids (LCFA)

Long-chain fatty acids are the most abundant type of fatty acids in the human diet and in adipose tissue, in the form of long-chain triglycerides (LCT) [1].

Oxidation of fatty acids, including LCFA, takes place predominantly in the mitochondria [5]. Moreover, LCFA and very long-chain fatty acids (VLCFA) can also be oxidized in peroxisomes [8, 9].

Transport of fatty acids from the cytosol into the mitochondria depends on their ability to cross mitochondrial membranes, in particular the highly selective inner mitochondrial membrane [10]. While short- and medium-chain fatty acids can freely diffuse into the mitochondria, LCFA cannot. In fact, transport of LCFA from cytoplasm to mitochondria occurs through a transport system known as the carnitine shuttle, described next [1, 5].

## LCFA mitochondrial transport system: carnitine shuttle

In the cytosol, a long-chain acyl-CoA synthetase esterifies the long-chain fatty acids to long-chain acyl-coenzyme A (-CoA), activating them for degradation [1, 11].

After activation, the fatty acids are then ready for transport and carnitine palmitoyltransferase I (CPT I), at the outer mitochondrial membrane, catalyzes the first transport step. At this step, long-chain acyl-CoA along with carnitine are converted into long-chain acyl-carnitine and coenzyme A [5, 12].

FAO is largely regulated at the CPTI reaction, as it is sensitive to inhibition by malonyl-CoA. Malonyl-

CoA is formed by carboxylation of acetyl-CoA, a compound that is a convergence point of various metabolic pathways, namely it is a product of glycolysis and a precursor for FA synthesis / a product of FA oxidation [1]. This entails that in the fed state, in a state of abundance of glucose and other substrates, the metabolic homeostasis shifts towards the anabolic pathways of energy storage. It then makes sense that carboxylation of acetyl-CoA into malonyl-CoA for the formation of fatty acids should inhibit the opposite pathway of fatty acid degradation [9, 13, 14].

The long-chain acylcarnitines are then imported into the mitochondria by carnitine-acylcarnitine translocase (CACT) in exchange for a free carnitine molecule [1].

Then, carnitine palmitoyltransferase II (CPT II) on the inner mitochondrial membrane, catalyzes the reverse reaction by transferring back the acyl group from carnitine to coenzyme A, reassembling acyl-CoA. The carnitine released in this step returns into the intermembrane space of the mitochondrion through the CACT and is available for re-transporting fatty acids (Figure 1). Thus, produced acyl-CoA is then available for β-oxidation [5, 12].

Acyl-CoA β-oxidation produces acetyl-CoAs that can enter the tricarboxylic acid (TCA) cycle where production of reducing equivalents for oxidative phosphorylation later results in ATP production. Alternatively, acetyl-CoA may be directed to the ketone body synthesis pathway in the liver [1].

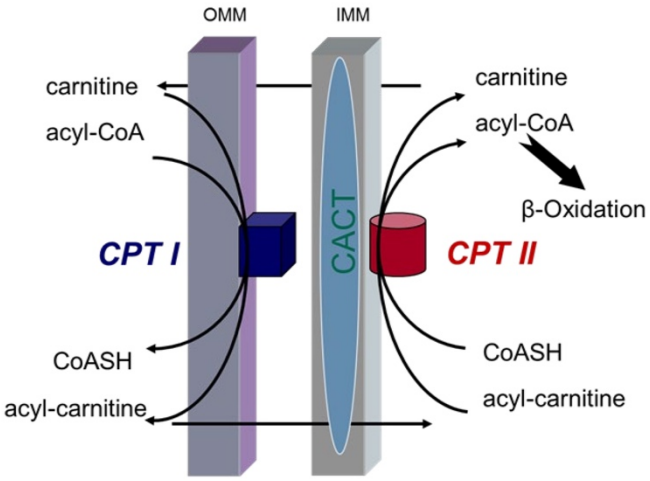


Figure 1. Transport system for long-chain fatty acids across the mitochondrial membranes (OMM: outer mitochondrial membrane; IMM: inner mitochondrial membrane; CPT I & II: carnitine palmitoyltransferase I and II; CACT: carnitine-acylcarnitine translocase; CoASH: free Coenzyme A). [5]

## LCFA oxidation disorders

Pathogenic mutations in the genes encoding for the previously described enzymes result in an impaired LCFA transportation. Carnitine shuttle disorders may be due to deficiencies in any of these transport enzymes (CPT I, II and CACT), but may also be due to a primary carnitine deficiency. LCFA oxidation disorders may also be attributable to defects in any of the four steps of their β-oxidation in the mitochondrial matrix. These disorders give rise to a variety of clinical features especially in organs that rely on energy production by FAO, such as the heart, skeletal muscle, and liver [1, 15].

A characteristic feature of the signs and symptoms in LCFA oxidation disorders is the fact that they can be provoked, or aggravated, by energy requiring states such as fasting, prolonged exercise, illness, fever, or a combination of these factors [1].

## CPT II deficiency

Among the rare LCFA oxidation defects, CPTII deficiency is the most common inherited disorder [4, 5]. As with other in LCFAO disorders, CPTII symptoms arise or exacerbate during catabolic situations, such as fasting, (endurance) exercise, extreme temperatures, illness, and stress [1, 3, 4].

CPTII deficiency is an autosomal recessive disorder. Because of deficient CPTII activity, this disease is characterized by accumulation of long-chain acylcarnitines and depletion of carnitine in the serum [16, 17].

Signs and symptoms can manifest as early as a few hours after birth. The lethal neonatal form typically presents within days after birth and the severe infantile form may present up to the first year of life. These two phenotypes are multisystemic, so reduced CPTII enzyme activity is seen in multiple organs (predominantly hepatocardiomuscular), and frequently lead to an early death. Major clinical manifestations include liver failure, hypoketotic hypoglycemia, cardiomyopathy, cardiac arrythmias and seizures [5, 13, 16, 17].
The lethal neonatal form may also be associated with facial abnormalities or structural malformations, such as neuronal migration defects, liver calcifications and cystic dysplastic kidneys.
The severe infantile form may be accompanied by peripheral myopathy and the main cause of mortality during infancy is reported to be cardiac arrhythmia [5, 13, 16, 17].

On the other end of the severity spectrum, is the mild myopathic form of CPTII deficiency. This phenotype has a wide range of onset, 1$^{st}$ through to the 6$^{th}$ decades of life.
It is characterized by recurrent attacks of myalgia, mostly exercise-induced, but can also be precipitated by fasting, illness, extreme temperatures, and stress. The muscle pain may be associated with muscle weakness, sometimes accompanied with myoglobinuria and in extremis rhabdomyolysis.
Affected individuals generally do not have any symptoms in between attacks and the frequency of metabolic crises is highly variable with some patients being asymptomatic most of their lives, while others having frequent myopathy even with moderate intensity daily activities.
The myopathic form is the most common CPTII deficiency form and the most common disorder of lipid metabolism affecting skeletal muscle [5, 13, 16, 17].

## What are the objectives of this review?

The aim of this review is to contextualize the rationale behind the classic treatment for CPTII deficiency, to bring focus on new treatments currently being proposed and implemented, and to explore future research possibilities for treatment of this disease.

# CURRENT MANAGEMENT

## Daily management

<u>High-carbohydrate / low-fat regime; Medium chain triglyceride (MCT) supplementation</u>

A high-carbohydrate/low-fat diet supplemented with medium-chain fatty acids (MCT) is traditionally implemented in clinically ill individuals, and in asymptomatic newborns as well, to compensate for the reduced capacity to oxidize dietary LCFA [1, 16-18].

Carbohydrates should make up 70% of total calorie consumption and long-chain dietary fats only up to 20%, while covering the need for essential fatty acids [16].
Management of patients is also based on prevention of catabolism: avoidance of fasting and limitation of physical exercise and other situations which could increase the use of fatty acids as an energy substrate [1, 16-18].

Unfortunately, although a sound rationale, long-term dietary therapy, even with utilization of MCT, has not been effective in preventing the appearance of manifestations of CPTII deficiency. Indeed, exercise restriction continues to be required, muscle pain on exertion persists, and recurrent hospitalizations continue to occur [18, 19].

### Carnitine supplementation

The use of carnitine in LCFA oxidation disorders is controversial [20, 21]. Theoretically carnitine supplementation should aid carnitine transport and subsequently improve FAO, but unfortunately, evidence for the efficacy of carnitine supplementation to treat secondary carnitine deficiency is lacking [22].

Furthermore, the application of carnitine for the clearance of potentially toxic compounds is debated. On the one hand, carnitine may help in the clearance of potentially toxic long-chain acyl-CoAs by their conversion to acylcarnitines [16].
On the other hand, concerns have been raised about the safety of carnitine supplementation because it could also induce the accumulation of toxic intramitochondrial long-chain acyl-carnitines, and supplementation has been associated with ventricular fibrillation and rhabdomyolysis [23-25].

## Treatment of acute episodes

Patients with LCFAO disorders are incapable, or limited in their capacity, to utilize fatty acids as an alternative resource of energy when glucose stores become depleted [1].

For this reason, in case of metabolic crisis, acute treatment should be based on full body rest and supplementation with sufficient glucose to prevent cell damage, in particular in muscles. Recommendations for the amount of glucose infusion vary widely because various factors such as residual enzyme activity, age, and the level of stress due to anxiety or fever must be considered, and so there is no clear consensus. Furthermore, normoglycemia is not a sign that a catabolic crisis is averted. Even without hypoglycemia, patients may still develop rhabdomyolysis and so should still receive glucose. Hyperglycemia should be prevented with an insulin drip [1, 3].

In rhabdomyolysis, acute renal failure is the main possible complication. Therefore, early, abundant intravenous fluid resuscitation is the standard of care, improving hypovolemia, acute renal failure, and clearance of myoglobin. Electrolyte disturbances should also be monitored and corrected to avoid life-threatening arrythmias [3]. Intravenous sodium bicarbonate has been theorized to alkalinize urine, resulting in a reduction of myoglobin precipitation, but previous studies have not demonstrated significant benefit [26].

Other than in rhabdomyolysis, infusions of glucose are also recommended during intercurrent infections for prevention of catabolism. Unfortunately, oral glucose cannot achieve this effect [16].

# THERAPIES UNDER INVESTIGATION

## Anaplerotics: triheptanoin

Supplementation with MCT oil for CPTII deficient patients was assumed to prevent clinical CPTII deficiency symptoms, as the medium-chain fats it contains can completely bypass the carnitine shuttle for entry into the mitochondria and follow through with β-oxidation.
However, clinical symptoms persisted in these patients, and it is hypothesized to be due at least in part to depletion of odd-chain fatty acid-derived TCA cycle intermediates, with a subsequent persistent energy deficiency [1, 15].

In this context, the anaplerotic compound triheptanoin (heptanoyl-triglyceride), a triglyceride with odd numbered fatty acids (C7), has been tested [27].

Upon ingestion, triheptanoin is rapidly digested to heptanoate in the small intestine. Its complete oxidation in the mitochondria produces 2 acetyl-CoAs (C2) and a propionyl-CoA (C3). The 3-carbon compound is further metabolized to succinyl-CoA and succinate, resupplying the TCA cycle intermediates that are hypothesized to be deficient [15].

Early case reports on efficacy led to a significant compassionate-use experience with the medication. Two retrospective studies demonstrated considerable improvement in treated patients, specifically reductions in episodes and hospital days related to hypoglycemia, cardiomyopathy, and rhabdomyolysis [28, 29].

This led to the development and FDA approval of pharmaceutical-grade triheptanoin. Triheptanoin is available commercially as an oral liquid supplied in a 500-mL bottle (supplying 8.3 kcal/ mL). The target daily dose is up to 35% of the patient's total prescribed daily caloric intake divided into 4 or more doses administered at mealtimes or with snacks [28].

A recent double-blind randomized controlled trial included 32 subjects with different LCFA oxidation disorders and compared the effects of a 4-month diet containing 20% of total energy from triglycerides containing either C8 or C7 fatty acids. Results seemed promising for cardiac symptoms as the left ventricle wall mass decreased and an increase in ejection fraction was observed in patients in the C7 group, but it should be noted that all the included patients had normal cardiac function [30].
Beneficial effects of triheptanoin for cardiac symptoms have also been described in a few case studies [29, 31].

## Fibrates

The peroxisome proliferator-activated receptors (PPARs) are nuclear fatty acid receptors, that act as transcription factors regulating gene expression of many cellular processes [15, 32].

The three PPAR subtypes, α, γ, and δ, have distinct tissue expression patterns, sense different components of lipoproteins and regulate lipid homeostasis based on the need of the specific tissue, and are targets for current drug therapies [15, 32].

PPAR α is primarily expressed in the liver. It upregulates genes involved in fatty acid oxidation in the fasted state and is the molecular target of the lipid-lowering fibrates.
PPAR γ is highly expressed in adipose tissue and is essential for adipocyte differentiation and insulin sensitivity. As so, it mediates the activity of the insulin-sensitizing thiazolidinediones.

PPAR δ is the most abundant receptor in the muscle among the PPARs. Just as PPAR α in the liver, it promotes fatty acid mobilization and oxidation in the muscle [15, 32].

Bezafibrate, a relatively broad-spectrum PPAR agonist has been investigated as a treatment for LCFA oxidation disorders as stimulator of residual FAO enzymatic activity [15].

A complete restoration of palmitate oxidation accompanied with increased protein and mRNA levels was achieved in CPTII-deficient fibroblasts, myoblasts, and myocytes of patients with considerable residual enzyme activity [33, 34].

These promising findings led to the investigation of bezafibrates in clinical trials that however produced contradictory findings.

The first trial, which was an open-label, 6-month pilot study with a 3-year extension, showed increased level of whole-body fat oxidation, improved quality of life (QOL) scores, reduced creatinine kinase levels, and diminished occurrence of rhabdomyolysis [35, 36].

Results of a double-blind, randomized, placebo-controlled study failed to demonstrate a benefit of bezafibrate over placebo in clinical symptoms or FAO capacity during exercise [37].

Finally, frequency of myopathic attacks was not reduced in an open-label study; however, QOL scores were improved [38].

## Resveratrol

Polyphenol resveratrol is another compound that has been shown to increase residual LCFAO in fibroblasts from CPTII-deficient patients [39, 40].

By activation of sirtuin 1 (SIRT1) and the ensuing effector peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α), resveratrol promotes mitochondrial biogenesis.

It is possible that this mechanism may increase enzyme activity if the mutated enzyme has preserved some residual activity [41].

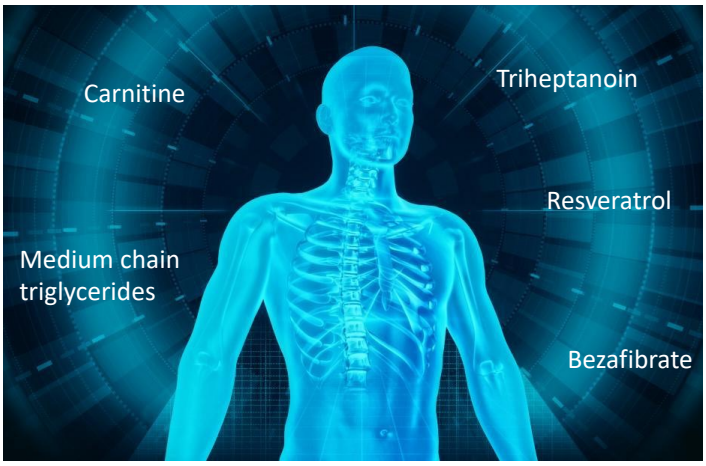


Figure 2. Compounds currently used for the management of CPTII deficiency.

# DISCUSSION / CONCLUSION

Since the discovery of this disease by DiMauro and DiMauro in 1973, significant progress has been made on the knowledge of its clinical manifestations, their subdivision in different phenotypes, the increasing number of mutations and polymorphisms associated, and in some of its biochemical consequences.

Unfortunately, a not so significant progress has been achieved in terms of the therapeutical management of CPTII deficiency (as well as other LCFAO disorders). The same dietary regimen with MCT oil supplementation is being used since its emergence. Supplementation with carnitine remains controversial.

Based on the recognition that a high-carbohydrate diet and physical inactivity for controlling disease symptoms may be more detrimental in the long term for these patients than its short-term benefits, Negro et al. propose a new approach to this disease. Specifically, a no higher than 50-55% carbohydrate consumption, 25-30% protein intake, and a maximum of 20% of fat ingestion, considered the minimum to ensure adequacy for essential FA and fat-soluble vitamins, is proposed. Also, instead of a total avoidance of exercise, the proposal is of personalized exercised programs focusing on medium intensity and high intensity interval trainings for short periods of time [4].

More recently, new compounds such as triheptanoin, bezafibrate, and resveratrol seem promising in their capacity to control disease manifestations, but unfortunately much remains to be done. Moreover, a range of supplements with different objectives is also proposed by Negro et al. From creatine, whey protein, and vitamin D for muscle bioenergetic performance; to omega-3, beetroot juice, pomegranate juice, and tart cherries juice to attenuate exercise-induced muscle damage and inflammation; as well as curcumin and ginger for the management of pain. Future research efforts will certainly have to focus on these topics, considering age, gender, different carbohydrates/proteins intake and the metabolic responses to the proposals discussed [4].

## Abbreviations

ATP - adenosine triphosphate
CACT - carnitine-acylcarnitine translocase
CoA - coenzyme A
CPTI - carnitine palmitoyltransferase I
CPTII - carnitine palmitoyltransferase II
FA - fatty acids
FAO - fatty acid oxidation
FDA - Food and Drug Administration
IMM - inner mitochondrial membrane
LCFA - long-chain fatty acids
LCFAO - long-chain fatty acid oxidation
LCT - long-chain triglycerides
MCT - medium chain triglyceride
OMM - outer mitochondrial membrane
PPAR - peroxisome proliferator-activated receptors
QOL - Quality of Life
SIRT1 - sirtuin 1
PGC1α - peroxisome proliferator-activated receptor gamma coactivator 1-α
TCA - tricarboxylic acid
VLCFA - very long-chain fatty acids

# References


1. Knottnerus SJG, Bleeker JC, Wust RCI, Ferdinandusse S, L IJ, Wijburg FA, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. Rev Endocr Metab Disord. 2018;19(1):93-106.

2. Bartlett K, Eaton S. Mitochondrial beta-oxidation. Eur J Biochem. 2004;271(3):462-9.

3. McCormick BJ, Chirila RM. Carnitine palmitoyltransferase-II deficiency: case presentation and review of the literature. Rom J Intern Med. 2021;59(4):420-4.

4. Negro M, Cerullo G, Parimbelli M, Ravazzani A, Feletti F, Berardinelli A, et al. Exercise, Nutrition, and Supplements in the Muscle Carnitine Palmitoyl-Transferase II Deficiency: New Theoretical Bases for Potential Applications. Front Physiol. 2021;12:704290.

5. Joshi PR, Zierz S. Muscle Carnitine Palmitoyltransferase II (CPT II) Deficiency: A Conceptual Approach. Molecules. 2020;25(8).

6. Schulz H. Regulation of fatty acid oxidation in heart. J Nutr. 1994;124(2):165-71.

7. McGarry JD, Foster DW. Regulation of hepatic fatty acid oxidation and ketone body production. Annu Rev Biochem. 1980;49:395-420.

8. Violante S, Achetib N, van Roermund CWT, Hagen J, Dodatko T, Vaz FM, et al. Peroxisomes can oxidize medium- and long-chain fatty acids through a pathway involving ABCD3 and HSD17B4. FASEB J. 2019;33(3):4355-64.

9. Dambrova M, Makrecka-Kuka M, Kuka J, Vilskersts R, Nordberg D, Attwood MM, et al. Acylcarnitines: Nomenclature, Biomarkers, Therapeutic Potential, Drug Targets, and Clinical Trials. Pharmacol Rev. 2022;74(3):506-51.

10. Lemasters JJ. Modulation of mitochondrial membrane permeability in pathogenesis, autophagy and control of metabolism. J Gastroenterol Hepatol. 2007;22 Suppl 1:S31-7.

11. Grevengoed TJ, Klett EL, Coleman RA. Acyl-CoA metabolism and partitioning. Annu Rev Nutr. 2014;34:1-30.

12. Morillas M, Lopez-Vinas E, Valencia A, Serra D, Gomez-Puertas P, Hegardt FG, et al. Structural model of carnitine palmitoyltransferase I based on the carnitine acetyltransferase crystal. Biochem J. 2004;379(Pt 3):777-84.

13. Sigauke E, Rakheja D, Kitson K, Bennett MJ. Carnitine palmitoyltransferase II deficiency: a clinical, biochemical, and molecular review. Lab Invest. 2003;83(11):1543-54.

14. McGarry JD, Brown NF. The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. Eur J Biochem. 1997;244(1):1-14.

15. Vockley J. Long-chain fatty acid oxidation disorders and current management strategies. Am J Manag Care. 2020;26(7 Suppl):S147-S54.

16. Wieser T. Carnitine Palmitoyltransferase II Deficiency. Seattle (WA): University of Washington, Seattle; 2004. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1253/.

17. Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med. 2004;25(5-6):495-520.

18. Djouadi F, Bastin J. PPARs as therapeutic targets for correction of inborn mitochondrial fatty acid oxidation disorders. J Inherit Metab Dis. 2008;31(2):217-25.

19. Roe CR, Yang BZ, Brunengraber H, Roe DS, Wallace M, Garritson BK. Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy. Neurology. 2008;71(4):260-4.

20. Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, et al. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. J Inherit Metab Dis. 2009;32(4):488-97.

21. Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, et al. Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop. J Inherit Metab Dis. 2009;32(4):498-505.

22. Nasser M, Javaheri H, Fedorowicz Z, Noorani Z. Carnitine supplementation for inborn errors of metabolism. Cochrane Database Syst Rev. 2012;2012(2):CD006659.

23. Exil VJ, Gardner CD, Rottman JN, Sims H, Bartelds B, Khuchua Z, et al. Abnormal mitochondrial bioenergetics and heart rate dysfunction in mice lacking very-long-chain acyl-CoA dehydrogenase. Am J Physiol

Heart Circ Physiol. 2006;290(3):H1289-97.

24. Corr PB, Heathers GP, Yamada KA. Mechanisms contributing to the arrhythmogenic influences of alpha 1-adrenergic stimulation in the ischemic heart. Am J Med. 1989;87(2A):19S-25S.

25. Watanabe K, Yamada K, Sameshima K, Yamaguchi S. Two siblings with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency suffered from rhabdomyolysis after l-carnitine supplementation. Mol Genet Metab Rep. 2018;15:121-3.

26. Somagutta MR, Pagad S, Sridharan S, Nanthakumaran S, Arnold AA, May V, et al. Role of Bicarbonates and Mannitol in Rhabdomyolysis: A Comprehensive Review. Cureus. 2020;12(8):e9742.

27. Roe CR, Mochel F. Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. J Inherit Metab Dis. 2006;29(2-3):332-40.

28. Vockley J, Marsden D, McCracken E, DeWard S, Barone A, Hsu K, et al. Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment--A retrospective chart review. Mol Genet Metab. 2015;116(1-2):53-60.

29. Vockley J, Charrow J, Ganesh J, Eswara M, Diaz GA, McCracken E, et al. Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. Mol Genet Metab. 2016;119(3):223-31.

30. Gillingham MB, Heitner SB, Martin J, Rose S, Goldstein A, El-Gharbawy AH, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. J Inherit Metab Dis. 2017;40(6):831-43.

31. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. J Clin Invest. 2002;110(2):259-69.

32. Lee CH, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. Endocrinology. 2003;144(6):2201-7.

33. Djouadi F, Bonnefont JP, Thuillier L, Droin V, Khadom N, Munnich A, et al. Correction of fatty acid oxidation in carnitine palmitoyl transferase 2-deficient cultured skin fibroblasts by bezafibrate. Pediatr Res. 2003;54(4):446-51.

34. Djouadi F, Aubey F, Schlemmer D, Bastin J. Peroxisome proliferator activated receptor delta (PPARdelta) agonist but not PPARalpha corrects carnitine palmitoyl transferase 2 deficiency in human muscle cells. J Clin Endocrinol Metab. 2005;90(3):1791-7.

35. Bonnefont JP, Bastin J, Behin A, Djouadi F. Bezafibrate for an inborn mitochondrial beta-oxidation defect. N Engl J Med. 2009;360(8):838-40.

36. Bonnefont JP, Bastin J, Laforet P, Aubey F, Mogenet A, Romano S, et al. Long-term follow-up of bezafibrate treatment in patients with the myopathic form of carnitine palmitoyltransferase 2 deficiency. Clin Pharmacol Ther. 2010;88(1):101-8.

37. Orngreen MC, Madsen KL, Preisler N, Andersen G, Vissing J, Laforet P. Bezafibrate in skeletal muscle fatty acid oxidation disorders: a randomized clinical trial. Neurology. 2014;82(7):607-13.

38. Shiraishi H, Yamada K, Oki E, Ishige M, Fukao T, Hamada Y, et al. Open-label clinical trial of bezafibrate treatment in patients with fatty acid oxidation disorders in Japan; 2nd report QOL survey. Mol Genet Metab Rep. 2019;20:100496.

39. Bastin J, Lopes-Costa A, Djouadi F. Exposure to resveratrol triggers pharmacological correction of fatty acid utilization in human fatty acid oxidation-deficient fibroblasts. Hum Mol Genet. 2011;20(10):2048-57.

40. Aires V, Delmas D, Le Bachelier C, Latruffe N, Schlemmer D, Benoist JF, et al. Stilbenes and resveratrol metabolites improve mitochondrial fatty acid oxidation defects in human fibroblasts. Orphanet J Rare Dis. 2014;9:79.

41. Bleeker JC, Houtkooper RH. Sirtuin activation as a therapeutic approach against inborn errors of metabolism. J Inherit Metab Dis. 2016;39(4):565-72.

# Anexo 1. Reporting guidelines

## Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

### 1) Justification of the article's importance for the readership

The importance is not justified. — 0
The importance is alluded to, but not explicitly justified. — 1
The importance is explicitly justified. — 2

**2**

Página 9: "What are the objectives of this review? The aim of this review is to contextualize the rationale behind the classic treatment for CPTII deficiency, to bring focus on new treatments currently being proposed and implemented, and to explore future research possibilities for treatment of this disease."

### 2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

**2**

Página 9: "What are the objectives of this review? The aim of this review is to contextualize the rationale behind the classic treatment for CPTII deficiency, to bring focus on new treatments currently being proposed and implemented, and to explore future research possibilities for treatment of this disease."

### 3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

**0**

### 4) Referencing

Key statements are not supported by references. — 0
The referencing of key statements is inconsistent. — 1
Key statements are supported by references. — 2

**2**

Por exemplo página 13: "Negro et al. propose a new approach to this disease. Specifically, a no higher than 50-55% carbohydrate consumption, 25-30% protein intake, and a maximum of 20% of fat ingestion (...)".

### 5) Scientific reasoning

*(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)*

The article's point is not based on appropriate arguments. — 0
Appropriate evidence is introduced selectively. — 1
Appropriate evidence is generally present. — 2

**2**

Por exemplo página 11: "A recent double-blind randomized controlled trial included 32 subjects with different LCFA oxidation disorders (...)".

### 6) Appropriate presentation of data

*(e.g., absolute vs relative risk; effect sizes without confidence intervals)*

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
Relevant outcome data are generally presented appropriately. — 2

**2**

Por exemplo página 11: "A recent double-blind randomized controlled trial included 32 subjects with different LCFA oxidation disorders (...)".

**Sumscore** **10**

**Fig. 1** SANRA - Scale

## Anexo 2. Regras de formatação

https://www.lipidjournal.com/content/authorinfo

Author Information

Your Paper Your Way

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.