# Lipid Storage Myopathy Associated with Sertraline: A New Reality

# Miopatia por Acumulação de Lípidos Associados à Sertralina: Uma Nova Realidade

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## Abstract:

Disorders of fatty acid β-oxidation are hereditary metabolic diseases that may present in adulthood, with predominantly muscular symptoms. Multiple acyl-CoA dehydrogenase deficiency (MADD), or glutaric acidemia type II (MIM#231680, ORPHA:26791), is a treatable inherited mitochondrial disease; however, acquired forms associated with sertraline use have been described, mimicking its phenotype and biochemical profile. We present the case of a 73-year-old man with progressive muscle weakness, rhabdomyolysis, elevated acylcarnitine compatible with MADD, imaging and histopathological evidence of lipid infiltration of muscle, but without detection of pathogenic variants in the *ETFA, ETFB*, or *ETFDH* genes. After discontinuation of sertraline and initiation of riboflavin therapy, normalization of the biochemical profile and partial functional recovery were observed. This is the first nationally reported case of sertraline-induced MADD-like disease, highlighting the importance of recognizing this potentially reversible entity. Drug withdrawal and early metabolic treatment are essential for prognosis and prevention of recurrences.

**Keywords:** Lipid Metabolism, Inborn Errors/therapy; Multiple Acyl Coenzyme A Dehydrogenase Deficiency/genetics; Muscle, Skeletal; Neuromuscular Diseases; Riboflavin/therapeutic use; Sertraline/adverse effects.

## Resumo:

Os defeitos da beta-oxidação dos ácidos gordos são doenças hereditárias do metabolismo que podem manifestar-se na idade adulta, com sintomas predominantemente musculares. O défice da desidrogenase múltipla de acil-CoA (MADD) ou acidúria glutárica tipo II (MIM#231680), é uma doença mitocondrial hereditária potencialmente tratável; contudo, têm sido descritas formas adquiridas associadas ao uso de sertralina, que mimetizam o seu fenótipo clínico e perfil bioquímico. Apresenta-se o caso de um homem de 73 anos com fraqueza muscular progressiva, rabdomiólise e elevação de acilcarnitinas compatíveis com MADD, associadas a evidências imagiológicas e anatomopatológicas de infiltração lipídica muscular, sem identificação de variantes patogénicas nos genes *ETFA/B* ou *ETFDH*. Após suspensão da sertralina e início de terapêutica com riboflavina, observou-se normalização do perfil bioquímico e recuperação funcional. Este é o primeiro caso nacional descrito de MADD-*like* induzido por sertralina, reforçando a importância do reconhecimento precoce desta entidade potencialmente reversível, em que a retirada do fármaco e o tratamento metabólico adequado são fundamentais para o prognóstico e prevenção de recidivas.

**Palavras-chave:** Deficiência Múltipla de Acil Coenzima A Desidrogenase/genética; Doenças Neuromusculares; Erros Inatos do Metabolismo Lipídico/tratamento; Músculo Esquelético; Riboflavina/uso terapêutico; Sertralina/efeitos adversos.

## Introduction

Disorders of fatty acid β-oxidation are hereditary lipid metabolism diseases, rare in nature, and most frequently detected in childhood. Their clinical manifestations include recurrent hypoketotic hypoglycaemia, encephalopathy, liver failure, cardiomyopathy, rhabdomyolysis, and/or sudden death.[1] However, late-onset forms have been increasingly diagnosed and predominantly present with muscular symptoms, including exercise intolerance and rhabdomyolysis, often triggered by fasting, stress, or fever.

Multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric acidaemia type II, is an autosomal recessive inherited disorder with primary mitochondrial involvement, particularly affecting the respiratory chain, with an impact on energy synthesis. Impaired fatty acid and protein metabolism leads to excessive lipid accumulation in various tissues, as well as insufficient gluconeogenesis.[2,3]

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The disease is caused by biallelic pathogenic variants in the *ETFA*, *ETFB*, or *ETFDH* genes, and biochemical diagnosis is based on the analysis of plasma or dried blood spot acylcarnitines and urinary organic acids. The characteristic acylcarnitine profile includes elevations of C4–C18 acylcarnitines, corresponding to short-, medium-, and long-chain fatty acids, in addition to increased levels of multiple organic acids in the urine.[3] Treatment involves a low-fat and low-protein diet, avoidance of fasting, and supplementation with riboflavin, levocarnitine, and, in some cases, coenzyme Q10.

Recently, cases have been reported in which the use of sertraline, a commonly prescribed antidepressant, may be associated with a potentially reversible form of mitochondrial dysfunction that mimics MADD,[4,5] in the absence of pathogenic variants following negative genetic testing. We present a case with a biochemical profile similar to MADD associated with the use of this medication.

## Case Report

A 73-year-old man with a history of dyslipidaemia and type 2 diabetes *mellitus*, with microvascular involvement in the form of diabetic retinopathy. After retirement, he adopted a more sedentary lifestyle and developed depressive symptoms, for which sertraline 50 mg/day was initiated in early September 2023. In temporal association, antidiabetic therapy was reconciled, followed by significant weight loss (17% of total body weight).

Since then, he developed difficulty performing minor tasks, such as walking short distances and climbing stairs, associated with myalgias in all four limbs, predominantly proximal.

In March 2024, following an episode of syncope with prodromal symptoms, there was worsening of muscular complaints, the need for unilateral support for gait, and difficulty elevating the upper limbs, becoming unable to perform basic daily activities such as trimming his beard. He was evaluated in Primary Care, where polymyalgia rheumatica was excluded, but an elevated creatine kinase level of 624 U/L was documented.

He subsequently developed cervical hypotonia, prompting cervical magnetic resonance imaging (MRI), which identified cervical spondylotic myelopathy. Electromyography of the upper limbs revealed a sensory and motor axonal polyneuropathy, without signs of chronic neurogenic injury in any of the muscles studied bilaterally. He underwent elective neurosurgical intervention in July 2024, and at discharge was described as having grade 4+ tetraparesis with hyporeflexia, attributed to diabetic polyneuropathy. He initiated physiotherapy but evolved with worsening motor function, contrary to what would be expected, with progressive loss of autonomy for self-care as well as loss of ambulation capacity, denying diplopia, ptosis, dysphagia, or dysarthria.

In this context, he presented to the Emergency Department in October 2024 and was admitted for further investigation to the Neurology Department.

During an extensive inpatient workup, infectious, autoimmune, and neoplastic aetiologies were excluded. Of note, MRI of the lower limbs showed mild diffuse muscle atrophy and fatty replacement of the regional muscle groups of the pelvic girdle and thighs (Fig. 1). At discharge, he was referred to a Continuing Care Unit for rehabilitation, without further worsening of muscle involvement. Neurology outpatient reassessment revealed marked hyporeflexia and proximal grade 4 tetraparesis, with the ability to ambulate with unilateral support. Muscle biopsy results identified lipid accumulation, and the case was discussed with the inherited metabolic diseases group due to suspicion of late-onset hereditary myopathy.

Following case review, a causal relationship between symptom onset and the introduction of sertraline was considered, given recent reports of sertraline-induced hereditary lipid storage myopathy-like cases. Accordingly, sertraline was discontinued after the collection of serum acylcarnitine profiles and urinary organic acids. At that time, the patient showed worsening motor function and was wheelchair-bound. Riboflavin 100 mg twice daily was also initiated. Biochemical studies revealed an acylcarnitine profile with elevations of biomarkers C5, C6, C8, C10.1, C12, C14, and C14.1, compatible with MADD. Urinary organic acid analysis also showed findings suggestive of the disease. A genetic panel for hereditary myopathies was performed, with no pathogenic variants identified in the *ETFA*, *ETFB*, or *ETFDH* genes.

Two months after discontinuation of sertraline, normalization of the acylcarnitine profile and marked motor improvement (grade 4) were observed, with recovery of ambulation using unilateral support.

## Discussion

Late-onset presentations of glutaric acidaemia type II have been increasingly reported, not only due to greater awareness of its clinical manifestations but also because of easier diagnosis through acylcarnitine profiling.[1] Large cohorts, including 90 patients from China and 13 from France, have described late-onset MADD as a predominantly muscular disease, with common manifestations including muscle fatigue, exercise intolerance, rhabdomyolysis, bulbar symptoms, and dropped head syndrome; in all cases, the diagnosis was genetically confirmed.[1,6]

More recently, clinically and biochemically MADD-like presentations without identifiable pathogenic variants in *ETFA*, *ETFB*, or *ETFDH* have been reported in patients treated with sertraline. In these cases, clinical improvement after drug withdrawal suggests a potentially reversible, drug-induced mitochondrial dysfunction mimicking late-onset MADD.[5,7] In addition, sertraline has been associated with cases of rhabdomyolysis, further supporting its potential myotoxic effect and its role as a precipitating factor for muscle injury.[8]

The underlying mechanism of this alteration is not yet fully understood; however, studies indicate that sertraline

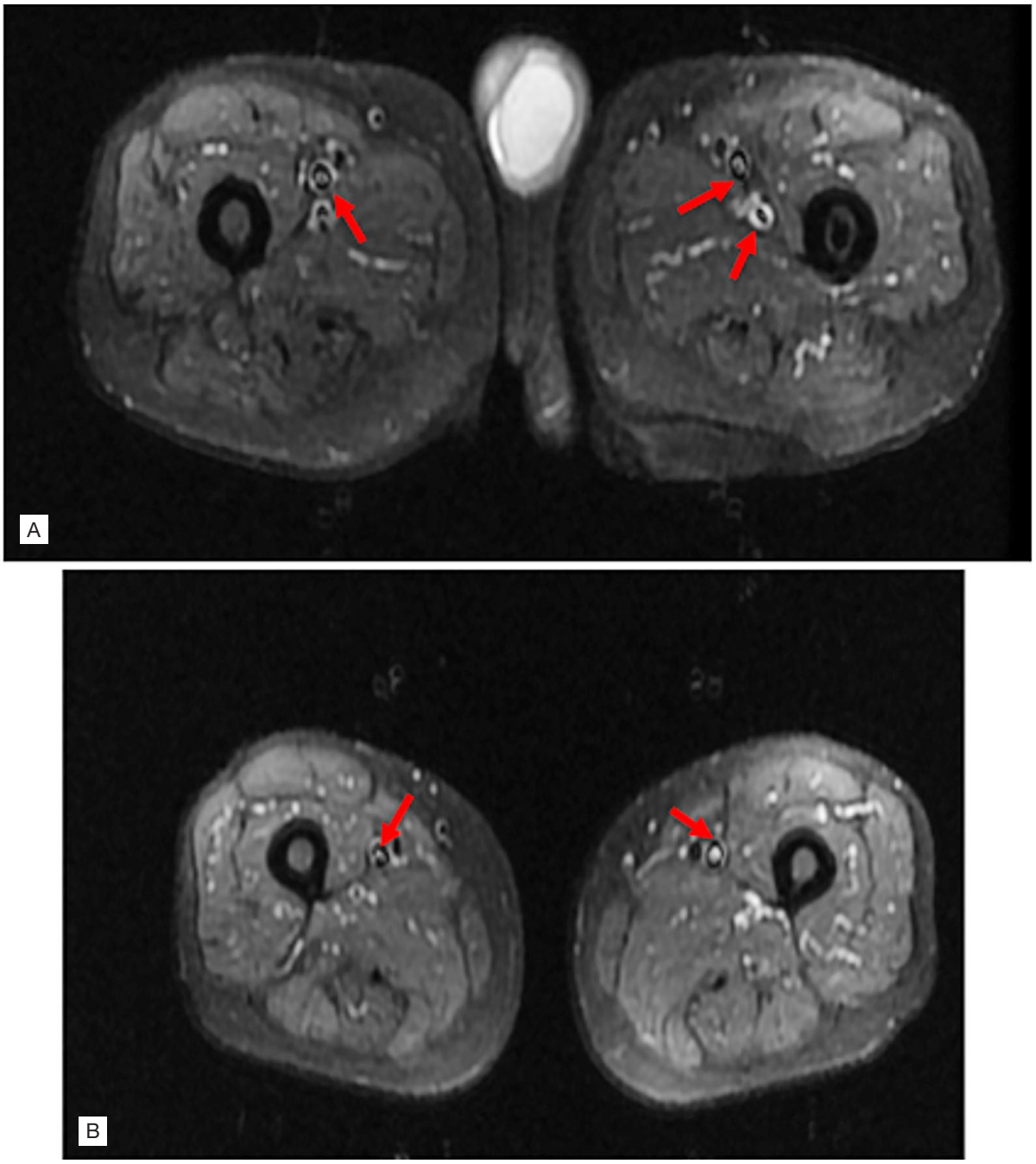


**Figure 1**: Magnetic resonance imaging of the lower limbs, sagittal sections, T2 STIR sequence. In images A and B, intramuscular fatty deposition sites (arrows) with associated inflammation can be identified.

may induce mitochondrial dysfunction through inhibition of oxidative phosphorylation complexes I and V,[5-7] leading to lipid accumulation. Variable doses and time intervals between treatment initiation and the onset of clinical manifestations have been reported.

In the present case, considering the patient's age, the muscular phenotype at presentation with associated rhabdomyolysis, the temporal relationship with sertraline introduction, abnormalities in the acylcarnitine profile, as well as imaging and muscle biopsy findings, suspicion was raised for a MADD-like form, prompting discontinuation of sertraline.

The absence of variants in the *ETFA*, *ETFB*, and *ETFDH* genes in a patient with clinical and biochemical features compatible with MADD completed the diagnosis of acquired metabolic myopathy.

Thus, taking into account the clinical improvement and normalization of the biochemical profile after drug withdrawal, we describe what is, to the best of our knowledge, the first reported case in Portugal of sertraline-induced MADD-like disease. It is important to emphasize that sertraline is a medication with a high safety and efficacy profile in depressive syndromes and is approved by the European Medicines Agency; therefore, its

use should not be restricted but rather monitored, particularly in patients who develop muscular complaints. Additionally, this effect does not appear to be class-wide among selective serotonin reuptake inhibitors, as in the reported case, the patient was switched to another drug within the same class without recurrence of symptoms.[5]

Given the severity of the clinical presentation, exacerbated by weight loss as well as by the degree of sarcopenia, it was decided not only to discontinue the suspected drug but also to initiate riboflavin therapy, considering the possibility of an acquired functional deficiency of mitochondrial flavoproteins. The patient's diet was adjusted to optimize nutritional intake, without compromising the metabolic disease, given the presence of some degree of sarcopenia. It should be noted that therapeutic approaches must be individualized according to each patient's clinical and metabolic characteristics. In this case, the phenotypic complexity and complementary investigations proved challenging, as the myopathic picture was masked by overlapping synergistic conditions contributing to motor impairment, namely polyneuropathy (clinically and neurophysiologically consistent with diabetic neuropathy) and compressive myelopathy. This highlights the need for a comprehensive approach to neuromuscular disorders, particularly when decompensating factors have been addressed and stabilized, yet clinical deterioration persists.

Data from Northern Europe indicate that sertraline-associated acquired lipid storage myopathy is possibly the most common form of lipid storage myopathy currently described, a phenomenon that may reflect the marked increase in prescription of this medication in the general population.[5] Recently, national data have also shown that sertraline is the most prescribed antidepressant in Portugal,[9] reinforcing the need to maintain a high index of clinical suspicion for this entity in patients treated with this drug who develop muscular symptoms. ■

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IMF, SR, FR, DP, DD, DQ, RSM, SR, AG – Manuscript preparation and revision.

All authors approved the final version to be published.

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Todos os autores aprovaram a versão final a ser publicada.

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