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Cholesterol deficiency in Smith-Lemli-Opitz syndrome: clinical and pharmaceutical relevance

Flávia Madalena Pinto Mendes [1] 0009-0003-0299-5910
Carla Maria Sanfins Guimarães Moutinho [1,2,3] 0000-0003-1310-4696

[1] Faculty of Health Sciences, Fernando Pessoa University, Porto, Portugal
[2] LAQV/REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Portugal
[3] RISE-Health, Faculty of Health Sciences, Fernando Pessoa University, Porto, Portugal

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Corresponding Author:
Flávia Madalena Pinto Mendes; Fernando Pessoa University - Faculty of Health Sciences, Porto, Portugal; 42290@ufp.edu.pt

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ABSTRACT

Introduction: Hypocholesterolemias, unlike hypercholesterolemias, constitute a heterogeneous group of rare disorders that remain poorly understood and are associated with high morbidity. In individuals with impaired cholesterol biosynthesis, abnormal embryonic development occurs, leading to the appearance of phenotypic alterations already in the prenatal period, since the transfer of cholesterol across the placental barrier is limited. Currently, approximately ten genetic disorders affecting the distal portion of the cholesterol biosynthetic pathway have been described, with Smith-Lemli-Opitz syndrome (SLOS) being the most frequent. This syndrome results from a deficiency of the enzyme 7-dehydrocholesterol reductase, responsible for the conversion of 7-dehydrocholesterol into cholesterol, and presents a very broad phenotypic spectrum, ranging from mild forms to severe cases with lethal congenital malformations. The most frequent clinical manifestations include syndactyly of the second and third toes, microcephaly, retrognathism, and anteverted nares.
Objectives: The aim of this work was to deepen knowledge on hypocholesterolemias, with particular emphasis on SLOS, highlighting the importance of early identification of cholesterol biosynthesis defects in order to improve diagnosis and therapeutic approaches.
Methodology: A narrative literature review was conducted based on scientific articles published between 2018 and 2024, retrieved from the PubMed, ScienceDirect, B-ON, and Google Scholar databases. Searches were performed using combinations of the keywords “Cholesterol synthesis”, “Inborn error”, “Hypocholesterolemias”, “Enzyme deficiency”, and “Smith-Lemli-Opitz syndrome” and their Portuguese equivalents, combined with the Boolean operators AND and OR. Articles were selected according to thematic relevance and alignment with the defined objectives, resulting in the analysis of 87 scientific articles.
Results: There is currently no proven effective treatment for SLOS. Dietary cholesterol supplementation and statin therapy remain controversial approaches. Cholic acid may improve cholesterol absorption, although it is insufficient to reverse the pathology. Miglustat has been considered a promising therapeutic option, particularly due to its potential impact on central nervous system alterations associated with the syndrome. In addition, supplementation with antioxidants such as vitamin E has shown the ability to inhibit the formation of oxysterols derived from 7-dehydrocholesterol, some of which exhibit relevant cellular toxicity. Despite these advances,

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available evidence remains limited, and continued scientific research is required. These disorders have a significant impact on human health, being associated with high morbidity, premature mortality, and persistent neurological impairments. Early recognition of hypocholesterolemias is essential to optimize clinical follow-up, implement individualized therapeutic strategies, and improve the quality of life of patients and their families.
Conclusion: Life expectancy of individuals with SLOS is often reduced, ranging from a few days to several decades, with premature death frequently resulting from severe congenital malformations. Although some clinical manifestations can be treated, most patients present persistent neurobehavioral abnormalities, reinforcing the need for more effective and targeted therapeutic approaches.