REVISTA NEUROCIÊNCIAS



# Frequency of scoliosis in myopathies: scope review

*Frequência de escoliose em miopatias: revisão de escopo*

*Frecuencia de escoliosis en miopatías: revisión de alcance*

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## Resumo

**Introdução.** A escoliose é caracterizada como um desvio lateral na coluna vertebral, que pode ser acompanhado de componente rotacional, resultando em uma curvatura com angulação variável, conforme medida pelo ângulo de Cobb. Escoliose é um achado descrito em doenças neuromusculares que levam a comprometimento de musculatura paravertebral, que deve ser monitorada para detecção e intervenção precoces. Assim, o objetivo desta revisão de literatura é investigar a ocorrência e frequência de escoliose nas várias miopatias, para aumentar o grau de suspeição clínica e intervenção no momento adequado. **Método.** As buscas foram realizadas no banco de dados da PubMed, para artigos publicados entre 1965-2023, com as palavras-chave "myopathy" e "scoliosis". 112 dos 229 artigos originais encontrados atenderam aos critérios de inclusão e todos os artigos selecionados foram avaliados criticamente por dois avaliadores independentes. As seguintes variáveis foram selecionadas desses artigos: autor, ano, tipo de miopatia, mutação associada, idade, sexo, severidade da escoliose e intervenção. **Resultados**. As miopatias associadas à escoliose nessa revisão foram, em ordem de frequência, as distrofias musculares congênitas (14-100%), as distrofias musculares progressivas como a forma de Duchenne (100%) e as miopatias congênitas (5-100%). A quantificação da intensidade da escoliose teve predominância de casos severos, seguido de casos leves. Em relação às intervenções, foram relatadas a fisioterapia e a intervenção cirúrgica, na maioria dos casos. **Conclusão.** Escoliose é um achado frequente em miopatias, porém com poucos dados prospectivos da intensidade e do impacto das intervenções em grande parte delas. Mais estudo são necessários nessa área.
**Unitermos.** Escoliose; Miopatias; Miopatias Congênitas

## Abstract

**Introduction.** Scoliosis is characterized as a lateral deviation in the vertebral column, which may be accompanied by a rotational component, resulting in a curvature with variable angulation, as measured by the Cobb angle. Scoliosis is a finding described in neuromuscular diseases that leads to impairment of paravertebral musculature, which should be monitored for early detection and intervention. Thus, the aim of this literature review is to investigate the occurrence and frequency of scoliosis in various myopathies to increase clinical suspicion and timely intervention. **Method.** Searches were conducted in the PubMed database for articles published between 1965-2023, using the keywords "myopathy" and "scoliosis". 112 out of 229 original articles found met the inclusion criteria, and all selected articles were critically evaluated by two independent reviewers. The following variables were selected from these

articles: author, year, type of myopathy, associated mutation, age, sex, scoliosis severity, and intervention. **Results.** The myopathies associated with scoliosis in this review were, in order of frequency, congenital muscular dystrophies (14-100%), progressive muscular dystrophies such as Duchenne's form (100%), and congenital myopathies (5-100%). The quantification of scoliosis intensity predominated severe cases, followed by mild cases. Regarding interventions, physiotherapy and surgical intervention were reported in the majority of cases. **Conclusion.** Scoliosis is a frequent finding in myopathies but with few prospective data on the intensity and impact of interventions in many of them. Further studies are needed in this area.
**Keywords.** Scoliosis; Myopathies; Congenital Myopathies

## Resumen

**Introducción.** La escoliosis se caracteriza como una desviación lateral en la columna vertebral, que puede ir acompañada de un componente rotacional, lo que resulta en una curvatura con angulación variable, según lo medida por el ángulo de Cobb. La escoliosis es un hallazgo descrito en enfermedades neuromusculares que conducen al deterioro de la musculatura paravertebral, que debe ser monitoreada para detección e intervención tempranas. Por lo tanto, el objetivo de esta revisión de literatura es investigar la ocurrencia y frecuencia de la escoliosis en diversas miopatías para aumentar la sospecha clínica y la intervención oportuna. **Método.** Se realizaron búsquedas en la base de datos de PubMed para artículos publicados entre 1965 y 2023, utilizando las palabras clave "miopatía" y "escoliosis". 112 de los 229 artículos originales encontrados cumplieron con los criterios de inclusión, y todos los artículos seleccionados fueron evaluados críticamente por dos revisores independientes. Se seleccionaron las siguientes variables de estos artículos: autor, año, tipo de miopatía, mutación asociada, edad, sexo, gravedad de la escoliosis e intervención. **Resultados.** Las miopatías asociadas con escoliosis en esta revisión fueron, en orden de frecuencia, las distrofias musculares congénitas (14-100%), las distrofias musculares progresivas como la forma de Duchenne (100%) y las miopatías congénitas (5-100%). La cuantificación de la intensidad de la escoliosis predominó en casos graves, seguidos de casos leves. En cuanto a las intervenciones, se informó fisioterapia y cirugía en la mayoría de los casos. **Conclusión.** La escoliosis es un hallazgo frecuente en las miopatías, pero con pocos datos prospectivos sobre la intensidad y el impacto de las intervenciones en muchas de ellas. Se necesitan más estudios en esta área.
**Palabras clave.** Escoliosis; Miopatías; Miopatías Congénitas

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## INTRODUCTION

Scoliosis is a condition characterized by the three-dimensional deformity of the vertebral column, often observed in patients diagnosed with various myopathies, which are genetic or acquired muscular diseases. This association implies a considerable impact on the functionality and quality of life of affected individuals, being associated with gait alterations and changes in the rib cage that can

lead to mobility restrictions, chronic pain, restrictive respiratory insufficiency, and even cardiopathy[1,2].

Regarding etiology, scoliosis can be classified into three subtypes: congenital, neuromuscular, and idiopathic. Congenital scoliosis is characterized by anatomical anomalies resulting from defects in the formation, segmentation, or mixed and complex shapes of the vertebral column. Neuromuscular scoliosis results from primary or secondary dysfunctions in the motor unit, which includes spinal roots, nerves, neuromuscular junction, and muscle. Among the causes of secondary scoliosis are neoplasms, rheumatoid arthritis, infections, metabolic disorders, spondylolisthesis, neurofibromatosis, and connective tissue diseases[3]. Idiopathic scoliosis is characterized by significant phenotypic complexity, encompassing variations in curvature morphology and magnitude, age of onset, and progression rate. Its prognosis is variable and may involve an increase in curve amplitude, stabilization, or even resolution due to growth[2,4].

The diagnosis of scoliosis is initially made through physical examination, evaluating the patient undressed, with the assistance of the Adams forward bending test (flexing the trunk forward) and observing asymmetries, such as the waistline triangle (formed by the aspect between the upper limbs and the trunk). Additionally, the measurement of the Cobb angle is used, which is an angular measure used to quantify the curvature of the spine, determined through panoramic radiographs of the spine. A curve may be

considered significant when the Cobb angle is equal to or greater than 10 degrees. Curves between 10 and 25 degrees are generally classified as mild, between 25 and 40 degrees as moderate, and curves above 40 degrees are considered severe, always considering age, maturity, and the presence of rotation. The Cobb angle is a fundamental tool in the diagnosis, classification, and monitoring of scoliosis[4,5].

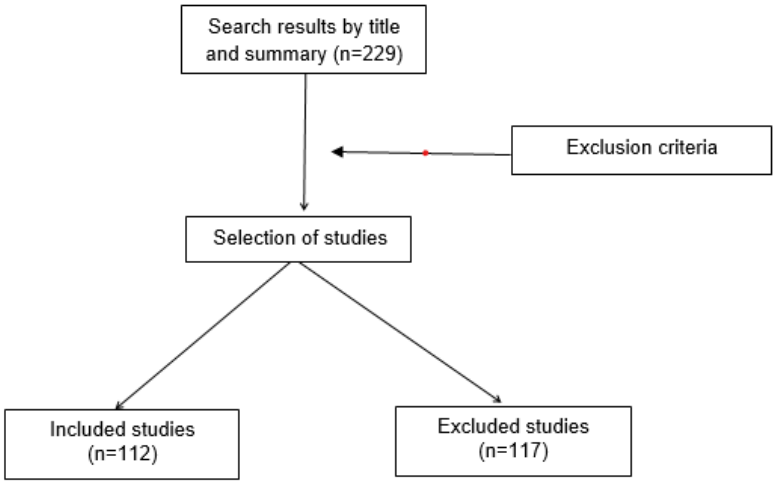
The differential diagnosis of scoliosis includes myopathies, collagen diseases, vertebral fractures, spinal tumors, metabolic disorders, infections, and idiopathic scoliosis, which is the most common form in children and adolescents, as well as other possible conditions that can cause spinal curvatures. Detailed clinical examinations, such as assessment of muscle strength, presence of weakness, and muscle atrophy, along with imaging tests such as magnetic resonance imaging and electromyography, help differentiate myopathies. Laboratory tests to evaluate specific biomarkers, such as serum levels of muscle enzymes and molecular genetic studies, are frequently used to confirm the diagnosis[6-8].

The objective of this review is to investigate the frequency of scoliosis in patients with myopathies, as the presence of scoliosis may indicate progression of the underlying myopathic disease and requires a multidisciplinary therapeutic approach to prevent additional complications and improve clinical outcomes.

## METHOD

Searches were conducted in the PubMed database for articles on the frequency of scoliosis in myopathies, in all languages, from 1965 to 2023, using the keywords "scoliosis" and "myopathy" in the title or abstract (Figure 1).

Figure 1. Systematic review flowchart, according to the PRISMA protocol.




Studies were excluded based on the following criteria: systematic reviews, animal studies, studies with individuals with myopathies without the presence of scoliosis, studies with individuals with scoliosis without a diagnosis of myopathy, cases of scoliosis with associated neuropathies, and studies with individuals with scoliosis in other pathologies. The search strategies identified 229 relevant studies. Based on the analysis of abstracts, 112 studies were included, while 117 articles were excluded for the following reasons: systematic review (n=24), book chapters (n=5),

articles not available for reading (n=9), individuals with neuropathies (n=10), animal study (n=2), repeated study (n=1), studies with myopathies without identification of scoliosis (n=34), and studies with scoliosis without a diagnosis of myopathy (n=32). The following data were collected from the included studies: author, year, type of myopathy, associated mutation, age, sex, scoliosis severity, and intervention. The myopathies were classified according to the GeneTable of Neuromuscular Disorders model (https://www.musclegenetable.fr).

## RESULTS

### Characteristics of Included Studies

Table 1 presents the characteristics of the 112 included studies, which were classified by groups and subgroups of myopathies.

Table 1. General characteristics and prevalence of scoliosis in myopathy subtypes.

| Myopathy group / subtype | Gene symbol | Sample (% scoliosis) | Age or Sex | Intensity of scoliosis | Interventions | Author |
|---|---|---|---|---|---|---|
| ***Congenital*** **1. Nemaline** | *KLHL40* | n=1 | 26 y/ M | - | - | Dofash 2023[8] |
| | *NEB* | n=33 (46) | ẍ 18 y/ (15F/ 18M) | - | - | Moreno 2023[9] |
| | *NEB* | n=1 | 54 y/ F | - | - | Wunderlich 2018[10] |
| | - | n=1 | 43 y /F | Severe | Physical therapy | Polastri 2019[11] |
| | *LMOD3* | n=3 (33) | 8 y/ F | Severe | - | Michael 2019[12] |
| | - | n=2 (100) | 19y (F) / 20y (M) | - | - | Topaloglu 1994[13] |
| | - | n=1 | 35 y/ M | - | - | Fukunaga 1980[14] |
| | *ACTA1/KLHL40/ TPM2-3* | n=30 (43) | 7F/ 6M | Mild/Severe | - | Gurgel-Giannetti 2022[15] |
| | *NEB* | n=1 | 6y / M | - | - | Scoto 2013[16] |
| **2. CNM** | *TNNT3* | n=1 | Neonate/M | - | | Sandaradura 2023[17] |
| | *DNM2* | n=1 | 17y/ F | Mild | - | Aghbolaghi 2017[18] |
| | *MYH7* | n=2 (50) | 1M | - | - | Li 2018[19] |
| | - | n=38 (11.4) | - | Severe | - | Ferreiro 2000[20] |

Table 1 (cont.). General characteristics and prevalence of scoliosis in myopathy subtypes.

| Myopathy group / subtype | Gene symbol | Sample (% scoliosis) | Age or Sex | Intensity of scoliosis | Interventions | Author |
|---|---|---|---|---|---|---|
| **3. Myotubular** | *XLMTM* | n=21 (40) | 44.0 to 15.09 | - | - | Franken 2022[21] |
| | *XLMTM* | n=1 | 15y/ M | Severe | Surgical treatment | Flaherty 2018[22] |
| | *MTM1* | n=1 | 6y/ F | Mild | | Jungbluth 2003[23] |
| **4.CCD** | - | n=1 | 76y/ F | - | Surgical treatment | Karunaratne 2021[24] |
| | *RUNX2* | n=1 | 58y/ M | Mild | - | Hsueh 2017[25] |
| | *RYR1* | n=5 (60) | 3F | Severe | - | Jeong 2018[26] |
| | *RYR1* | n=1 | Male infant | - | - | Brackmann 2018[27] |
| | - | n=8 (12.5) | 18 y | - | - | Ferreiro 2002[28] |
| | - | n=1 | 12y/ F | - | - | Merlini 1987[29] |
| | - | n=2 | 13 to 4y / 2M | - | Surgical treatment | Mertz 2005[30] |
| | - | n=11 (54) | 13 to 47y (5F/1M) | - | - | Quinlivan 2003[31] |
| | - | n=2 (100) | 14 to 17 y | Severe | Surgical treatment | Sestero 2005[32] |
| **5. CNMDU1** | - | n=1 | 13y/ F | Thoracic scoliosis 130° | Surgical treatment | Imagama 2012[33] |
| | - | n=1 | 3y/ M | - | - | Sakamoto 2006[34] |
| **6.MMD** | *RYR1* | n=1 | 14y/ M | Mild | - | Moon 2023[35] |
| | *MYH7* | n=3 (33) | 15 months / 1F | Severe | - | Beecroft 2019[36] |
| | *RYR1* | n=11 (54) | 7 to 10 y | Mild/Moderate | - | Jungbluth 2005[37] |
| | - | n=19 (5) | Neonatal | - | - | Jungbluth 2000[38] |
| | - | n=1 | 9y/ M | - | - | Myong 1993[39] |
| | - | n=1 | 3.5 y | - | Surgical treatment | Pellengahr 1998[40] |
| | - | n=3 (100) | 15 to 21y (2M/1F) | - | - | Rowe 2000[41] |
| **7. CFTD** | - | n=1 | 28y/ F | Mild | - | Mannil 2022[42] |
| | *TPM3* | n=1 | 10y/ F | - | - | Xu 2020[43] |
| | *RYR1* | n=1 | 22 y/ F | Severe | - | Blackburn 2017[44] |
| | *TPM3* | n=1 | 27y / M | Mild | - | Citirak 2014[45] |
| | - | n= 5 (20) | 3 y / M | - | - | Clancy 1980[46] |
| | *SEPN1* | n=8 (25) | 22 to 47 y/ F | - | - | Clarke 2006[47] |
| | *TPM3* | n=2 | 7 to 12y /1F/1M | Mild | - | Munot 2010[48] |
| | Translocation t (10; 17) (pl 1.2;q25) | n=1 | 22 y/ F | Mild | - | Gerdes 2008[49] |
| | *TPM3* | n=3 (100) | 20 to 45 y | - * | - | Schreckenbach 2014[50] |
| | *SEPN1* | n=41 (70) | Ÿ 10 y | Severe | Surgical treatment | Scoto 2011[51] |
| **8. NAM** | *STAC3* | n=4 (100) | 3F/1M | Severe | Walked with assistive equipment | Telegrafi 2017[52] |
| | *STAC3* | n=1 | 8 y/ M | Moderate | Surgical treatment | Grzybowski 2017[53] |
| | *STAC3* | n=1 | 26 y/ F | - | Surgical treatment | Mock 2021[54] |
| **9. Recessive CM with minicores (EMARDD)** | *MEGF10* | n=1 | 22 y/ M | - | - | Croci 2022[55] |
| | *MEGF10* | n=2 (100) | 2 M | - | - | AlMuhaizea 2021[56] |
| | *MEGF10* | n=1 | 44y/ F | - | Surgical treatment | Liewluck 2016[57] |
| | *MEGF10* | n=1 | 10y/ F | Mild | - | Boyden 2012[58] |

Table 1 (cont.). General characteristics and prevalence of scoliosis in myopathy subtypes.

| Myopathy group / subtype | Gene symbol | Sample (% scoliosis) | Age or Sex | Intensity of scoliosis | Interventions | Author |
|---|---|---|---|---|---|---|
| **10. CM lato senso** | *PAX7* | n=5 (100) | 7 to 14 y (2F/3M) | Moderate/Severe | - | Feichtinger 2019[59] |
| **Myopathic** | *FKBP14* | n=1 | 14 y | Severe | - | Baumann 2012[60] |
| **P1** | *RYR1* | n=3 | 2F/ 1M | Severe | Surgical treatment | Rocha 2014[61] |
| **P1** | - | n=2 | 5 and 11y /1F/1M | - | - | Meng-Chuan 2011[62] |
| **P1 / core-like** | - | n= 16 (73) | 7 to 56 y | - | - | Lossos 2005[63] |
| **Freeman-Sheldon** | - | n=1 | 8y/ F | Severe | Surgical treatment | Lu 2012[64] |
| **20 cores** | | n=104 (43) | - | Severe (42,8%) | Surgical treatment | Benito 2021[65] |
| **5 NM** | *Myotonic Type 1* | n=1 | 13 y/ F | Moderate | Surgical treatment | Agrawal 2021[66] |
| **3 CNM** | | | | | | |
| **2 CFTP** | | | | | | |
| ***Dystrophies*** | *Duchenne* | N=13 (100) | 13 M | - | Surgical treatment | Nedelcu 2016[67] |
| ***Emery Dreyfuss*** | *FHL1* | n=1 | 7y/ M | - | - | Mota 2021[68] |
| | *FHL1* | n=1 | 11 y/ M | - | - | Chen 2021[69] |
| | *FHL1* | n=11 (45) | 4F/1M | Mild | - | Schessl 2009[70] |
| ***LGMD*** | *COL6A1/ COL6A2* | n=1 | 28 y/ F | Severe | Surgical treatment | Li 2021[71] |
| | *COL6A2* | n=1 | 7 y/ F | - | - | Saito 2022[72] |
| | *COL6A1* | n=23 (30.4) | 3 to 19y | - | Surgical treatment | Silverstein 2023[73] |
| | *CAPN3* | n=57 (-) | 7 to 78 y | - | - | Barp 2019[74] |
| ***CMD*** | *SEPN1* | n= 132 (77) | F (50.8) /M | - | - | Villar-Quiles 2020[75] |
| | *SEPN1* | n=7 (57) | 4F | - | 3 BRACE / 1 Surgical treatment | Caggiano 2017[76] |
| | *SEPN1* | n= 60 (75) | 12.1y | - | Surgical treatment | Silwal 2020[77] |
| | *SEPN1* | n=1 | 23 y/ F | Severe | - | Kazamel 2019[78] |
| | *TRIP4* | n=6 (100) | 2F/ 4M | - | - | Villar-Quiles 2020[79] |
| | *SEPN1* | n=1 | 8 y (M) | - | - | Tajsharghi 2005[80] |
| | *SEPN1* | n= 62 (28) | 9M / 8 F | - | - | Ferreiro 2002[81] |
| | *chromosome 1p35-p36* | n=4 (100%) | 3M/ 1F | - | Surgical treatment | Flanigan 2000[82] |
| | *SEPN1* | n=1 | 21y/ M | Mild | - | Sponholz 2006[83] |
| | - | n=1 | 7y /M | Mild | - | Murakami 2005[84] |
| | - | n=1 | 13y/ F | Mild | Surgical treatment | Nomizu 1992[85] |
| | - | n= 21 (14) | 5 to 62 y | Severe | - | Schilling 2013[86] |
| | - | n=1 | 5y/ M | Severe | Surgical treatment | Goebel 2001[87] |
| ***Canalopaties*** | *SCN4A* | n=1 | 27 y/F | Severe | - | Waldrop 2019[88] |
| | *SCN4A* | n=2 (100) | 18 to 21 y/M | Mild | - | Gonorazky 2017[89] |
| | *SCN4A* | n=1 | 7y/ M | - | - | Elia 2020[90] |
| | *STIM1* | n=1 | 41y/ F | - | - | Noury 2017[91] |
| ***Myofibrillar*** | *TinTin* | n=1 | 19y/ M | - | Physical therapy | Alawneh 2023[92] |
| | *TNNT3* | n= 30 (66) | 9F/ 13F | Mild | - | Rees 2021[93] |
| | *TNNT3* | n=1 | 3 y/ M | Severe | - | Calame 2021[94] |
| | *CRYAB* | n=1 | 2 y/ F | - | - | Shan-shan 2023[95] |
| | *FLNC* | n=1 | 41y/ F | - | - | Matsumura 2021[96] |
| | - | n=1 | 14 y / F | Severe | Surgical treatment | Finsterer 2011[97] |

Table 1 (cont.). General characteristics and prevalence of scoliosis in myopathy subtypes.

| Myopathy group / subtype | Gene symbol | Sample (% scoliosis) | Age or Sex | Intensity of scoliosis | Interventions | Author |
|---|---|---|---|---|---|---|
| ***Mitochondrial*** | *MSTO1* | n=1 | 3y/ M | - | - | Liu 2022[98] |
| | *MSTO1* | n=1 | 32y/ F | Mild | - | Newstead 2022[99] |
| | *MSTO1* | n=1 | 30y/ M | - | - | Schultz-Rogers 2019[100] |
| | *MSTO1* | n=2 (100) | 10y/ 2F | Severe | Surgical treatment | Loh 2016[101] |
| | *MGME1* | n=1 | 40y/ F | - | - | Rocha 2023[102] |
| | - | n=1 | 16 y/ M | - | Surgical treatment | Zheng Li 2015[103] |
| | - | n=1 | 65y/ F | - | - | Hiniker 2014[104] |
| | - | n=40 (62.5) | 15 y | - | - | Smuts 2010[105] |
| ***Metabolic*** | Lipodystrophy Type 4 | n=2 (100) | 11 to 13y/ F | Moderate | Physical therapy | Akinci 2016[106] |
| | *CGL4* | n=74 (9.5) | 13 to 50y | - | - | Akinci 2017[107] |
| | Pompe disease (*GAA)* | n=7 | - | - | - | De Blasiisa 2021[108] |
| Lipid Storage Myopathy | - | n=2 (100) | 2 to 3y /1F/1M | - | - | Nogami 1983[109] |
| ***Others*** | | | | | | |
| *RSS* | - | n=1 | 20 Y/F | Moderate | - | Akiyama 1992[110] |
| *RSS* | - | n=8 (87.5) | - | - | - | Merlini 1989[111] |
| *RSS* | - | n=1 | 15y / F | Severe | - | Todorović 1989[112] |
| Scoliosis and myopathy | *LBX1* | n=1 | 12 y/ F | - | Medical corset | Fernández-Jaén 2014[113] |
| Distal myopathy | *MYH7* | n=21 (57) | 9 to 18 y | - | - | Lamont 2014[114] |
| Distal myopathy | *MYH7* | n=1 | 14y/ M | Mild | Surgical treatment | Stalpers 2011[115] |
| Distal myopathy | *MYH7* | n=14 (42) | 11 to14y | - | - | Oda 2015[116] |
| Cytoplasmic Body Myopathy | - | n=1 | 17y / M | Severe | - | Sekijima 1995[117] |

CNM (Centronuclear myopathy); CCD (Cleidocranial dysplasia); CFTD (congenital fiber-type disproportion); CM (Congenital Myopathy); MmD (*Multi-minicore* disease); CMD (Congenital muscular dystrophies); CNM (*Centronuclear* myopathy); *KLHL40 (*Kelch Like Family Member 40); *NEB* (Nebulin); *LMOD3* (Leiomodin 3); *TNNT3 (*Troponin T Type 3); *DNM2* (Dynamin 2); *RUNX2* (RUNX Family Transcription Factor2); *TPM3* (Tropomyosin 3); NAM ( Native American myopathy); *STAC3* (SH3 And Cysteine Rich Domain 3); *MEGF10* (Multiple EGF Like Domains 10); *XLMTM* (Myotubularin 1); *PAX7* (Paired Box 7); *RYR1* (Ryanodine Receptor 1); *FHL1* (Four and A Half LIM Domains 1); *COL6A1* (Collagen Type VI Alpha 1 Chain); *COL6A2* (Collagen Type VI Alpha 2 Chain); *CAPN3* (Calpain 3); *SEPN1* (Selenoprotein N); *TRIP4 (*Thyroid Hormone Receptor Interactor 4); *STIM1* (Stromal Interaction Molecule 1); *CRYAB* (Crystallin Alpha B); *MSTO1* (Misato Mitochondrial Distribution And Morphology Regulator 1); *MGME1* (Mitochondrial Genome Maintenance Exonuclease 1); *CGL4* (Congenital generalized lipodystrophy type 4); *GAA* (Alpha Glucosidase); EMARDD (Early-onset myopathy, areflexia, respiratory distress, and dysphagia); LGMD (Limb girdle muscular dystrophy); CNMDU1 (Congenital neuromuscular disease with uniform type 1 fiber), MMD (Multiminicore disease) P1 (type 1 fiber predominance).

## Congenital Myopathies

In nemaline myopathies, the genes KLHL40, NEB, LMOD3, ACTA1, KLHL40, and TPM2-3 were associated with cases of scoliosis. The highest percentage of scoliosis was observed in cases associated with the NEB gene. The average age of patients was in the third decade, with a balanced distribution between sexes. The severity of scoliosis

ranged from mild to severe, with a description of physiotherapy intervention for a case of severe scoliosis[8-16].

In centronuclear myopathies (CNM), the genes TNNT3, DNM2, and MYH7 were associated with cases of scoliosis, with ages ranging from a neonate to 17 years old. The severity of scoliosis ranged from mild to severe, depending on the specific gene. No specific information was provided regarding interventions for each case[17-20].

For cases of scoliosis in myotubular myopathy, the genes XLMTM and MTM1 were associated, with the majority of cases linked to the XLMTM gene. The average age was in the third decade, with a predominance of male cases due to the X-linked transmission characteristic of the XLMTM gene. Interventions included surgical treatment for a severe scoliosis case associated with the XLMTM gene, while the case associated with the MTM1 gene was of mild intensity[21-23].

In the group of myopathies with cores, in central core disease (CCD), the genes associated with cases of scoliosis included RUNX2 and RYR1. The average age was in the fourth decade, with a slight female predominance. The severity of scoliosis was described as mild to severe. Interventions included surgical treatment for some cases of scoliosis, especially those associated with the RYR1 gene[24-32].

In congenital myopathy with type 1 uniformity (CNMDU1), we found two case reports with no specification of the associated gene, aged 3 and 13 years, with an equal

distribution between sexes, severe scoliosis, and surgical treatment[33,34].

In Multiminicore Disease (MMD), the genes RYR1 and MYH7 were associated with cases of scoliosis. The average age of the patients was in the second decade, with severity ranging from mild to moderate in the RYR1 gene and severe in the MYH7 gene. Interventions included surgical treatment[35-41].

In Congenital Fiber-Type Disproportion Myopathy (CFTD), the genes associated with cases of scoliosis included TPM3, RYR1, SEPN1, and one case associated with translocation t(10;17) (pl 1.2;q25). The average age of the patients was in the second decade of life, with a predominance of females. Interventions included surgical treatment for some cases of scoliosis, especially those associated with the SEPN1 and TPM3 genes[42-51].

The only gene associated with cases of scoliosis in Native American Myopathy (NAM) was STAC3. The average age of the patients was in the second decade of life, with a balanced distribution between sexes. Interventions included surgical treatment for two cases of scoliosis and walking assistance devices for four cases with severe scoliosis[52-54].

Early-Onset Myopathy with Arthrogryposis, Respiratory Distress, and Dysphagia (EMARDD) had the MEGF10 gene associated with cases of scoliosis. The average age of the patients was in the second decade, with a similar distribution between sexes. Interventions included surgical treatment for one case of scoliosis[55-58].

In the group of congenital myopathies in a broad sense, we included patients not classified in the previous groups. The PAX7 gene was associated with a case of scoliosis in patients between the first and second decades of life, with a predominance of males. The severity of scoliosis was described as moderate to severe, and no specific information was provided regarding interventions for each case[59,60].

In myopathies with predominance of type I fibers, with or without cores, three out of 21 patients had mutations in the RYR1 gene. The average age of the patients was in the second decade of life, with a similar distribution between sexes, and three had a severe condition requiring surgical intervention. For Freeman-Sheldon syndrome, a single case was reported, involving a female patient in the first decade of life. The degree of scoliosis was classified as severe, requiring surgical intervention[61-64].

A single retrospective cohort study in pediatric patients, conducted by Benito *et al*.[65], with cross-sectional data collection carried out at a single center, reports the clinical, histopathological, and molecular characterization of 104 patients with congenital myopathy. The study observed scoliosis in 43% of the overall patients. A definitive molecular diagnosis was achieved in 65 out of 104 patients (62%), with RYR1 (24/104) and TTN (8/104) being the most frequent causative genes. The severity of scoliosis was severe in almost half of the subgroup associated with the RYR1 gene.

***Dystrophies***

In a single report of Myotonic Dystrophy Type 1 (DM1), the patient was in the second decade of life and was female, with moderate scoliosis requiring surgical intervention[66].

In Duchenne Muscular Dystrophy, all reported cases involved male patients. No information was provided about the severity of scoliosis, but all cases underwent surgical treatment[67].

The gene associated with scoliosis cases in Emery-Dreifuss Muscular Dystrophy was FHL1, with an average age in the first decade, with a slight female predominance, and scoliosis classified as mild[68-70].

Reports of Limb-Girdle Muscular Dystrophy (LGMD) were associated with the genes COL6A1, COL6A2, and CAPN3, with the average age of patients in the third decade and surgical treatment as intervention for cases associated with the genes COL6A1 and CAPN3[71-74].

Cases of scoliosis in Congenital Muscular Dystrophy were associated with the genes SEPN1, TRIP4, and the chromosomal region 1p35-p36. The average age of patients was in the second decade, with a higher frequency in males. The severity of scoliosis ranged from mild to moderate to severe. Different interventions, including surgical treatment, the use of braces (orthopedic appliance BRACE), and physiotherapy, were reported[75-87].

### *Channelopathies*

In channelopathies, the genes SCN4A and STIM1 were associated with cases of scoliosis. The average age of the patients was in the third decade, with a male predominance in cases associated with the SCN4A gene. The severity of scoliosis ranged from mild to severe. There were no reports of intervention in any of the cases[88-91].

### *Myofibrillar Myopathy*

Cases of scoliosis in Myofibrillar Myopathy were associated with the genes TinTin, TNNT3, CRYAB, and FLNC. The average age of the patients was in the second decade, with a similar distribution between sexes. The severity of scoliosis ranged from mild to severe, and intervention included physiotherapy for one case[92-97].

### *Mitochondrial Myopathy*

The genes MSTO1 and MGME1 were associated with mitochondrial myopathy with scoliosis. The average age of patients was in the third decade. There was a similar distribution between sexes in cases associated with the MSTO1 gene. The severity of scoliosis ranged from mild to severe. Interventions included surgical treatment for some cases of scoliosis associated with the MSTO1 and MGME1 genes. Unfortunately, the specific number of cases requiring surgical intervention was not provided[98-105].

### *Metabolic Myopathies*

Metabolic myopathies with scoliosis were associated with the genetic conditions Lipodystrophy Type 4, CGL4 (Congenital Generalized Lipodystrophy Type 4), and Pompe disease (GAA). The average age was in the second decade, with a predominance of females in cases associated with Lipodystrophy Type 4. The severity of scoliosis was moderate for Lipodystrophy Type 4. Intervention for Lipodystrophy Type 4 cases included physiotherapy. Cases of scoliosis associated with Lipid Storage Myopathy occurred in the first decade, with a similar distribution between sexes[106-109].

### *Other*

Cases of scoliosis associated with Rigid Spine Syndrome (RSS) occurred in the second decade, with a similar distribution between sexes. The severity of scoliosis ranged from moderate to severe[110-112].

Cases of scoliosis in Distal Myopathy were associated with the MYH7 gene, with the average age of participants in the second decade. The severity of scoliosis in one case was mild. Interventions included surgical treatment[113-116].

There was a case of Scoliosis and Myopathy, with the LBX1 gene, and one of Cytoplasmic Body Myopathy (CBM) without a specific gene[117.]

## DISCUSSION

Scoliosis is a common complication in myopathies, and the studies on scoliosis in different myopathies found in this

review revealed a variety of genes associated with the condition, as well as distinct clinical characteristics. Subgroup analysis was challenging due to the limitation of data in literature, as the vast majority of studies are case reports, and scoliosis may take time to develop and be diagnosed in the absence of follow-up protocols that include periodic panoramic radiographs of the spine.

With the caveat that few studies reported the age of onset of scoliosis, scoliosis associated with MMD-type myopathies tended to be described in younger patients, starting from the first decade of life. Meanwhile, metabolic and distal-type myopathies tended to be described in adolescent patients in the second decade of life. Generally, nemaline-type myopathies tend to be described in adults, starting from the third decade of life. On the other hand, CCD described the only case of myopathy in an elderly patient.

In addition to this deficiency in detailed participant information, few studies characterized the degree of intensity as mild (10 to 25º), moderate (25 to 40º), and severe (above 40º)[5,7]. Additionally, few studies described the Cobb angle, which is important in the assessment and monitoring of scoliosis, providing a quantitative measure of the severity of spinal curvature and guiding treatment planning. In the present review, mild scoliosis was more commonly described in CFTD and CMD, while moderate scoliosis was observed in MMD, NAM myopathies, and one case of dystrophy, and severe scoliosis in congenital myopathies. Regardless of severity, scoliosis can lead to a

series of complications, such as postural imbalance causing discomfort and chronic pain, restricted movement affecting mobility and quality of life, and physical and social impact since altered physical appearance due to scoliosis can have a significant impact on self-esteem and emotional quality of life for patients. In more severe cases, spinal curvature can lead to respiratory impairment, making ventilation difficult and reducing lung capacity[7,32].

The evaluated studies demonstrated that the prevalence of scoliosis in myopathies varies according to the specific type of myopathy, with some showing significantly higher incidence than others. The myopathies most frequently associated with the occurrence of scoliosis in this review included, as cited by other authors, dystrophies such as Duchenne-Becker muscular dystrophy (DMD/DMB), limb-girdle muscular dystrophy, congenital muscular dystrophy (CMD), myotonic dystrophy (DM), and Emery-Dreifuss muscular dystrophy (EDMD)[2,6,66,67]. However, we emphasize the occurrence of scoliosis in other myopathies, such as congenital myopathies, channelopathies, myofibrillar myopathies, mitochondrial myopathies, and metabolic myopathies.

These myopathies can lead to progressive muscle weakness and muscular imbalance, contributing to the development of scoliosis. Due to the significant association between scoliosis and paravertebral muscle imbalance, numerous authors have studied potential alterations through muscle biopsy of the spinal rotator muscles, which may

elucidate the etiology of scoliosis[1,4,31]. The frequent manifestation of scoliosis in patients with congenital myopathies, such as central core disease (CCD) and nemaline myopathy, which exhibit a predominance of type I muscle fibers, suggests that the abnormal distribution of these fibers in the paravertebral muscles is likely an underlying pathogenic factor of scoliosis[118,119]. The occurrence, also in patients with adolescent idiopathic scoliosis, of a predominance of type I muscle fibers in the paravertebral muscles, specifically on the convexity of the scoliotic curve[4,31], raises the possibility that adolescent idiopathic scoliosis may be a manifestation of CCD. Recently, the anatomopathological presence of CCD has been reported in patients with idiopathic scoliosis, even in the absence of any clinical signs of muscle weakness in the upper or lower limbs[1].

Recent evidence indicates a broad clinical spectrum of CCD, suggesting that the true incidence of this condition may be considerably higher than previously reported[1,104].

It is important to note that the occurrence of scoliosis may vary among different subtypes and stages of progression of each myopathy, as well as due to methodological differences between studies, with variability in the definition, assessment, and diagnosis of scoliosis in different populations and clinical settings. Additionally, the focus in myopathies is often centered on other more prominent musculoskeletal or systemic complications. Finally, the scarcity of large studies specifically dedicated to

scoliosis in myopathies may result in underestimation of the true prevalence and lack of understanding about the progression and management of this condition.

The treatment of scoliosis can vary depending on the severity of the curve, the patient's age, the stage of skeletal growth, and other individual factors. The most common interventions recommended in the literature include physiotherapy, orthoses, regular monitoring, and surgery. In our review, surgical treatment was the most indicated in the cases of myopathies reported in the studies.

Idiopathic and congenital scoliosis may present associations with myopathies, although the underlying mechanisms may vary. In both types of scoliosis, the presence of myopathies can complicate the clinical picture, affecting the progression of the curve, the effectiveness of treatment, and the patient's quality of life. Therefore, patients with idiopathic scoliosis need to be comprehensively evaluated to identify any underlying myopathy and tailor the treatment plan according to their individual needs[1,3,4,7].

Long-term studies investigating the occurrence, frequency, severity, progression, and therapeutic response of scoliosis in different myopathies are necessary to improve the quality of life and survival in myopathies overall.

## CONCLUSION

Patients with myopathies should undergo periodic scoliosis assessments. The high incidence of scoliosis in individuals with myopathies, associated with primary or

secondary (disuse) changes in the paravertebral muscle fiber, indicates the need for evaluation of the onset and progression of the scoliotic curve in these patients.

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