A review of several myopathy related to mitochondrial dysfunction

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Abstract. The balance of protein production and consumption in muscles depends to a large extent on normal mitochondrial function. Mitochondrial dysfunction is inseparable from the occurrence of myopathy. This study explores the relationships between statin-induced myopathy, steroid myopathy, and skeletal muscle illness caused by alcohol addiction, as well as the relationship between these conditions and mitochondrial abnormalities.

Web of Science (WOS) central archive was analyzed for alcoholic myopathy research papers from 1999 to 2021, CiteSpace and WOS databases were used for evaluation the number of written articles, distribution of publications by region, research organizations, co-cited literature analysis, and keyword identification.

A total of 1,255 publications were collected after screening, with the number of published articles continually increasing. The annual average number of publications is 54.56. Six countries publish the majority of the literature. The United States has published 383 papers in total, which places it first among all countries. It also has the most centrality, meaning that other countries value its scientific achievements more. There are 34 core authors and 238 papers published. Through cluster analysis, there are 9 categories that are significant clusters. Key words of co-occurrence research show that keywords such as nanoparticles, apoptosis, mitochondrial disorders, and inflammation are very common.

Key word: Citespace; alcoholic myopathy; statins and steroid; mitochondrial dysfunction;

Аналіз міопатій, пов’язаних з мітохондріальною дисфункцією

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Анотація. Баланс синтезу і споживання білка в м’язах значною мірою залежить від нормальної функції мітохондрій. Мітохондріальна дисфункція невід’ємна від виникнення міопатії. У цьому досліджені аналізуються взаємозв’язки між міопатією, яка індукувана статинами, стероїдною міопатією та захворюванням скелетних м’язів, спричиненим алкоголю залежністю, а також взаємозв’язок між цими станами та мітохондріальними аномаліями.

Центральний архів Web of Science (WOS) був проаналізований на предмет досліджень алкогольної міопатії з 1999 по 2021 рік, бази даних CiteSpace і WOS використовувалися для оцінки кількості написаних статей, розподілу публікацій за регіонами, дослідницьких організацій, аналізу спільно цитованої літератури та ідентифікація ключового слова.

Загалом, після аналізу було виділено 1255 публікацій, при цьому кількість опублікованих статей постійно збільшується. Середньорічна кількість публікацій – 54,56. Більшість літератури публікують шість країн. Загалом Сполучені Штати опублікували 383 статтей, що займає перше місце серед всіх країн. Вони також займають центральну позицію у цій сфері досліджень, тобто інші країни більше використовують їх наукові досягнення. Виділено 34 основних авторів та 238 статей. За допомогою кластерного аналізу виділено 9 категорій, які є значущими кластерами.

Ключові слова: Citespace; алкогольна міопатія; статини і стероїди; мітохондріальна дисфункція.

INTRODUCTION

Myopathy is usually a non-fatal muscle disease, the main clinical manifestations are skeletal muscle weakness, tenderness and pain. There are many reasons for myopathy, such as myopathy caused by statins, steroid myopathy, skeletal muscle disease caused by alcoholism, etc.1–6. Because alcoholism is also a risk factor for the other two myopathies, the pathophysiological mechanisms of these three myopathies must be
investigated. In recent years, when people study the side effects of alcoholism, statins and steroid drugs on muscles, they will focus on the mechanisms of mTOR, IGF-1, Ca\(^{2+}\), and mitochondrial biogenesis (HMG-CoA) reductase inhibitors (ie statins) have muscle toxicity. Although relatively rare (0.1%), they can cause serious muscle toxicity and complications. Muscle biopsy tends to mitochondrial dysfunction\(^7\). Alcoholic myopathy appears to be a common complication of alcoholism in approximately 50% of patients. In steroid myopathy, a significant reduction in glycogen phosphorylase activity has been observed, and this effect is more prominent in type II fibers\(^8\). When studying the above three myopathy, people either study the signal pathways related to protein synthesis and decomposition, or study whether there is excessive ROS (reactive oxygen species) formation. No matter which direction it is, it is vaguely pointing to the mitochondria. Mitochondrial homeostasis is maintained by mitochondrial biogenesis, mitochondrial fusion, fission and mitochondrial autophagy\(^9\).

So are these myopathy all related to mitochondrial dysfunction, and can they all be treated with antioxidant therapies? This review, which employs CiteSpace as a methodology, focuses mostly on this topic.

This article analyzes articles related to myopathy treatment research in the Web of Science (WOS) core database in the United States from 1999 to 2021, and analyzes the overall development trend of the article, research institutions, authors, citations, keywords and emergent words. The purpose is to provide valuable information for the treatment of myopathy in the future.

1.1 Data Sources

The data comes from the US WOS database. This article uses the retrieval method of Chaomei Chene et al\(^10,11\). Keyword search 1: Subject: (myopath*) OR Subject: ("skeletal muscle diseases") OR Subject: ("m"uscle diseases"); Keyword 2: Subject: (glutathione) OR Subject: (glutathion) OR Subject: (glutathione hormone) OR Subject: (l-glutathione) OR Subject: (glutathione) OR Subject: (glutarate) OR Subject: (acid glutathione) OR Subject: (glutathione-s-transferase) AND document type: (Article OR Review); Search Keyword 3: Subject: (fullerene C60) OR Subject: (fullerene C70) OR Subject: (nanoparticles) OR Subject: (buckminster fullerene) OR Subject: (polyphenols); Search Keyword 4: Subject: (antichotic factor) OR Subject: (vitamin d) AND Document Type: (Article OR Review); Keyword 5: Subject: (thiamine) OR Subject: (vitamin b1) AND Document Type: (Article OR Review); Keyword 6: Subject: (fertility vitamin) OR Subject: (vitamin e) AND Subject: (therapy) AND document type: (Article OR Review); search key 7: subject: (IGF-1) AND document type: (Article OR Review); Search Keyword 8: Subject: (alcohol*) OR Subject: (ethanol) AND Document Type: (Article OR Review); Search Keyword 9: Subject: (antioxidant NEAR/5 therapy) AND Document Type: (Article OR Review); Time span: 1985-2020, retrieval time is February 28, 2021. Search Keyword 10: Subject: ("nemaline myopathy") AND (therapy) AND Document Type: (Article OR Review); Search Keyword 11: Subject: ("Duchenne's muscular dystrophy") AND (therapy) AND Document Type: (Article OR Review); time span: 1985-2021, retrieval time is February 28, 2021.

Search strategy: Combine keyword 1 with 2, 3, 4, 5, 6, 7, 8, and 9 in an "AND" manner.

When Keyword 9 is combined with Keyword 1, there are only nine documents, so we use the citation report function of WOS again \(^1\) to get 189 documents. In the end, this research obtained a total of 1807 documents.

1.2 Analysis methods, data inclusion, and exclusion criteria

CiteSpace was founded in 2004 by Dr. Chaomei Chen. This program can analyze data from the literature. The content that can be analyzed includes author, organization collaboration, keyword co-occurrence analysis, and emergency monitoring, which can help researchers in a specific field understand the evolution pattern of research topics, emerging hot spots and their period, important authors and institutions, and so on. As visual bibliometric applications, this software has been widely used in a number of scientific research fields. As a consequence, we selected this program for bibliometric analysis.

Literature inclusion criteria: ① All literature related to myopathy; ② The types of literature can be clinical case analysis, experimental research, theoretical discussion; ③ The types of literature resources are mainly journal articles, meta-analysis reviews and reviews. Exclusion criteria: ① Repeated publications; ② Documents whose full text is not available; ③ Documents mainly discussing Alzheimer's disease; ④ Documents whose main research object is liver disease.

1.3 Literature compilation and data analysis

Export the documents that meet the inclusion criteria in plain text format, and use R software to count the publication time of the documents; import the data into CiteSpace5.7.R2 software, and after deduplication processing, import the converted data into the software again. Set 1999-2021 as the analysis time (because the system defaults to mark the data of the unpublished year as 1999), select the author, institution, citation, and keywords as the node type, and draw the corresponding visual knowledge graphs respectively for the myopathy author, cooperation with institutions, citing article analysis, and keyword co-occurrence, clustering and emergence analysis. Each visualized knowledge map employs a 1-year partition process, as does the keyword knowledge map. The top 50 things are chosen, rated from high to low frequency, i.e., Top N per slice is 50, and the cutting method is Pathfinder, Pruningsliced networks, and Pruning the combined network.

RESULT

2.1 Analysis of publication year

From 1999 to 2021, 1807 articles related to myopathy were published. Because our search time was February 28, 2021, only 6 articles were retrieved in 2021. From 1999 to 2021, the number of publications in this area increased in a phased manner. Prior to 2009, the rate of publication growth was sluggish. Since 2010, the number of publications in this sector has almost steadily
increased year after year. The amount of articles published before 2009 accounted for 25.70 % of the total amount of articles published, and the amount of articles published in the past 5 years accounted for 43.66 % of the total. It can be seen that the research on myopathy is getting more and more attention. Overall, the average number of posts is 56.77. Use R "forecast" package for data processing. Use Holt’s exponential smoothing to fit the time series with horizontal terms and trend terms (slope), and take the log value of the number of posts. The formula is $Y_t=\text{level}+\text{slope}*t+\text{irregular}$. We get Figure 1 and Table 1. There will be about 202 articles published in 2021, with a 95 % confidence interval of [154.9020, 264.3448].

![Forecast of the number of publications in the next 3 years](image)

**Figure 1.** Forecast of the number of publication in the next 3 years

The X axis is the time of publication of the literature, and the Y axis is the Log value of the number of publications; this figure predicts the number of publications related to myopathy in the next 3 years starting from 2021. The specific values are shown in Table 1.

**Table 1**

|       | Mean   | Low 80 % | Low 95 % | High 80 % | High 95 % |
|-------|--------|----------|----------|-----------|-----------|
| 2021  | 202.3550 | 169.9137 | 154.9020 | 240.9902  | 264.3448  |
| 2022  | 218.0333 | 183.0785 | 166.9037 | 259.6620  | 284.8261  |
| 2023  | 234.3472 | 196.7770 | 179.3919 | 279.0907  | 306.1377  |

Mean: mean; Low 80 %: lower limit of 80 % confidence interval; High 80 %: upper limit of 80 % confidence interval; Low 90 %: lower limit of 90 % confidence interval; High 90 %: upper limit of 90 % confidence interval.

2.2 Regional distribution of high-volume publications from 1999 to 2021

According to the countries and regions where 1807 papers were written, the United States published the most (383), followed by the United Kingdom (123), Italy (109), China (105), France (98), and Germany (91). See Table 2 and Figure 2 for more details. There is a purple band in the outermost circle of the nodes in the United States, the United Kingdom, Germany, France, Spain, and Canada, showing that these countries' research is central, and their research findings are more noticed by other countries. The United States produces a large number of papers. The color of the nodes shows that myopathy study in the United States has strong consistency, and the centrality is also the strongest (0.57).
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Figure 2. Distribution of relevant literature publication countries from 1999 to 2021

Table 2

High publication volume of literature on myopathy from 1999 to 2021 Regional distribution (the top 6 regions in terms of post volume)

| Rank | country / region | Amount of papers/articles | centrality |
|------|------------------|---------------------------|------------|
| 1    | USA              | 383                       | 0.57       |
| 2    | ENGLAND          | 123                       | 0.30       |
| 3    | ITALY            | 109                       | 0.09       |
| 4    | CHINA            | 105                       | 0.01       |
| 5    | FRANCE           | 98                        | 0.12       |
| 6    | GERMANY          | 91                        | 0.21       |

2.3 Distribution of research institutions

Set the network node to “Institution” to generate a network map of research institutions. The top 10 research institutions with publication volume are located in the United States, France, the United Kingdom, Australia and other countries. Kings College London published 31 journals, accounting for 20.9% of articles published by the top ten institutions. In recent years, the institution has focused on experimental therapies for myopathy. The next most productive institutions are INSERM, accounting for 13.50%, and Harvard Univ, accounting for 10.13%. See Table 3. In particular, in the field of myopathy, Kings College London and Harvard University collaborated in 2006. This research expands on the anti-oxidative damage mechanism of alcohol-induced skeletal myopathy and provides a theoretical foundation for myopathy antioxidant treatment. In terms of centrality, the centrality value of Kings Coll London is 0.11, which is twice that of the second place, which fully demonstrates the institution’s recognition in myopathy research. Overall, there is a limited network of cooperation among the top 10 institutions.

Table 3

High publication volume of literature on alcoholic myopathy from 1999 to 2021 Institution distribution (the top 10 institutions in terms of post volume)

| Rank | institution         | Amount of papers/articles | centrality |
|------|---------------------|---------------------------|------------|
| 1    | Kings Coll London   | 31                        | 0.11       |
| 2    | INSERM              | 20                        | 0.05       |
| 3    | Harvard Univ        | 15                        | 0.06       |
| 4    | McMaster Univ       | 14                        | 0.04       |
| 5    | CNRS                | 14                        | 0.02       |
| 6    | Kobe Univ           | 11                        | 0.01       |
| 7    | Penn State Univ     | 11                        | 0.01       |

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2.4 Analysis of Knowledge Graph of Document Authors’ Cooperation Network

With the authors of the literature as the network node, the author’s cooperation in the past 23 years is generated through software, as shown in Figure 4. The graph consists of 726 nodes and 825 links. The size of the nodes in the graph represents the amount of articles published by authors, the links between nodes represent cooperation between authors, and the thickness of the links represents the degree of cooperation. VR PREEDY, CHARLES H LANG, and J FERNANDEZSOLA et al. specifically research alcoholic myopathy, investigating the pathogenic mechanism and treatment strategies. Authors with Nowak and Nigel G LAIN as the core have mainly studied the pathogenic mechanism and application of alpha-actin protein or its gene in skeletal myopathy in recent years. KATASHI OKOSHI, Gomes and others mainly study the theory and application of antioxidant therapy in skeletal myopathy. According to Price’s Law (ZONG Shuping 2016), calculate whether the target author is the core author, and the calculation formula is $N = 0.749 \times \sqrt{n_{\text{max}}}$, the number of papers published by the authors who published the most papers during the statistical era is referred to as $n_{\text{max}}$. Calculate the value of $N$, as long as the number of papers written is greater than $N$. These authors are referred to as core authors. The maximum number of papers involved in this study is 27, and $N=3.892$ can be calculated by the formula. Therefore, in this study, authors with $\geq 4$ papers are the core authors. There are 34 core authors, and the total number of published papers is 238, accounting for 18.96% of the total number of included documents.

2.5 Co-cited literature analysis

The co-citation cluster analysis of a document can objectively reflect the degree of recognition of the document by academia. While doing citation analysis, you can also perform cluster analysis to find research hotspots and trends. Therefore, in order to further analyze the current status of myopathy research, this study conducted an in-depth analysis of the highly cited documents and the highly cited documents involved in each cluster. Through cluster analysis, meaningful and significant clusters are divided into 9 categories, as shown in Table 4. Use the software to analyze the document co-citation and obtain a visual map with $N = 1052$ and $E = 2625$ (Figure 5). The most representative article in the label #0 cluster is the article published by Preedy et al. on EUROPEAN JOURNAL OF NEUROLOGY. The most representative of the label #1 cluster is the article published by

| 1 | 2          | 3 | 4 |
|---|------------|---|---|
| 8 | Univ Barcelona | 11 | 0.00 |
| 9 | Univ Univ    | 11 | 0.00 |
| 10| Univ Western Australia | 10 | 0.08 |
by Laufs et al. on treatment options for statin-associated muscle symptoms\textsuperscript{30}. Another example is the label #20 cluster represented by Gomes\textsuperscript{21}. The research group mainly studies the role of oxidative stress in the formation of skeletal myopathy.

![Knowledge Atlas of Collaborative Network of Authors from 2000 to 2020](image1)

**Figure 4.** Knowledge Atlas of Collaborative Network of Authors from 2000 to 2020

![Co-cited and clustering map of articles in the field of alcoholic myopathy from 1999 to 2021](image2)

**Figure 5.** Co-cited and clustering map of articles in the field of alcoholic myopathy from 1999 to 2021

| ID | Silhouette | Year | Cluster Label(LLR)                      |
|----|------------|------|-----------------------------------------|
| 0  | 0.973      | 1999 | alcohol-induced muscle disease; ethanol treatment |
| 1  | 0.986      | 2014 | statin intolerance; treatment option     |
| 6  | 0.963      | 2005 | defective regulation; skeletal myopathies |
| 8  | 0.995      | 2009 | red yeast rice                          |

**Table 4**

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2.6 keywords visualization and analysis

In this study, the keyword co-occurrence and highlighted word map were obtained through the analysis of CiteSpace software (Figure 6, 7, 8). Through keyword co-occurrence analysis, the hot keywords in the field of myopathy from 1999 to 2020 are myopathy, oxidative stress, vitamin D, vitamin D deficiency, mitochondrial myopathy, alcoholic myopathy, antioxidant therapy, statin, therapy, glutathione, nanoparticle, vitamin E, coenzyme Q10, IGF-1 and other high-frequency keywords. From the analysis of keyword time zone and highlighted word map, it can be concluded that the new keywords in the past 5 years are nanoparticle (2016–2021), autophagy (2017–2021), dysfunction (2017–2019), activation (2016–2019), inflammation (2018–2021), mitochondrial dysfunction (2019–2021). And the highlighting word map analysis can show that the popularity of keywords such as nanoparticle, autophagy, and mitochondrial dysfunction will continue until 2021, Figure 9. The label of the largest node in the middle is myopathy, which contains various types of myopathy, such as myopathy caused by alcoholism, the relationship between vitamin D and myopathy, myopathy caused by statins. The node corticosteroid represents myopathy caused by steroid hormones (Figure 6, 8). The node ethanol represents the research of alcoholic myopathy. At the same time, it can be discovered from the connection relationship between the nodes that alcoholic myopathy can be treated with antioxidant therapy (Figure 6). In addition, we can also see that vitamin E and coenzyme Q10 are a kind of antioxidant therapy. In the network diagram of another node therapy (Figure 7), we can find that nanoparticle is one of many ways to treat myopathy. From the graph of the network nodes in Figure 8, we can see that corticosteroid is directly or indirectly related to coenzyme Q10 and mitochondrial dysfunction. It can be seen from Figure 9 that the most intense and hottest highlight keywords are nanoparticle and mitochondrial dysfunction. The study included in mitochondrial dysfunction by Moacir Wajner et al. revealed that fatty acid accumulation can interfere with energy balance in the mitochondria, inhibit oxidative phosphorylation, decrease ATP synthesis, and increase free radical output. Nanoparticles can be used in many different fields. For example, fullerene C60 is a free radical scavenger with better performance. Nanoparticles are foreign to the human body, similar to bacteria, viruses, parasites, and can stimulate cells to produce autophagy. In general, nanoparticles can play a protective antioxidant role in the body, and autophagy produced by nanoparticles can also remove oxidative stress.

|   |   |   |   |
|---|---|---|---|
| 13 | 0.966 | 2006 | congenital myopathies |
| 14 | 1 | 2012 | idiopathic inflammatory myopathy |
| 20 | 1 | 2015 | oxidative stress |
| 26 | 0.992 | 2000 | neurotoxic protein |
| 29 | 0.983 | 2016 | statin toxicity |

The end of the table 4
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DISCUSSION

Myopathy has been on the rise in recent years, with the disease becoming more common with each passing year. Myopathy has attracted more attention because of its increasing prevalence and the numerous damage it causes to people's bodies and minds. This work analyzes the literature on myopathy in the WOS database using bibliometrics and discovers that the number of literature publications has a wave-like increase tendency over time, indicating that research is increasing rapidly and people are paying more and more attention to it. In terms of research countries and areas, the United States has published more publications in this field than other countries (regions) and has done a significant amount of work in the subject of myopathy research. However, in Europe, there are more countries (regions) involved in myopathy research.

We can observe from the term emergence map that numerous new study directions have arisen in the last three years. Some hot keywords have a high intensity, such as nanoparticle (10.89), while others have a low intensity, such as mitochondrial dysfunction (5.33), yet this term is a new hot area that has emerged in the last two years. The explanation for the low intensity could be that we only found 18 references in the 2021 literature. Many new study topics have appeared in the last ten years, such as “autophagy,” which has been a...
research hotspot from 2017 to 2021, with an outbreak value of 10.87. However, the term "mitochondrial dysfunction" first appeared in 2019. Although the new research direction has a low burst value, it is 5.3. However, it is possible that this direction may become the next research hotspot in the future.

Under normal conditions, mitochondrial homeostasis is dependent on a number of activities, including biogenesis, fusion, and fission. Any disruption to these processes will result in mitochondrial malfunction. Alcoholic-fed rats have higher acetaldehyde levels in their mitochondria, which disrupts the electron transport complex (CI-IV), resulting in an excess of reactive oxygen species (ROS)\(^3\). In addition, long-term use of corticosteroid drugs can also induce excessive production of reactive oxygen species (ROS), leading to mitochondrial dysfunction and apoptosis in myogenic cells\(^25\). Statins can also impair the mitochondrial respiratory chain's activity, lowering ATP and boosting ROS generation\(^31\). The three reasons described above can cause an increase in the concentration of ROS in the body. Of course, because the concentration of ROS has increased, "nanoparticle" can be employed to reduce the concentration of ROS. Figure 9 also shows that "nanoparticle" has been a popular study topic since 2016.

SUMMARY

It is expected that the study focus of these three myopathies will shift to a more in-depth investigation of the mechanism of mitochondrial malfunction in the next years. Of course, future research hotspots are not restricted to this. For example, the creation of nanoparticle therapeutics for myopathy and the investigation of myopathy's autophagy process have been research hotspots in recent years, and they may continue to be so in the future.

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