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The Effect of Aerobic Training on the Liver in Obesity: A Bibliometric Analysis

Amir Hesam Salmasi-Fard[1], Mohammad Ali Azarbayjani[1*], Farhad Riazi-Rad[2], Maghsoud Peeri[1], Hasan Matinhomaee[1]
[1]Department of Exercise Physiology, CT.C, Islamic Azad University, Tehran, Iran.
[2]Department of Medical Immunology, Pasteur Institute of Iran, Tehran, Iran.

Abstract
Obesity can destroy tissues and cause metabolic and chronic diseases. It is well-established that obesity damages liver tissue, and it is a risk factor for hepatocellular carcinoma Regular physical activities, especially aerobic exercise, have been introduced as a beneficial non-drug treatment without side effects and improves liver function under obesity conditions. Evidence Acquisition: This bibliometric article analyzes trends in publications relating to aerobic training on the liver under obesity conditions. The Magiran database was used, and articles without the desired keywords were collected. Journals that published more articles in this field, keywords were used more by authors, and prolific authors were analyzed and identified by VOS viewer software. Results: The results showed that aerobic exercise, obesity, and the liver, especially at the cellular level, are an attractive and relatively novel topics for researchers. The articles in recent years have had an upward trend, and the journals of Ardabil University of Medical Sciences and the Yafteh Journal of Medical Sciences have the highest number of publications. Conclusions: In general, studying the impact of aerobic training on the liver in obesity cases represents a novel area of research. Investigating this at the cellular and molecular levels will provide more insightful insights.

Keywords: Aerobic training, Liver, Obesity

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Corresponding Author:
Mohammad Ali Azarbayjani, Department of Exercise Physiology, CT.C, Islamic Azad University, Tehran, Iran.
Email: m_azarbayjani@iauctb.ac.ir
Orcid ID: 0000-0002-3502-7487
Tell: (98) 912 317 2908

Introduction

Obesity is increasing alarmingly, and this trend has spread globally (1). Obese people have tripled over the last 50 years. It is predicted that this number will grow rapidly, and more than 1 out of 5 people will be considered obese (2). Obesity results from energy imbalance; in this condition, adipocytes are hypertrophied, and adipokine secretion pattern is changed. Increased release of inflammatory adipokines in obesity conditions is the molecular basis of many diseases caused by obesity (3). Fat is associated with mild chronic inflammation and can induce several metabolic diseases, including insulin resistance, type 2 diabetes (T2D), high blood pressure, dyslipidemia, non-alcoholic fatty liver, and cancer (4).

Obesity can increase oxidative stress and disturb the homeostasis between the antioxidant system and reactive oxygen species (ROS). An inverse relationship exists between increased fat mass and antioxidant capacity (5). An increase in tissue oxidative stress can further damage DNA and lead to genomic instability and mutations (6,7). On the other hand, chronic systemic inflammation caused by obesity can induce epigenetic changes such as DNA methylation and histone changes that change the expression of oncogenes and lead to cancers (such as colon, liver, and breast cancer). Among other common diseases caused by obesity, liver diseases such as non-alcoholic fatty liver (NAFLD) (renamed metabolic dysfunction-associated steatotic liver disease (MASLD)), non-alcoholic steatosis (NASH, renamed MASH: metabolic dysfunction-associated steatohepatitis), liver cirrhosis and hepatocellular carcinoma (HCC) (8).

The liver is a vital organ in the human body. It has many responsibilities, including participating in the digestive process, metabolism, vitamin storage, detoxification, immune processes, and many other functions. Hepatocytes are liver cells, and liver functional units are called lobules. The lobules are hexagonal, and the bile duct, hepatic venous, and arterial networks are triangular. Hepatocytes significantly influence beta-oxidation, cholesterol synthesis, amino acid catabolism, and gluconeogenesis. Glycolysis, lipogenesis, ketogenesis, and the formation of some amino acids can also be mentioned (9,10).

Chronic liver disease and its related diseases contribute to many deaths around the world. These diseases include non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD), liver cirrhosis, and finally, liver cancer (11,12). Obesity can lead to chronic liver diseases such as NAFLD or Hepatocellular carcinoma (HCC) (13). Obesity can disrupt hepatocyte metabolism through the down-regulation of factors such as PGC-1α and HGF and the up-regulation of some signalling pathways such as JAK/STAT, leading to liver diseases such as liver fibrosis and hepatocellular carcinoma (14-16).

Another significant factor in HCC risk is obesity. Obesity's role in HCC development is complex and involves multiple signalling pathways (17). Obesity is often associated with insulin resistance, which means hyperinsulinemia can contribute to HCC (18). Insulin resistance and hyperinsulinemia activate the PI3K/Akt/mTOR pathways, which promote cell growth, proliferation, and survival. Chronic activation of this pathway and hyperinsulinemia can cause HCC progression. One adverse effect of chronic hyperinsulinemia is hepatic fat accumulation. This accumulation can lead to NAFLD, which is recognized as a risk factor for HCC (18-20).

Liver dysfunction has a direct relationship with obesity; increasing the accumulation of fat cells in the liver tissue will be associated with NAFLD disease, which can be due to an increase in the flow of free fatty acids (FFA) or lipogenesis (13,21). Continuing this process can cause NASH and eventually lead to liver fibrosis, cirrhosis, and liver cancer. Mitochondrial oxidative stress, as well as

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peroxisomal, microsomal, and ER stress, plays an essential role in NAFLD pathogenesis. Excessive production of ROS and reactive aldehyde derivatives results in oxidative stress and cell death by reducing ATP, glutathione, and cellular NAD levels. It also causes DNA damage. ER stress-induced cell death is mediated through calcium disturbance, ROS production, and activation of the JNK signaling pathway (6,22-24). On the other hand, several studies show that exercise, especially aerobic training, reduces oxidative stress, apoptosis, and inflammation. Aerobic training can control, moderate, or inhibit these processes by activating and expressing various factors. Among other things, we can mention the increase in Nrf2 expression in aerobic training and the inhibition of the JAK2/STAT3 signaling pathway, ultimately leading to better liver function. Exercise and physical activity activate AMPK, which promotes fatty acid oxidation and glucose uptake while inhibiting lipogenesis and gluconeogenesis. AMPK activation also increases energy consumption and improves insulin sensitivity (25).

Exercise also increases adiponectin production, a hormone secreted by the adipose tissue. Adiponectin improves insulin sensitivity, reduces inflammation, and enhances fatty acid oxidation (26). Obesity often disrupts these signaling pathways that contribute to obesity development and maintenance. For example, decreasing AMPK and increasing mTOR activity can lead to enhanced lipogenesis and decreased fatty acid oxidation.

This results in excessive fat accumulation Dysregulation of PPARγ, adiponectin, and the myokine pathways can also contribute to obesity-related metabolic abnormalities (27). Aerobic training affects obesity, at least in part, by modulating various signaling pathways. These pathways regulate energy metabolism, lipid metabolism, and inflammation. Dysregulation of these pathways in obesity helps create and maintain obesity (28). Obesity management requires lifestyle changes, such as regular exercise (29). Aerobic training is the most effective exercise and activity for weight loss because various studies have shown that exercise or aerobic exercise can significantly increase fat oxidation and energy consumption (30, 31). The research results showed that the gene expression of anti-obesity factors such as irisin and FNDC5 increased, and on the other hand, the levels of factors such as adipolin decreased (32,33). Aerobic training reduces fat in liver cells without losing body weight (34). Evidence shows that aerobic training reduces liver fat more than other training systems (35). Also, liver enzyme levels have been adjusted to aerobic exercise (36,37). Aerobic training improves liver health. Studies have shown that exercise and aerobic training positively affect the fatty liver, increase fat oxidation in the liver, and modulate or inhibit the signaling pathways for lipogenesis (38,39).

Also, in hepatocellular carcinoma, aerobic training suppresses expansion pathways and tumor progression such as Akt/GSK-3b/b-catenin, JAK/STAT, and Akt/PI3K or by modulating and reducing hypoxia (HIF-1α) and increasing blood perfusion in the tumor have moderated or inhibited liver cancer progression (14,40,41). Due to the growth and development of studies by Iranian researchers, no bibliometric analysis has been done on studies conducted in the field of the effect of aerobic exercise on the structure and function of the liver in obesity conditions. The results of this study can provide valuable information about the process of studies conducted in this field. It can also identify existing information gaps for researchers.

Evidence acquisition

Research design

This research was conducted based on a bibliometric analysis conducted by a scientific network of publications on the effects of aerobic training on the liver in obesity conditions based on similar research.

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Data source

The Magiran database was used to collect data. This database is one of the most widely used databases researchers in Iran utilize for analysis based on the exhaustive list of validly indexed journals in Iran (42,43).

The data was extracted from the Magiran database on March 5, 2024. The advanced search keywords were as follows: (obesity) or (overweight) or (adipose tissue) or (aerobic training) or (aerobic exercise) or (aerobic activity). Or ("aerobic physical activity") and ("liver") or ("liver tissue") or ("hepatocytes"). The articles were limited to scientific journals. There was no time limit, and the articles were extracted up to the indicated date. The data set was downloaded in the format of a "plain text file" and the English output of "RIS," and the data graph was analyzed with Microsoft Excel software (version 2021) and VOSviewer software for network shapes. Among 58 articles, 33 were selected from this review's study area.

Analyze

To compile the present article based on existing studies, Keywords, Authors, Universities, and journals that did the most research in this field were analyzed. Complete records of this manuscript and cited references were imported into EXCEL software (2021-Microsoft Corporation) and VOSviewer (CWTS, Leiden University, Leiden, The Netherlands) for bibliometric analysis.

Results

The process of publishing articles by year

In general, 33 articles were found in this field, of which 32 were research articles (original) and a review article. A breakdown of the years 2010 to 2024 was selected. In 2010, 2012, and 2013, no articles with the keywords of this article were found in the readers' database. Figure 1 shows published articles by year. The years 2021, with 9 articles, and 2022, with 7 articles, had the highest numbers.

The most popular journals

The journals that published articles in this field were analyzed. The Journal of Medical Sciences of Ardabil University and the Journal of Medical Sciences (Lorestan Medical Sciences) produced the most articles. Considering that there is an h-index in some domestic journals of Iran, the index was not considered in this analysis due to the lack of access to this section. Table 1 lists the journals that published the most articles in this field.

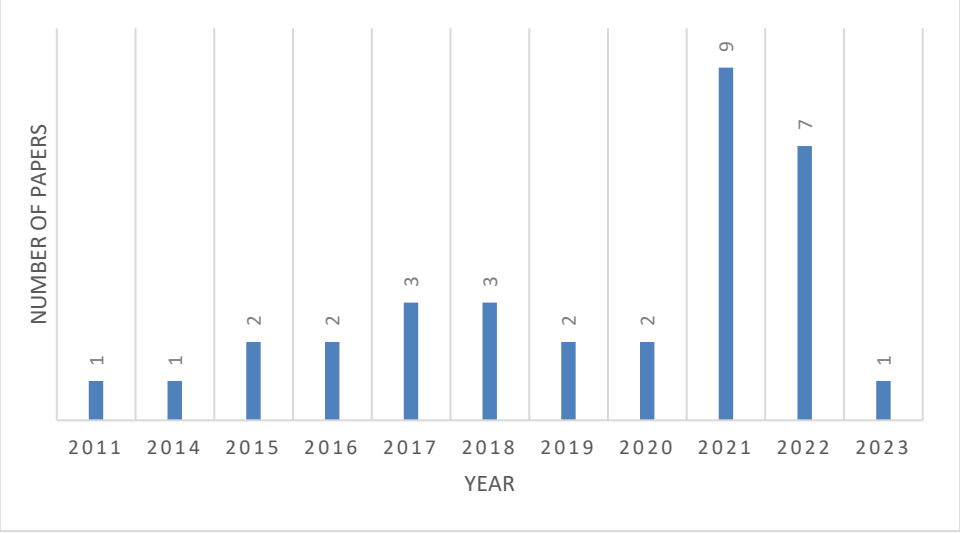


Figure 1. Number of articles published per year

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Table 1. Top 10 journals publishing combined aerobic training (or activity), liver and obesity

Rank	Journal	Number of Paper	SJR2022
1	Journal of Ardabil University of Medical Sciences	3	scientific-research
1	Yafteh	3	scientific-research
2	Sport Physiology	2	scientific-research
2	Armaghane-danesh	2	scientific-research
2	Journal of Applied Exercise Physiology	2	scientific-research
2	Journal of Animal Biology	2	scientific-research
3	Sport Biosciences	1	scientific-research
3	Medical Journal of Mashhad University of Medical Sciences	1	scientific-research
3	Iranian Journal of Rehabilitation Research in Nursing	1	scientific-research
3	Journal of Neyshabur University of Medical Sciences	1	scientific-research

Highly cited articles

Table 2 shows the articles with the most citations. The article entitled "Reviewing the physiological effects of aerobic and resistance training on insulin resistance and some biomarkers in non-alcoholic fatty liver disease" by Azam Moosavi-Sohroforouzani et al., published in Feyz Medical Sciences Journal, had the most citations, with 118.

Discussion

Research results indicate that regular aerobic exercise can alter the liver's antioxidant defense, inflammation, and metabolism by influencing the expression of proteins involved in cellular processes. These alterations may include an increase in antioxidant capacity, such as superoxide dismutase (SOD), a reduction in malondialdehyde (MDA) levels, an increase in antioxidant signaling, including Nrf2, and a decrease or inhibition of the phosphorylation of inflammatory signaling pathways like the Jak2/STAT3 pathway. Furthermore, in diabetic mice, exercise significantly lowers serum levels of ALT, AST, TNF-α, IL-6, cholesterol, and triglycerides (15,57). A study found that 8 weeks of aerobic training can improve non-alcoholic fatty liver disease by enhancing insulin signaling through increased glypican-4 and decreased Fetuin-A (55).

Additionally, another study revealed that 10 weeks of aerobic resistance training reduced serum RBP4 concentrations, reduced abdominal obesity, improved insulin sensitivity, and lowered fasting glucose, triglycerides, LDL, and AST in postmenopausal women with a fatty liver (54). Their 2023 study, "Aerobic Exercise Ameliorates Liver Injury in Db/Db Mice by Attenuating Oxidative Stress, Apoptosis, and Inflammation through the Nrf2 and JAK2/STAT3 Signaling Pathways," examined seven-week-old male mice with type 2 diabetes (db/db) and age-matched m/m mice. These mice were randomly assigned to either a control or an experimental group that underwent aerobic exercise. Over 12 weeks, the experimental group engaged in treadmill exercise at 10 m/min. Results indicated that aerobic exercise reduced inflammation, oxidative stress, and apoptosis, likely due to increased Nrf2 expression and suppression of the JAK2/STAT3 signaling cascade. This intervention effectively reversed liver dysfunction in DB/dB mice suffering from T2DM (14,58). Engaging in regular physical activity also benefits obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). It enhances mitochondrial function by elevating PGC-1α expression within liver tissue, which decreases hepatic steatosis, inflammation, fibrosis, and tumor development. Therefore, consistent physical activity is a valuable strategy for mitigating obesity and its impacts on liver health, especially NAFLD. This method may be connected to interactions between the liver, fat tissue, muscle tissue, and the microbiome (59).

Twelve weeks of exercise training, including high-intensity interval aerobic training (HIAT), moderate-intensity continuous aerobic training (MICT), and resistance training (RT), can reduce hepatic fat accumulation, regardless of weight loss or visceral fat.

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Table 2. Most cited articles

Rank	Author	Title	Citation	University	Journal
1	Azam Moosavi-Sohroforouzani et al (2016) (44)	Reviewing the physiological effects of aerobic and resistance training on insulin resistance and some biomarkers in non-alcoholic fatty liver disease.	118	University of Isfahan	Feyz Medical Science Journal
2	Gholam Rasool et al (2014) (45)	The effect of aerobic training and diet on lipid profile and liver enzymes in obese women with type II diabetes	23	Ferdowsi University of Mashhad	Daneshvar Medicine
3	Omid Yaghoobpour Yekani et al (2018) (38)	Effect of type of training on markers of hepatocyte apoptosis in rats fed a high-fat diet.	14	Islamic Azad University, Central Branch	Yafteh
4	Mohammadreza Esmaelzadeh Toloee et al (2017) (46)	Effect of Aerobic Training with Ginger Supplementation on Some Liver Enzymes (AST, ALT, GGT) and Resistance to Insulin in Obese Women with Type 2 Diabetes.	13	Shomal University	Medical Journal of Mashhad University of Medical Sciences
5	Hossein Nikroo et al (2011) (47)	The effect of a restricted diet with or without an aerobic training program on cardio-respiratory fitness and anthropometric indices in patients with non-alcoholic steatohepatitis.	12	Ferdowsi University of Mashhad	Journal of North Khorasan University of Medical Sciences
6	Maryam Izadi Ghahfarokhi et al (2015) (48)	The Impact of 10 weeks of Aerobic Exercise and Supplementation of Green Tea on Lipid Profile, Insulin Resistance and Liver Enzymes (GGT, ALT, AST) in Obese Diabetic Women (type 2).	9	University of Sistanand Baluchestan	Armaghane-danesh
7	Somayeh Rajabi et al (2021) (49)	The Effect of Resistance- Aerobic Interval Training on the Fatty Liver Grade, Liver Dimensions, and Liver Enzymes in Obese or Overweight Women with Fatty Liver.	5	Hakim Sabzevari University,	Community Health Journal
8	Azadeh Nabizadeh Haghighi et al (2015) (50)	Comparison of drug therapy with exercise program on body composition and cardio-pulmonary fitness in patients with nonalcoholic fatty liver disease.	5	Islamic Azad University, Rasht Branch	Iranian Journal of Rehabilitation Research in Nursing
9	Mozhgan Sahraei et al (2021) (51)	Protective Effect of Berberine Chloride and Aerobic Training on Liver Nrf2/HO-1 Pathway and PPARγ in Streptozotocin-induced Diabetic Rats	4	Islamic Azad University, Ayatollah Amoli Branch	Journal of Ardabil University of Medical Sciences
10	Shahsanam Gheibi et al (2018) (52)	Investigation of tissue and blood indices of liver and metabolic syndrome in patients with nonalcoholic fatty liver during 36 sessions of exercise training	2	Urmia University of Medical Sciences	Journal of Applied Exercise Physiology
11	Hamdollah Iraji et al (2021) (53)	Effect of Two Exercise Modalities on Some Liver Enzymes and Lipid Profile of Adolescents with Fatty Liver	1	University of Isfahan	Sport Physiology
11	Masoumeh Norouzpour et al (2021) (54)	The Effect of Aerobic-Resistance Exercise on Serum Level of Retinol-Bonded Protein 4, Abdominal Obesity, and Metabolic Markers in Postmenopausal Women with Non-Alcoholic Fatty Liver	1	University of Isfahan	Journal of Applied Exercise Physiology
11	Bahar Zandi et al (2021) (55)	Effects of Aerobic Training with Ginger Consumption on Plasma Levels of Adipokine Glipican-4 and Hepatokine Fetuin-A in Rats with Non-alcoholic Fatty Livers	1	Islamic Azad University, Central Branch	Iranian Journal of Nutrition Sciences & Food Technology
11	Fatemeh Habibzadeh Bizhani et al (2017) (56)	Effect of 8 weeks aerobic exercise and Vitamin C on Liver transaminases activities in obese 8-11 years girls	1	Islamic Azad University, Sari Branch	Journal of Gorgan University of Medical Sciences

HIAT also enhances hepatic stiffness; thus, this method can be recommended for individuals with suspected NAFLD fibrosis. Additionally, exercise can effectively manage NAFLD, even without concurrent dietary changes or therapy (60). Six weeks of aerobic training in obese rats' liver tissue showed an increase in PGC-1α gene expression. Aerobic training was performed at a moderate intensity, and obese rats' weight decreased compared to the obese group without training.

Also, in hemoptocytic histopathology, the amount of collagen in the liver tissue was lower than in the obese group without training.

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On the other hand, there were no significant differences between the healthy control group and the non-healthy control group. Therefore, aerobic training modulates obesity's adverse effects (15). Also, 6 weeks of aerobic training increased the HGF gene expression in the liver tissue of obese rats. HGF is a signal that increases hepatocyte survival and protects against complications caused by obesity and insulin resistance (16).

The present bibliography was extracted from 33 published studies, 32 original studies, and 1 review study on aerobic training or aerobic exercise (that lasted between 4 and 10 weeks), obesity, and liver studies in the database of readers from 2010 to 2024, and was analyzed. 81 authors have published articles in a cluster. In 2010, 2012, and 2013, articles with the searched keyword were not found in this database. In the years before 2010, no continuity was found on this topic. From 2015 to 2022, articles increased, reaching their peak in 2021 and 2022. The majority of articles were published in 2021. After 2022, a decreasing trend can be observed. This can be influenced by the fact that authors prefer to send their articles to journals outside Iran with international profiles.

The present article analyzes 23 journals, including the Ardabil University Medical Sciences Journal and the Medical Quarterly that produced the most articles in this field. Each of these journals publishes 3 articles in the field. Other journals were Sports Physiology, Armaghane Danesh, Journal of Applied Sports Physiology, Journal of Animal Biology, Journal of Sports Biology, Journal of the Faculty of Medicine of Mashhad University of Medical Sciences, Journal of Rehabilitation Research in Nursing, and Journal of the Faculty of Medicine of Neishabur University of Medical Sciences, respectively. One of the reasons more articles have been published in Ardabil medical science journals is that these journals accept articles from different fields of health sciences. More articles are sent to the mentioned journals.

Conversely, the article by Azam Moosavi-Sohroforouzani et al. (2016), entitled "Reviewing the Physiological Effects of Aerobic and Resistance Training on Insulin Resistance and Some Biomarkers in Non-Alcoholic Fatty Liver Disease," received the most citations (118 citations) from Isfahan University, where the Feyz Medical Sciences Journal was published.

The high citation of this article compared to other articles is because it was a review in this field.The article writing in this field was slow and minimal. Also, authors with a high number of articles had little or no cooperation. Two authors were recognized as prolific: Ahmad Abdi with 4 articles and Parveen Farzangi with 3 articles. The prolificity of these authors can be attributed to their academic status at the Islamic Azad University of Iran.

This is because they have more postgraduate students and face a wide range of subjects. Parvin Farzangi has collaborated with 7 authors, which is the most in this regard. The article "Reviewing the physiological effects of aerobic and resistance training on insulin resistance and some biomarkers in non-alcoholic fatty liver disease" was the most cited. This review aimed to analyze studies conducted concerning the effects of aerobic and resistance exercise on insulin status and some biomarkers in non-alcoholic fatty liver patients. 300 articles were reviewed (abstract review). 107 articles were selected based on their relation to the title of the article and on meeting the entry requirements. They were also subject to secondary reviews. The effect of both resistance and aerobic training on non-alcoholic fatty liver disease is considered in this article. The results show that, regardless of its type, regular exercise can improve inflammation, obesity, and insulin resistance in patients with non-alcoholic fatty liver disease. The most used keyword was obesity, with 10 repetitions in the articles' titles, which were repeated more between 2019 and 2021.

After that, the keyword exercise with 7 repetitions (the most repetition between 2020

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and 2021), where both the keywords obesity and exercise were in the same cluster, aerobic exercise with 6 repetitions (the most repetition between 2019 and 2021), the word Liver enzymes with 5 repetitions (the most repetition between 2018 and 2020), the words lipid profile (the most repetition between 2018 and 2020) and insulin resistance (the most repetition between 2017 and 2019) with 4 repetitions and the word aerobic training The had the most repetitions with 3 repetitions (the most repetitions between 2017 and 2019). There are some limitations to this study. The data was taken from Magiran's database, and bibliometric research for articles from inside Iran has been limited. On the other hand, since the search was done from a database, some articles on the same topics may be missing.

This database was chosen because it is widely used and has advanced search capabilities. Information was extracted using bibliometric tools, which may bias.The present article shows that more recent research focuses more on the effect of physical activity, exercise, antioxidant supplements, bioactive supplements, and herbal extracts. This is about obesity, a high-fat diet, and the liver and liver tissues. It seems that combined exercises (aerobic exercise and resistance exercise) (58) Combine aerobic training or high-intensity exercises (HIIT) (53,59,60) have received more attention, and research has shown that this type of exercise, compared to continuous aerobic exercises, can probably have a higher effect and improve various physical fitness factors faster. This bibliometric analysis provides an overview of the results of aerobic training, obesity, and liver disease in Iran from 2010 to 2024. During these years, research has grown, although the trend has been slow. Research in this field, especially at the cellular and molecular level, along with complementary-nutritional interventions, are topics expected to gain increasing interest among researchers. Islamic Azad University of Iran was the most productive university in the field. Also, the most prolific authors were Ahmad Abdi and Parveen Farzangi; the Journal of Ardabil University of Medical Sciences and the Journal of Medical Sciences found more priority for researchers related to aerobic training, obesity, and the liver. The effect of various exercises on the liver can be described as a research gap: What type of exercise with what intensity can positively affect hepatocyte function?

Conclusion

This article focuses primarily on quantifying keywords across various categories in bibliometrics. However, upon reviewing the article, several research gaps emerged. Most of the articles are animal studies, making it challenging to draw general conclusions and apply them to humans. Additionally, obesity and high-fat feeding protocols used in animals can influence some of the factors being evaluated.

The liver is crucial for the body's metabolism. Consequently, factors measured in liver tissue or related to the liver have been less studied in metabolomics. The influence of these factors on the tissue and their impact on the overall metabolic process has not received adequate attention. Investigating systematic signaling pathways in hepatocytes related to obesity appears to be a relatively underexplored area of research. Therefore, this topic presents an attractive field for future researchers.

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Conflict of Interest

The authors declare no conflicts of interest.

Authors' contributions

AH.SF: Extraction and analysis data, interpreting results, up-to-date reference lists, performing software analysis, and creating summary tables of findings.

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MA.A: Writing the report, arbitrating potentially eligible studies, extracting and analyzing data, and interpreting the results. He contributed to data extraction and provided feedback on the report.

F.RR, M.P and H.M: Screening potentially eligible studies.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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