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Review Article

The relationship of irisin hormone released during physical exercise and Alzheimer's disease: a literature review

Relação do hormônio irisina liberado durante o exercício físico e a doença de Alzheimer: uma revisão da literatura

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ABSTRACT: The growing population of older people has increased the number of diseases, such as Alzheimer's Disease, characterized by the deterioration of neurons and significant losses in brain functions. Myokines are released during physical exercises, including Irisin (produced and activated by skeletal muscles), promoting beneficial effects on cognitive functions and overall brain plasticity. Therefore, physical exercises are one of the known factors for delaying the neurodegenerative process and play an important role in the lives of older people. Thus, the present research work is a systematic review seeking to point out the benefits derived from practicing physical exercise in preventing this specific pathology.

Keywords: Irisin; Alzheimer's disease; Physical exercise.

RESUMO: Com o aumento no número de idosos, observa-se também um aumento no aparecimento de algumas doenças, como a Doença de Alzheimer, caracterizada pela deterioração dos neurônios, com consequentes perdas significativas nas funções cerebrais. Durante o exercício físico, ocorre a liberação de mioquinas, dentre elas a irisina, produzida e ativada pelos músculos esqueléticos, promovendo efeitos benéficos na função cognitiva e na plasticidade geral do cérebro. Sendo assim, os exercícios físicos são um dos fatores conhecidos por retardar a neurodegeneração, desempenhando papel importante na vida dos idosos. Assim, este trabalho constitui uma revisão sistemática que busca apontar os benefícios trazidos pela prática de exercícios físicos na prevenção da patologia em questão.

Palavras-chave: Irisina; Doença de Alzheimer; Exercícios físicos.

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INTRODUCTION

The number of older people has been growing worldwide due to the overall population's increased life expectancy. The increased emergence of characteristic diseases as people get older has been observed concomitantly and herein, especially Alzheimer's disease[1].

AD occurs due to the deterioration of neurons, the fundamental structures where information processing occurs in the nervous system. Amyloid fibril deposits are found on the walls of blood vessels, related to different types of senile plaques and the accumulation of TAU proteins. Hence, the formation of neurofibrillary tangles, inflammation, and neural and synaptic loss occur[2]. The extracellular accumulation of β-amyloid peptide (Aβ) and the TAU protein deposition inside the neuron soma cause breakdown and cellular death[3].

Some studies have shown the benefits of physical exercise on mental health, considering that while it is taking place, the increase of neurotransmitters occurs, which act on maintaining the cognitive function of older people[1]. Such a fact could be further proven during the Covid-19 pandemic. According to a study performed at "Escola de Educação Física e Esporte de Ribeirão Preto" (Ribeirão Preto Sports and Physical Education School) (EEFERP) at USP, individuals who practiced physical activities were better able to bear anxiety and stress during the quarantine[4].

Myokines are released into the bloodstream while performing physical exercises through endocrine activity due to the contraction of muscular fibers, promoting positive effects on cognitive functions and overall plasticity of the brain. It thereby delays or inhibits the emergence of neurodegenerative diseases[5].

Irisin is a myokine codified by the FNDC5 gene. It is involved in the darkening of the white adipose tissue, whose purpose is similar to brown adipose tissue. This process favors spending energy, making irisin a therapeutic endogenous agent for metabolic diseases. The physiological benefits of irisin are observed because the circulating levels are positively related to skeletal muscle mass and aerobic capacity. Furthermore, acute and chronic physical exercise increases the release of irisin in the bloodstream[5].

Irisin plays an important role among myokines, as its release is prompted by physical exercise after the cleavage of type III fibronectin. That hormone can protect the hippocampus. This region is related to learning and memory for stimulating the expression of neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF). Moreover, irisin promotes an increase in thermogenesis and energy consumption of the adipose tissue by transforming white adipose tissue into brown adipose tissue[5].

As the hippocampus is a region of the brain involved in learning and memory, the favorable effect of irisin can inhibit or delay the emergence of neurodegenerative diseases, including AD. Besides that, the factors involved in the formation of irisin seem to suppress the aggregation of β- amyloid, which is the pathological marker for this affliction[6].

Specific beneficial effects have been reported as to how exercise includes increased bloodstream flow and volume of the hippocampus in human beings, morphological changes in the dendrites and dendritic spines, increases in the plasticity of synapses, and, even more importantly, neurogenesis in the dentate gyrus in various types of exercises in mice. Neurogenesis in the adult brain is observed in only two areas, and the hippocampus dentate gyrus is one of them. Exercise is one of the few stimuli known to promote neurogenesis. The hippocampus is one of the areas most benefitted from physical exercise in the brain, as it decreases neuroinflammation and increases bloodstream flow[5].

Therefore, as irisin transforms white adipose tissue into brown, the tissue with the greatest thermogenesis generates energy for the organism, increases hippocampus bloodstream flow, promotes neurogenesis, and reduces neuroinflammation by releasing such neurotrophic factors as BNDF[5].

This hormone increases the energetic metabolism and regulates glucose homeostasis and resistance to insulin, a risk factor for AD, which can improve neuropathy, reduce neuroinflammation, and increase the synaptic functions of the brain[7].

Another interesting approach refers to lipidomic since lipids highly enrich the brain and the cessation of lipid homeostasis is related to neurological disorders and neurodegenerative diseases such as AD. Therefore, considering that aging is linked to changes in lipid composition, the suggestion to analyze lipidome can contribute to identifying biomarkers for the prevention, diagnosis, and prognosis, as well as discovering new therapeutic options[3].

Furthermore, the factors involved in the formation of irisin inhibit the aggregation of the beta-amyloid protein, considering that higher levels of this protein increase oxidative stress, which makes the cells more susceptible to apoptosis[6].

The Amyloid Cascade Hypothesis considers the neurotoxic effects of beta-amyloid as a key factor in developing diseases. The accumulation of soluble forms of these peptides causes synaptic toxicity and neurotoxicity, provoking the rupture of calcium homeostasis, induction of oxidative stress, and mitochondrial disorder. Beta-amyloid is derived by proteolytic cleavage of APP through the action of beta and gamma secretases. Under normal conditions, it is degraded by enzymes and removed from the encephalon through a balance between efflux and influx. These processes are mediated by the LDL receptor

protein and receptors for the final products from advanced glycosylation[8].

In DA, there is an imbalance between the production and the clearance of beta-amyloid, causing oligomers to deposit this peptide (especially A42) in the extracellular space, causing the potential inhibition of long-duration hippocampus and synaptic plasticity. Recent studies have also revealed an excessive production of intraneuronal beta-amyloid, which can cause neuronal lysis and the formation of senile plaques. Those plaques end up triggering astrocytic and microglial activation and the production of an inflammatory response, generated in the surroundings of beta-amyloid deposits and hence contribute to the neuronal death and cholinergic neurotransmitter, serotoninergic, noradrenergic deficit and due to the reduction of somatostatin and corticotropin levels[8].

In this context, irisin can be a future target, potentially improving AD pathology and preventing it from starting. This article focuses on seeking to understand and report on both aspects[7].

METHOD

This study is a systematic review, a type of research based on a specific subject. Regarding this, the review incorporated the preparation of an analysis on AD and irisin, seeking to understand how physical exercise improves the prognostic of this type of illness.

This study contributes to structuring the presented theme based on theoretical grounds and preexistent scientific production analysis, enabling the identification of knowledge gaps for drafting new studies.

Thus, to answer the guiding question – "Does the release of irisin while performing physical exercises benefit in preventing AD?" – the terms were defined for performing bibliographic searches based on keywords on the most relevant concepts regarding this research, based on structured vocabularies in the healthcare field, presented as keywords on the subject – Medical Subject Headings (MESH), and coordinated by the United States National Library of Medicine (US NLM).

Six authors of this review performed bibliographic research searches in November 2021 from three databases. They were: PubMed, Google Scholar, "Plataforma CAPES" (CAPES Platform) "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior" (Coordination of Improvement of Higher Education Personnel), LILACS, SciELO, and "Biblioteca Virtual em Saúde" (Virtual Health Library) (BVS). The following keywords were used to define the research terms: irisin [All Fields] AND "alzheimer disease"[MeSH Terms] OR alzheimer[Text Word] as keywords for collecting data from the past ten-year period (2011-2021).

The authors analyzed the selection of articles in this study and adhered to the following inclusion criteria: literature meta-analysis studies and literature review and free access to Portuguese, Spanish, and English articles related to this review. The following were exclusion criteria: duplicate articles and/or that did not address physical exercise and AD, nor addressed irisin.

After the authors read the article titles, although they confirmed they had first searched for the keywords, but they found many studies that were unrelated to the subject addressed in this study. Hence, a total of 2951 articles were identified as primary articles, 387 were found in Google Scholar, 272 in Capes periodicals, and 2292 in PubMed. After concluding the search in all the electronic databases, the findings were exported to the trial version of the EndNote bibliographic manager.

Six independent reviewers read all the titles and abstracts, and after reading the abstracts, there were only 35 remaining articles, and, in the end, only 22 articles addressed all the inclusion criteria. The authors used those in this study. The selection strategy of the articles is presented in Figure 1, as recommended by the PRISMA group[9].

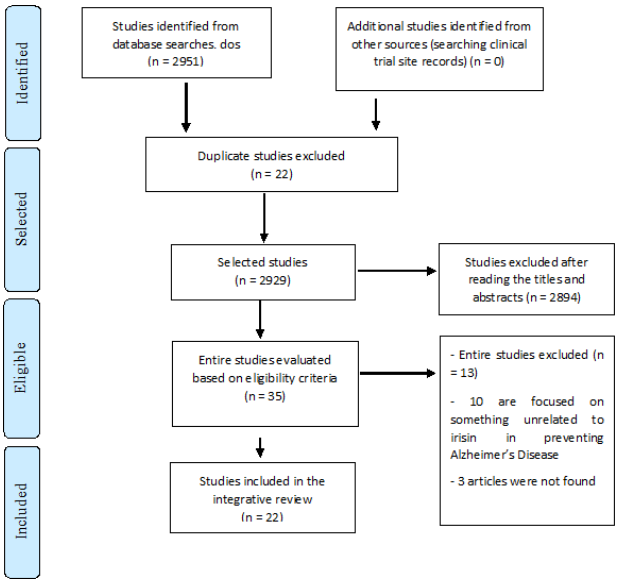

Figure 1 – Primary study identification flowchart included in the review.

RESULTS

The authors analyzed twenty-two articles; thirteen articles were published in English, two in Spanish, and seven in Portuguese. The publication period was concentrated and identified as (77.2%) were published in the last three years; among those, 29.4% were published in 2019 and 41.1% in 2021.

This revision identified 22 articles that presented the physiology of the irisin hormone and its release while performing physical exercise, and its relationship to preventing AD is shown in (Chart 1).

Chart 1 – The following are the articles included in the systematic review.

Article	Author	Country	# of participants	A #	Type of Study
A1 – The influence of irisin on the memory of patients who suffer from Alzheimer's disease: a narrative review.	Baltokoskik; Accardo [5]	Brazil	-	2021	Narrative Review
A2 – The influence of the release of irisin prompted by physical exercise in treating Alzheimer: a literature review.	Rios et al.[3]	Brazil	-	2021	Literature Review
A3 – A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's Disease in older adults.	Beckett et al.[21]	Canada	20,326	2015	Systematic Review
A4 – Alzheimer's Disease and Exercise: A Literature Review.	Cass[22]	USA	-	2016	Literature Review
A5 – From Exercise to Cognitive Performance: The Role of Irisin.	Pesce et al.[23]	Italy	-	2021	Systematic Review
A6 – Physical Exercise Modulates Brain Physiology Through a Network of Long- and Short-Range Cellular Interactions.	Consorti et al. [10]	Italy	-	2021	Systematic Review
A7 – Activating Irisin Hormone by Physical Exercise for Older People's Health with Alzheimer's Disease.	Silva et al.[1]	Brazil	-	2021	Systematic Review
A8 – The Role of PGC- 1α/UCP2 Signaling in the Beneficial Effects of Physical Exercise on the Brain.	Bristot et al.[11]	Brazil	-	2019	Systematic Review
A9 – Memory deficit and recovering synaptic plasticity in Alzheimer models linked to stimulated myosin by physical exercise.	Oliveira et al.[15]	Brazil	-	2019	Systematic Review
A10 – Physical Activity and Brain Health.	Liegro et al[17]	Italy	-	2019	Systematic Review
A11 – Practice physical exercises as a non-pharmacological strategy in treating Alzheimer's Disease.	Doine et al.[16]	Brazil	-	2020	Systematic Review
A12 – Protective actions of exercise-related FNDC5/Irisin in memory and Alzheimer's disease.	Freitas et al.[13]	Brazil	-	2020	Systematic Review
A13 – Harnessing the effects of endurance exercise to optimize cognitive health: Fundamental insights from Dr. Mark P. Mattson.	Jachim et al.[14]	USA	-	2020	Systematic Review
A14 – Molecular and Functional Interaction of the Myokine Irisin with Physical Exercise and Alzheimer's Disease.	Jin et al. [6]	Korea	-	2018	Systematic Review
A15 – The Role of Irisin in Alzheimer's Disease.	Kim; Song [7]	Korea	-	2018	Systematic Review
A16 – The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases.	Liu Y, et al. [20]	USA	-	2019	Systematic Review
A17 – Possible Neuroprotective Mechanisms of Physical Exercise in Neurodegeneration.	Mahalakshmi et al.[19]	Vietnam	-	2020	Systematic Review
A18 – Exercise and some molecular mechanisms underlying improved performance in cognitive tasks.	Montero et al.[24]	Costa Rica	-	2020	Systematic Review
A19 – Molecular Mechanisms Underlying the Beneficial Effects of Exercise on Brain Function and Neurological Disorders.	Nay et al. [25]	Australia	-	2021	Systematic Review
A20 – The effect of physical exercise on neurotropic factors in treating patients with Alzheimer's Disease.	Castro[12]	Brazil	-	2012	Systematic Review
A21 – FNDC5/Irisin System in Neuroinflammation and Neurodegenerative Diseases: Update and Novel Perspective.	Pignataro et al.[18]	Italy	-	2021	Systematic Review
A22 – Irisin/FNDC5 how exercise can prevent cognitive deterioration in Alzheimer's Disease.	Arribas[26]	Spain	-	2019	Systematic Review

Source: the authors of this study, Poços de Caldas, MG, Brazil, 2021.

DISCUSSION

Physical Activity

Twenty-two articles were analyzed in this review on irisin and its relation to AD. Skeletal muscles, in prolonged physical exercise activates the 1α coactivator of the γ receptor, activated by the peroxisome proliferator (PGC-1 α) through the protein kinase 5' AMP-activated (AMPK). PGC-1α increases irisin concentration in the bloodstream, controlling the expression of protein 5 and causing irisin cleavage. Physical activities improve through PGC-1α/BDNF by signaling the circulating irisin and that strengthens the synapses and, in the brain, performs a type of antidepressant effect and adds neuroprotection to animal models[10].

These neuroprotector effects are empowered by the antioxidant effects from UCP2, expressed by the

increased levels in the neurons as a response to exercise. Evidence sources suggest that irisin plays a role /UCP2 in the subjacent mechanism by benefitting from physical exercise in the CNS, so peptide can be a potential target for improving brain functions and preventing or even treating neurological and neurodegenerative diseases[11].

A study was performed on intervention by performing voluntary physical exercises, and normalization was observed in hypothalamic inflammation and neurodegeneration. That suggests that physical exercise prevents the progression of AD through a mechanism mediated by the hypothalamus[11]. BDNF benefits result from physical exercise impacting all endocrinal and autocrinal effects, as its greatest contribution is delaying the harmful effects caused by AD[12].

When they were submitted to daily swimming exercise for five weeks, mice demonstrated higher levels of FNDC5/irisin and expression of BDNF compared with their sedentary equivalents[27]. Several studies have also reported increased levels of FNDC5/irisin in response to aerobic exercises, such as swimming and running[13].

Physical exercise is responsible for having an active effect on neuroinflammation, promoting neurogenesis and synaptogenesis, and reducing the risk of neurological and neuropsychiatric disorders. It is suggestive as being one of the best interventions in the style of life for aging and patients who suffer from neurodegenerative diseases, such as AD. Hence, exercising contributes to improved performance in memory tasks of the hippocampus, such as remembering stories, lists of words, and discrimination mnemonics in human beings. Furthermore, aerobic activities improve even more cognition and avoid reductions in the cerebral volume associated with the age of an older person[14].

The hypothesis treated in this review is that practicing physical activities contributes to preventing AD. It has been supported by the analysis of external articles, as stated in the study in 2021, which concluded that physical exercise is a non-medicinal alternative to diseases such as AD. Exercises linked to cognitive activities protect the intellect, mitigating the characteristic symptoms of the disease. Another research study confirmed that the irisin is secreted by myocytes and can protect the hippocampus from stimulating the expression of BDNF, a factor involved in neuroplasticity, neurogenesis, neuronal survival, synaptogenesis, and cognition. The effect of FNDC5/irisin-BDNF would impact the result from neurodegenerative diseases such as AD.

Alzheimer's Disease

Many studies analyzed the neuroprotector action of specific factors released by practicing physical exercises. Lourenço et al.[27] reported that the irisin levels are reduced in mice who suffer from AD. Hence, the increased levels of FNDC5/irisin by practicing aerobic physical exercises contributed to recovering synaptic plasticity of the hippocampus and improved the performance and recognition of objects in new tasks in the mouse model of AD[13]

In two recent studies, Lourenço et al.[27] investigated the relationship between the alteration of FNDC5/irisin levels and AD. The silencing of FNDC5 by RNA was demonstrated by a specific small clamp that was consequential in the potential long-term potentiation (LTP) loss at the hippocampus level in the brains of the mice. It was possible to observe a similar loss of LTP, prompted in the AD model by injecting Amyloid β oligomers (AβOs), causing behavioral and memory defects. Those LTP losses and behavioral alterations processes can be reverted by injecting recombined irisin in the glycosylated format[15].

An adenovirus expressing FNDC5 in the brain was used in an additional approach, as AβOs were injected after six days, thereby obtaining an analogous recovery of animals. Another contributing factor for the reversal of behavioral defects by injecting AβO was PE, supporting the idea that the induction of FNDC5 in the hippocampus was mediated the same way[15].

In 2020, during the study on patients with AD and control individuals, Lourenço et al.[13] suggested a positive correlation between the irisin and BDNF levels in the cerebrospinal fluid (CSF) and memory. That proves the previous data on the relationship between FNDC5/irisin-BDNF and neuroplasticity in the brain. Thus, there is proof of a connection between PE and cognitive functions. However, the activation through PCG-1α/BDNF can contribute to the antidepressant effect of PE by the irisin jointly with the serotonin. In 2019, the level of FNDC5/irisin was proven to be reduced in the brains of people who suffer from Alzheimer's disease[3].

All these findings jointly demonstrate that the activation of the FNDC5/irisin system can be in such a way as PE prompts neurogenesis on a molecular level, indicating an important association between irisin and BDNF[16]. The higher the concentration of irisin, the higher the BNDF will be. When this is active in the hippocampus, it demonstrates how it is an effective agent in the process of neurogenesis and neuroprotection. Hence, physical activity is understood to be and uses irisin as a biomarker, as it is responsible for improving cognitive function[3].

Patients with Alzheimer's have low levels of irisin in their brains. By stimulating PGCI-alfa-FNDC5-irisin through physical exercise, there is an increase in the expression and secretion of the neurotrophic factor derived from the brain, which can increase the survival of nerve cells, neurogenesis, and synaptogenesis, as well as stimulating the neural and synaptic differentiation and plasticity. These factors are directly related to learning, cognition, and memory[16].

Furthermore, there are external studies that

corroborate the hypothesis that exercise is beneficial to patients who suffer from AD. One research study confirmed that the specialized literature demonstrates several benefits on the cognitive level when addressing regular physical exercises in patients with AD, as it reduces the advance of AD in physically active patients and stimulates the improved function of the nervous system. Also, a systematic review in 2019 concluded that regular physical activities contribute to the preservation or even temporary improvement of various cognitive functions in patients with AD.

Irisin

Physical exercise stimulates the release of irisin by the muscle. Irisin, the cleaved extracellular proteolytic part of protein 5, contains fibronectin type III domains (FNDC5). It is a myosin whose expression depends on PGC-1α and is positively regulated by muscular contraction. Hence, as FGF21, when released into the systemic circulation, irisin can contribute to the darkening of the adipose white tissue[17].

The increase prompted by exercise from the release of FNDC5/irisin from the periphery results in the increase of FNDC5/irisin in the neurons, as well as the increased production of BDNF in the neuron. Decreased neurotrophin levels, such as BDNF, were shown in various brain regions affected by AD[17]. As BDNF is a crucial regulator of cerebral plasticity, decreased circulating BDNF can cause the potential risk of reduced memory and cognitive function caused by AD[6].

Recent results have demonstrated that irisin is reduced in the hippocampus and the cerebrospinal fluid (CSF) and in AD mouse models (transgenic mice APPswe/PS1ΔE9 and wild-type mice that were injected with soluble Aβ)[4].

The restoration of central or peripherical irisin levels, whether by exercise or molecular manipulation, resulted in improved synaptic plasticity and the memory of mice in AD models[18]. Irisin can generate benefits from practicing physical exercise to cognitive function protecting the brain against degeneration and increasing the expression of the neurotropic factor of the brain, attributing improvement in learning skills, memory, and the aging process[16].

Basically, the importance of irisin in neurodegenerative diseases and the possible crosstalk between the peripherical levels of irisin and its role in CNS are increasingly emerging, but further studies are necessary, focused on the slight cognitive compromised condition and the decline of subjective cognition[19].

The studies at the "Universidade Federal do Rio de Janeiro" (Rio de Janeiro Federal University) (UFRJ) have demonstrated the same, as the increase in irisin, as well as the FNDC5 protein, reduces the memory and learning deficit of rodents with Alzheimer. Also, tests at the "Instituto Oswaldo Cruz" (Oswaldo Cruz Institute) on mice have shown that irisin improves communication between neurons, preserving the synapses and, besides that, supports the fact that the hormone acts on preventing the loss of memory and recovery of memory losses, emphasizing that hypothesis in this revision.

Review process limitations

This review was based on 22 articles from diverse databases: Systematic and Metanalysis Reviews. Systematic reviews are the strategy for improved performance to evaluate the totality of the available evidence on the subject. However, there can be some limitations that can affect its integrity. The publication bias (and other similar types, such as language bias), risks of bias in the selected primary studies for the revision (such as methodologic limitation of the main studies), as well as some difficulties in matching the studies, such as the populations, interventions, comparers, and defining the outcomes (clinical heterogeneity).

This review was necessary as it observed little knowledge on the subject, so a clear-cut relationship can be established regarding what is known about the role of irisin in preventing AD. Practicing physical exercises, which consequently release myokines in the bloodstream, demonstrates the benefit to mental health, and this review also plays a role in making this clear.

CONCLUSION

After reading all 22 articles, the authors concluded that performing physical exercises is beneficial to preventing AD. The levels of irisin have been demonstrated to increase in individuals who practice physical activities and diminish in patients who suffer from AD, showing how the hormone, skeletal muscular activation, and the prevention of neurodegenerative disease correlate.

Public healthcare must consider a major emphasis on encouraging physical exercises in older adults, as these are known for delaying the neurodegenerative process[20]. Although the mechanisms are still not completely understood, the evidence has shown that moderate to high physical activity is associated with improved quality of life and modulates the potential risk factors for developing dementias and other neurodegenerative disorders[20]. Considering how current medications are incapable of reversing the effects of AD, a change in direction to prevent and delay the pathology from starting must be emphasized[21].

Considering the relevance of an advance in the treatment and cure for AD and the diversity of current studies on the influence of releasing irisin while practicing physical exercises in preventing the respective pathology

shows how important it is to continue the research on this subject from this optic, as well as stimulating individuals to perform physical activities to favor a better future on the rates of the population affected by this disease.

Authors' participation: The authors GCG, LHV, LMCS, LB, LRJ, and SOC have actively participated in the selection of the databases for researching, analyzing, and interpreting the data and the redaction, and the author JGPC performed the critical revision of the manuscript.

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