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REVIEW ARTICLE

The Potential of Sirtuin 1 (SIRT1) Gene as a Biomarker of Frailty Syndrome in the Elderly: A Systematic Review

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ABSTRACT

The global population of older adults is steadily increasing, with aging inevitably linked to frailty, a condition characterized by physical weakness and vulnerability. Frailty in the elderly is often a precursor to chronic diseases, as the body experiences cumulative changes that compromise health over time. To mitigate the onset of chronic diseases in aging individuals, early detection of frailty is critical. One potential biomarker for frailty is the SIRT1 gene, which has garnered attention for its role in regulating aging and preventing degenerative conditions. This article explores the relationship between the SIRT1 gene, aging, and frailty. The SIRT1 gene, known for its role in cellular regulation and protection, is believed to be crucial in the aging process. As people age, maintaining high levels of SIRT1 activity can help prevent the onset of frail conditions and, in turn, reduce the likelihood of chronic diseases such as cardiovascular disorders, diabetes, and neurodegenerative diseases. Studies have shown that increased SIRT1 activity promotes resilience against cellular stress and inflammation, both of which contribute to frailty. Current research suggests that SIRT1 not only plays a role in aging but is also directly linked to frailty syndrome, making it a promising biomarker for early detection. The ability to identify individuals at risk of frailty through SIRT1 levels could pave the way for preventive interventions, potentially enhancing the quality of life for older adults. In conclusion, the SIRT1 gene holds significant promise as a biomarker for frailty, offering insight into the complex relationship between aging and chronic disease prevention.

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1. Introduction

The world's population aged 60 years and over will increase in the next 30 years (2020-2050) from 1.4 billion to 2.1 billion, while the number of people aged 60 years and over in Indonesia There are 9.92% (26.82 million) people aged 60 years and over. The addition of the accumulated population of people aged 60 years and above is also associated with the calculation of the dependency ratio, which is the ratio between the productive-age population and the non-productive-age population, including people aged 60 years and over. With an increasing number of people aged 60 years and above considered as a non-productive group, it becomes a burden that must be borne by the population of the productive group (World Health Organization, 2016).

This burden is caused by the aging process, where a gradual decline in physiological function results in cumulative changes, which eventually result in chronic diseases related to the aging process, such as cardiovascular disease, musculoskeletal disorders and arthritis, neurological problems, and cancer (de Magalhães *et al.*, 2017). Decreasing physiological function also causes frailty in the elderly, besides causing several chronic diseases, which can cause fatal problems such as falls, frequent hospitalizations, disability, dependence on others, and even death in the elderly. It also increases health and care costs for a long time (Cesari *et al.*, 2016; Pivetta *et al.*, 2020; Wong *et al.*, 2010).

Frailty increases with age, ranging from 4 to 59% in the elderly community-living population, and is more significant in women than men. Authentic prevalence rates in a population are related to chronic disease conditions such as depression, nutritional status, and socioeconomic and educational level (Ofori-Asenso *et al.*, 2019).

Sirtuin 1 (SIRT1) plays a key role in modulating longevity through calorie restriction, and its circulating levels tend to be higher in younger individuals (Danese *et al.*, 2018). In animal models, SIRT1 is a biomarker of potential aging (Fujitsuka *et al.*, 2016; Satoh *et al.*, 2013), and thus, sirtuin may serve as a frailty biomarker.

2. Main Body

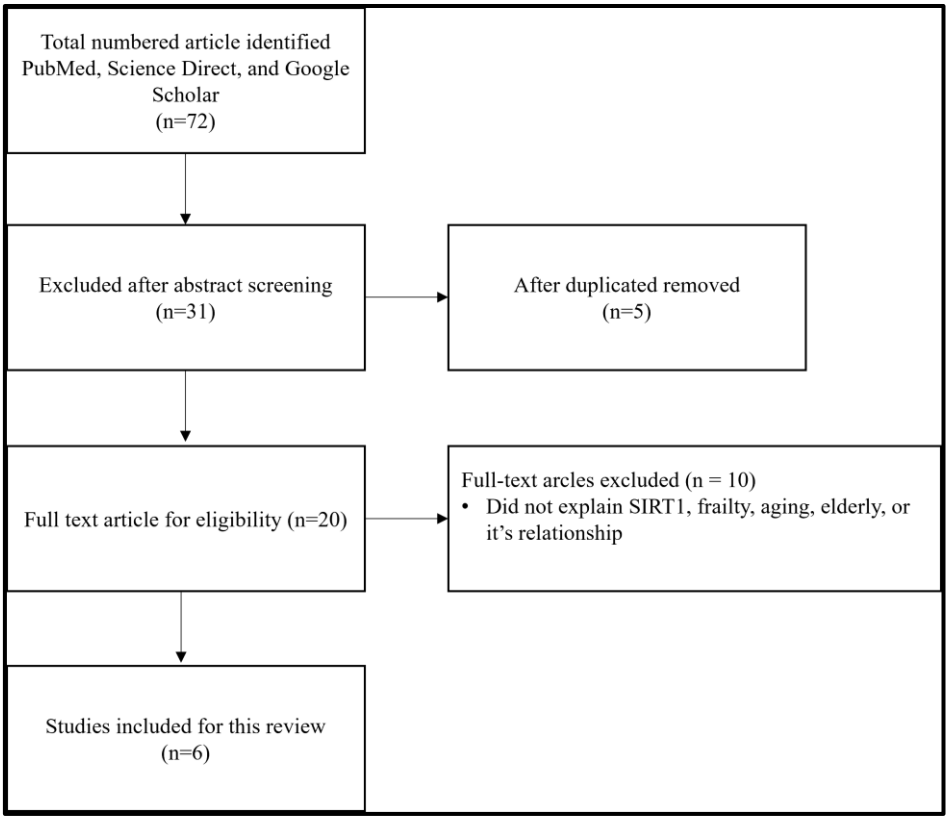
Method

Literature search. The method used in this systematic review is the PRISMA method as the basis for the search strategy. The purpose of the literature search in this systematic review is to find related articles. The search was conducted using PubMed, ScienceDirect, and Google Scholar.

Study characteristics. The characteristics of the article search used are to select by entering the keywords "SIRT1 and Frailty," "SIRT1 among Elderly," "Relationship SIRT1 among Elderly," and "Measured SIRT1 in Elderly."

Selection of articles. Initially, the papers were evaluated based on their title and abstract. After this initial selection, the full text of the selected studies was read and analyzed to confirm that they met the eligibility criteria. The PRISMA diagram below shows (figure 1.)

Figure 1. PRISMA flow diagram showing the database search and selection process



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Result

Table 1. Result Studies of SIRT1

Study Population	Sample	Result	Citation
1705 men aged 70 years and older	Serum	The relationship between nutrition and aging suggests that SIRT1 could potentially impact aging indirectly.	(Razi *et al.*, 2017)
The study group consisted of 88 apparently healthy subjects 31-65 years old. There were 41 men and 47 women	Serum	A comparison of SIRT1 plasma levels between groups experiencing accelerated aging and those with healthy aging, as determined by the DNAm PhenoAge epigenetic clock, revealed a notable disparity.	(Kolesnikova *et al.*, 2023)
Selected healthy 120 children (57 male/ 63 female), 15 adults (103 male/ 12 female), and 103 older people (67 male/ 36 female) were recruited from people who came to Bezmialem Vakif University Hospital for routine examination.	peripheral blood leukocytes of blood samples	The alterations in SIRT1 levels associated with aging in humans are crucial for gaining a deeper molecular insight into the role of the longevity gene SIRT1 and its protein product in the aging process.	(Kilic *et al.*, 2015)
47 obese patients and 48 nonobese were consecutively recruited among patients referring to the Department of Clinical and Experimental Medicine of the University of Pisa for laparoscopic bariatric surgery	Microvessel	SIRT1 serves as a new key regulator of the initial microvascular damage triggered by age and obesity.	(Mengozzi *et al.*, 2022)
One hundred sixty patients over the age of 60 years visiting Geriatric Medicine Outpatient Department of AIIMS, New Delhi	Serum	SIRT1 and SIRT3 are promising candidates as protein markers for frailty, whereas other SIRTs such as SIRT2, SIRT4, SIRT5, SIRT6, and SIRT7 do not exhibit strong associations with frailty.	(Kumar *et al.*, 2016)

25 human subjects and mice from Hadassah Medical Center Institutional	serum of human individuals and mice	An elevated ratio of serum NT/CT SIRT1 was found to be associated with osteoarthritis in both mouse models and human subjects.	(Batshon *et al.*, 2020)

The systematic review depicted in Figure 1 involved several steps in study selection. Initially, 72 articles were identified through electronic database searches. After eliminating duplicate records, 67 unique articles remained. Through screening of titles and abstracts, 31 articles were deemed irrelevant and excluded. Subsequently, the full texts of 20 studies were reviewed, leading to the exclusion of 10 studies due to insufficient explanation of SIRT1 and aging. Ultimately, 6 studies were chosen for qualitative synthesis. These studies focused on hospital patients and utilized serum samples. They primarily investigated two aspects of SIRT1: gene expression or protein expression (Table 1).

Discussion

Aging is a multifactorial biological process that can reduce physiological function and lead to increased susceptibility to aging-related chronic diseases, such as cancer, metabolic, cardiovascular, musculoskeletal, and neurodegenerative diseases (Kennedy *et al.*, 2014). The aging process is followed by the disappearance of the tissue's ability to repair itself and maintain its normal function, which results in the tissue not being able to survive the damage that occurs. The aging process in the elderly slowly results in a decline in the structure and function of organs in physical, psychological, mental, and social aspects, so the elderly are vulnerable to various diseases (Nurfatimah *et al.*, 2017).

Sirtuin 1 (SIRT1) is located on chromosome 10q21.3 and consists of 11 exons and 10 introns. SIRT1, known as NAD+-dependent histone deacetylase, acts as a transcription factor and cofactor and targets histone and non-histone proteins (Salminen *et al.*, 2008). SIRT1 protects cells from oxidative stress, regulates glucose/lipid metabolism, and enhances DNA stability by binding and deacetylating several substrates. Due to its protective role against several age-related pathologies, SIRT1 is considered one of the candidate molecules to promote healthy aging.

The SIRT1 gene plays an important role in mediating cell death/survival processes and has been implicated in the pathogenesis of cardiovascular disease in the elderly (Matsushima & Sadoshima, 2015). In addition, SIRT1 protein levels can regulate several disease-related conditions, such as obesity, cardiovascular disease, and neurodegeneration. In addition, SIRT1 demonstrates the importance of epigenetics in several age-related diseases to promote health in the aging process by developing new therapies that can prevent or attenuate the development of several diseases (Elibol & Kilic, 2018).

The SIRT1 gene enhances endothelial function to prevent atherosclerosis by increasing endothelial relaxation through eNOS expression and nitric oxide production. Later, many studies revealed that low SIRT1 is associated with eye diseases, including cataracts, age-related macular degeneration, diabetic retinopathy, and glaucoma, while upregulation of ectopic SIRT1 protects against eye disease (Zhou *et al*., 2018).

Given the role of SIRT1 in calorie restriction, the CHAMP researchers hypothesized that the differences were due to food consumption and nutritional status. They conducted a second study and found identical results to the first: frail older adults had low plasma SIRT1 expression. Nutritional conditions and body composition may be more closely related to plasma SIRT1 levels than aging and frailty (11). In a study of Indian individuals, plasma SIRT1 levels decreased with age, and this reduction was more pronounced in individuals with frailty and cognitive impairment (Kumar *et al*., 2014).

3. Conclusion

The SIRT1 gene plays a crucial role in the aging process and is a potential biomarker for frailty in the elderly. It regulates cellular metabolism, protects against oxidative stress, and supports DNA stability, making it a strong candidate for monitoring frailty onset. Studies show consistent associations between lower SIRT1 levels and increased frailty or age-related conditions. SIRT1 expression varies depending on age, nutritional status, and disease state, supporting its role as a biomarker and potential therapeutic target. Measurement of SIRT1 levels could lead to personalized interventions promoting healthier aging and reducing chronic illness burden among the elderly population.

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