



The Role of Insulin Resistance and Myokines in Cardiovascular Aging: Possibility of Treatment

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Abstract

Unfortunately, although life expectancy has increased in the last decades, old age is often complicated by multiple chronic conditions that place a significant burden on social and healthcare systems. The presence of these chronic comorbidities is often the result of a lack of optimal preventive measures throughout life—specifically regarding the potential to slow aging processes at all levels, but particularly within the cardiovascular system. It is well known that, despite significant advances in the prevention and treatment of cardiovascular diseases, they remain the leading cause of death. Therefore, it is essential to identify and investigate the biological mechanisms driving cardiovascular aging and to determine whether interventions targeting these mechanisms can promote healthy aging. The aim of this narrative review is to examine the scientific literature on two topics that strongly influence the aging process: insulin resistance, which has a negative impact, and myokines, which have a positive one.

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Introduction

Over the last decades, average life expectancy has increased significantly, particularly among women [1]. This has been achieved for various reasons, first and foremost, the shift in hygiene standards—with the access to clean water and soap, the presence of sewage systems, and food refrigeration. However, another important factor that has emerged in recent decades is the progress made in the treatment of diseases in general, and cardiovascular conditions in particular [2]. Unfortunately, this increased longevity is accompanied by the presence of two or more chronic conditions that diminish quality of life and significantly increase the socioeconomic and healthcare burden associated with these individuals [3, 4]. A paradigm shift in geriatric cardiology is therefore needed: rather than viewing clinical frailty and chronological age as inevitable drivers of decline, research must focus on the modifiable cellular, metabolic, and molecular mechanisms that initiate the aging of the heart and blood vessels early in life. Identifying these mechanisms would allow for early intervention to slow the aging process and promote healthy aging. Four interconnected pillars of this process are insulin resistance (IR.), cellular senescence, cardiovascular stiffening, and the protective role of myokines (M) [5, 6]. However, these mechanisms have been only partially elucidated. Indeed, much remains to be clarified, particularly regarding the deleterious effects of IR and associated hyperinsulinemia (HI) on pathological cardiovascular aging and, conversely, the beneficial and protective effects of M.

Methods.

The aim of this narrative review of the scientific literature is just to examine the role of IR and M in cardiovascular aging, while also assessing potential preventive therapeutic interventions. To this end, the authors independently searched for and analyzed studies, published in English in peer reviewed journals from 1975 to 2026, using major search engines—such as PubMed, ScienceDirect, Scopus, ResearchGate, and Google Scholar—employing the following keywords: cardiovascular aging, cellular senescence, insulin resistance, hyperinsulinemia, and myokines. Finally, they discussed the findings to draw conclusions and writhed the manuscript.

Insulin Resistance

Insulin resistance is a metabolic condition in which the biological effect of insulin—specifically regarding the regulation of glucose metabolism—is reduced and insufficient compared to normal. Consequently, to overcome this dysfunction and maintain glucose levels within the normal range, the pancreas is compelled—for as long as it is able—to produce and release increased amounts of insulin; this leads to the development of compensatory hyperinsulinemia, a state characteristically associated with insulin resistance [7–9].

IR with associated HI is a common condition among adult people, with a prevalence ranging from 25% to 50%, depending on the region and the socioeconomic and cultural conditions of the populations assessed, and is also progressively increasing among children [7, 10, 11].

IR, HI, and cellular senescence are closely interconnected and form a pathological vicious cycle [12, 13]. This triad accelerates biological aging and promotes metabolic and neurodegenerative diseases. When cells stop responding to insulin (insulin resistance), the pancreas produces more of it (hyperinsulinemia) [7]. This excess hormone damages tissues and drives cells toward a permanent halt in replication (senescence).

The chronic presence of high insulin levels in the blood constantly stimulates cellular signaling pathways: insulin stimulates the PI3K/AKT/mTOR pathway [14, 15]; chronic overstimulation of this pathway inhibits autophagy (cellular cleanup) and accelerates aging. Furthermore, excessive hormonal stimulation through insulin induces cellular stress that activates key senescence pathways (p53 and p21), forcing the cell to halt its life cycle [13].

Cardiovascular Cellular Senescence and Inflammaging

Cellular senescence is the permanent arrest of the cell cycle due to the accumulation of stress (DNA damage, telomere shortening, and oxidative stress) [16].

- Cardiovascular senescent cells [cardiomyocytes, endothelial cells, and fibroblasts] are not inert, but secrete the Senescence-Associated Secretory Phenotype (SASP) [17].
- The SASP is a hypersecretory phenotype adopted

by senescent cells, characterized by the massive release of pro-inflammatory bioactive molecules (such as IL-6, TNF- α , and GDF-15) that fuel chronic, low-grade systemic inflammation (inflammaging) into the surrounding microenvironment. Although senescent cells are in a state of permanent cell-cycle arrest, they remain highly metabolically active, profoundly altering neighboring tissues through this secretion [18].

- This microenvironment damages surrounding healthy cells, reduces myocardial contractility, and stimulates fibrosis [18].

IR and HI are the primary biological drivers of premature cardiovascular aging—a process that accelerates the structural and functional decline of the heart and blood vessels long before overt diabetes develops. In IR conditions, the constant surplus of insulin triggers systemic damage that causes the cardiovascular system to age prematurely [19-21].

These are the mechanisms by which IR/HI accelerates cardiovascular aging (Table 1):

Vascular Aging and Arterial Stiffness

Chronic hyperinsulinemia directly damages blood vessel walls through several pathways:

- Endothelial dysfunction: Excess insulin reduces the production of nitric oxide, the molecule responsible for vessel relaxation and vascular protection against atherosclerosis. The result is chronic vasoconstriction, increased blood pressure and premature onset of atherosclerotic process [22, 23].
- Cellular proliferation: Insulin stimulates the growth of smooth muscle cells in artery walls and increases collagen synthesis, making vessels stiff and less elastic—a hallmark of advanced aging [24, 25].
- Accelerated atherosclerosis: Insulin facilitates the transport of cholesterol into arterial walls and promotes plaque formation. This process is amplified by the "atherogenic dyslipidemia" typical of insulin resistance (high triglycerides, low HDL cholesterol, shift toward smaller, highly atherogenic low-density lipoproteins) [26-28].
- Cardiac remodeling and senescence (Table 1): The heart possesses specific insulin receptors. When insulin signaling is impaired at the cardiac level, profound structural changes occur:
- Myocardial hypertrophy: Excess insulin binds to insulin-like growth factor-1 (IGF-1) receptors, stimulating abnormal thickening of the left ventricular walls (concentric remodeling) [29, 30].
- Diastolic dysfunction: The heart muscle becomes stiff for hypertrophy, fibrosis, and increased epicardial and myocardial fat, and struggles to relax between beats, a condition that lays the groundwork for heart failure with preserved ejection fraction (HfPEF), which is typical in the elderly [30, 31].
- Oxidative stress and mitochondrial damage: IR alters the heart's energy metabolism, forcing it to rely almost exclusively on fatty acids. This generates an excess of free radicals that damage cellular mitochondria, accelerating myocardial cellular senescence [32, 33].

Table 1: Physiological vs IR-driven cardiovascular aging

	Physiological aging	Accelerated aging due to IR/HI
Blood Pressure	Gradual age-related rise in systolic pressure	Early-onset, difficult to control hypertension
Vessel structure	Progressive, slow loss of elasticity	Premature arterial stiffening and strong atherogenic drive
Lipid Profile.	Modest age-related changes	High triglycerides, low HDL, small dense LDL particles
Cardiac Function	Slight reduction in reserve under stress	Hypertrophic remodeling and early diastolic dysfunction

Myokines

Myokines are small proteins, peptides, or cytokines produced and released by skeletal muscle cells in response to muscle contraction, which act in autocrine, paracrine and endocrine manner. They work as chemical messengers

that allow the muscle to "communicate" with other organs, effectively transforming muscle tissue into an endocrine organ. Scientists and researchers have mapped over 600 different myokines, highlighting how physical activity serves as a genuine biological medicine for the entire body [34, 35].

Myokines play a fundamental role in counteracting biological aging, acting as chemical messengers released by skeletal muscle tissue. When muscles contract during physical activity, they secrete hundreds of these small protein molecules into the bloodstream. Through this intricate communication network, skeletal muscle ceases to be merely a motor for movement and becomes a true endocrine organ capable of interacting with the brain, bones, liver, and immune system, orchestrating a powerful systemic anti-aging response [36, 37].

Key Anti-Aging Mechanisms of Myokines (Table1)
Myokines act on multiple fronts to delay age-related functional decline:

- **Combating sarcopenia:** They protect muscle mass by promoting protein synthesis and stimulating satellite cells to repair damaged fibers [37 – 39].
- **Brain health and neuroprotection:** Certain myokines cross the blood-brain barrier to stimulate neurogenesis, enhance synaptic plasticity, and protect the brain against cognitive decline [40, 41].
- **Suppressing systemic inflammation:** They counteract inflammaging—the chronic, low-grade inflammatory state associated with aging [42 – 44].
- **Metabolic regulation:** They optimize glucose utilization, stimulate fat breakdown, and improve the efficiency of mitochondria, the cells' powerhouses [45 – 47].
- **Bone-muscle axis:** They preserve bone mineral density, protecting against the development of osteoporosis [48 – 50].

Map of Key Myokines and their Anti-Aging Functions.
With advancing age and a sedentary lifestyle, the secretion of protective myokines tends to decrease significantly. Restoring their optimal levels occurs in different ways depending on the biological stimuli:

Myokines Primarily Stimulated by Aerobic Exercise

- **Irisin:** Promotes mitochondrial biogenesis and supports neuronal health, acting as a potential

shield against neurodegenerative diseases such as Alzheimer's [40, 51, 52].

- **Apelin:** Considered a true longevity factor, it improves vascular function and reduces hypertension [53, 54].
- **BAIBA (Beta-Aminoisobutyric Acid):** Prevents metabolic diseases by stimulating the "browning" (activation) of adipose tissue and protecting mitochondria [55, 56].
- **Sestrin:** Helps prevent systemic metabolic degeneration and counteracts muscle atrophy [57, 58].

Myokines Primarily Stimulated by Anaerobic Exercise [Strength/Resistance]:

- **IGF-1 (Insulin-like Growth Factor 1):** Maintains muscle mass by activating muscle stem cells and stimulating new protein synthesis [59, 60].
- **Decorin:** Regulates tissue growth, promotes muscle regeneration, and supports tendon health [61, 62].
- **BMP-7:** Plays a key role in bone tissue formation and the maintenance of muscle strength [62].

Myokines Regulated by Both Types of Exercise

- **IL-15 (Interleukin-15):** Inhibits protein degradation and promotes cell proliferation [64].
- **IL-6 (Interleukin-6):** During exercise, it acts in an acute and beneficial manner, improving glucose homeostasis and lipid metabolism [65].
- **Myostatin (The exception):** It is a muscle growth inhibitor. Aging increases its levels, but physical exercise (both cardio and strength training) can reduce its secretion, thereby unlocking tissue regeneration [66].

Myokines, act through a "muscle-heart axis" to actively protect the cardiovascular system against the degradation of aging (Table - 2)[67].

Table 2: Direct Systemic Comparison of the Effects of Some of the Best Known Myokines

Myokins	Primary Vascular Target	Primary Cardiac Target	Key Anti-Aging Mechanism
Irisin	Endothelial cells	Cardiomyocytes	Prevents plaque buildup, lowers vascular stiffness
FSTL1	Endothelial matrix	Myocardium	Reverses fibrotic stiffening, repairs injury
BAIBA	Smooth muscle cells	Cardiomyocytes	Halts mitochondrial decay and cell death
Apelin	Arterial walls	Left ventricle	Lowers blood pressure, prevents remodeling

These are the primary myokines with documented anti-aging effects on the heart and arteries, categorized by their physiological impact:

Protective Effects on Arteries (Vascular Anti-Aging)

- Irisin: Stimulates endothelial cell migration, improves nitric oxide production, and directly combats vascular stiffness and endothelial dysfunction [68, 69].
- b. Apelin: Counters age-related hypertension, reduces the severity of ischemia-reperfusion injuries, and works as a direct systemic anti-aging factor in circulation [53, 54, 70].
- c. VEGF-A (Vascular Endothelial Growth Factor A): Promotes angiogenesis (the growth of new blood capillaries) to maintain healthy tissue perfusion in aging arterial beds [71, 72].
- d. Myonectin: Suppresses vascular inflammation, downregulates macrophage activation, and protects against the formation of atherosclerotic plaques [73, 74].

Protective Effects on the Heart (Cardiac Anti-Aging)

- FSTL1 (Follistatin-like 1): Enhances cardiac function, reduces pathological cardiac fibrosis (stiffening), and regulates autophagy to optimize mitochondrial quality in cardiomyocytes [75, 76].
- BAIBA (βeta-aminoisobutyric acid): Enhances mitochondrial survival and quality in cardiac tissue, significantly reducing age-related cardiomyocyte apoptosis (cell death) [55, 77].
- MG53 (Mitsugumin 53): Binds to cardiolipin to preserve myocardial cell membrane and mitochondrial integrity, preventing cardiac cell injury [78].
- IL-10 [Interleukin-10]: Acts as a potent anti-inflammatory agent that directly neutralizes "inflammaging" [chronic low-grade inflammation] within cardiac muscle tissue [79, 80].

While exercise increases the beneficial myokines listed above, it actively **suppresses Myostatin**. High levels of Myostatin are associated with accelerated vascular aging, increased aortic stiffness, and advanced atherosclerosis. Therefore, suppressing Myostatin is equally critical to protecting aging arteries [81].

Potential Treatments by Counteracting Insulin Resistance and Stimulating Myokine Secretion

As previously discussed, high insulin levels associated with IR—and the inability of cells to metabolically respond to this hormone—accelerate the deterioration of blood vessels and the heart through chronic inflammation, oxidative stress, and other key mechanisms that drive atherosclerosis and stiffness in both vascular and cardiac tissues. Therefore, an intervention aimed at countering IR, thereby reducing circulating insulin levels, should slow the process of cardiovascular aging and yield multiple beneficial effects.

To reverse insulin resistance and protect the heart, it is necessary to address three fundamental pillars:

Functional Nutrition [82, 83]

- Reduction of the glycemic load: eliminating or reducing refined sugars and white flours.
- Chrononutrition: Focus complex carbohydrate intake on the first part of the day.

- Intermittent fasting: Fasting windows [e.g., 16/8] to lower basal insulin levels.
- Healthy fats: Consume extra virgin olive oil, arugula, avocado, and omega-3s [oily fish].

Targeted Physical Activity [84– 86]

- Strength training: Building muscle increases glucose receptors and improves the translocation of GLUT-4 from the cytoplasm to the cell membrane surface, thereby enhancing glucose uptake.
- Low-intensity cardio: Brisk walking or cycling to improve mitochondrial efficiency.
- Post-meal walking: A 15-minute walk after meals blunts the blood sugar and insulin spikes.

Drugs and Natural Substances [87]

There are now many drugs or natural substances which improve IR and reduce circulating insulin levels. Among these the most studied are GLP-1 receptor agonists (GLP-1Ras), SGLT2 inhibitors (SGLT2 Is), metformin, berberine, quercetin, silymarin, pyrroloquinoline quinone and others omitted for brevity.

All these substances act via different mechanisms of action, with the exception of metformin and berberine, which share very similar mechanisms. Therefore, at the attending physician's discretion, they could—in certain cases—be used in combination to leverage a synergistic effect.

Among drugs, the recently introduced GLP-1 RAs and SGLT2 Is have already demonstrated remarkable efficacy in improving IR and cardiovascular outcomes in patients with heart disease—likely due, at least in part, to their beneficial effect in reducing insulin resistance [88 – 92]. Naturally, randomized controlled trials with adequate sample sizes and follow-up periods are needed to determine whether these drugs can be used in individuals with insulin resistance for primary prevention—specifically, to prevent or at least slow down cardiovascular aging.

Metformin is another long-established drug that has long been a first-line treatment for type 2 diabetes due to its recognized effect on insulin resistance [93]. It acts primarily by lowering liver sugar production and helping body cells absorb glucose better, through the activation of the energy sensor enzyme AMPK, which

shifts cell metabolism and the GLUT4 translocation to the outer cell membrane in insulin-sensitive tissue, thus improving glucose uptake and utilization. Naturally, as with GLP-1RAs and SGLT2 inhibitors, appropriate studies are needed to confirm its utility in preventing and/or slowing cardiovascular aging [94, 95].

Among natural substances, berberine is one of the most widely used due to its effectiveness in combating insulin resistance [96, 97]. Its mechanism of action is very similar to that of metformin. Unfortunately, however, its intestinal absorption is poor and inconsistent. For this reason, it is often used in combination with silymarin [97, 98]; silymarin exerts a synergistic effect on insulin resistance—particularly in the liver—and enhances berberine absorption, making it more consistent by inhibiting intestinal P-glycoprotein [97].

Another very interesting natural substance is quercetin. It is a natural flavonoid widespread in nature with antioxidant and anti-inflammatory properties, found in many plant-based foods (such as apples, onions, and capers) and commonly sold as a supplement.

Quercetin combats cardiovascular aging by acting as a powerful senolytic that targets cellular senescence, reduces chronic inflammation (inflammaging), and improves endothelial function [97, 99, 100].

Quercetin acts as a potent senolytic on endothelial cells, which in turn regulate overall vascular health through the production of nitric oxide (NO), thereby reducing vascular stiffness and counteracting hypertension and atherosclerosis [97]. Quercetin modulates the activity of fibroblasts depending on the pathological context. It inhibits the activation of fibroblasts into myofibroblasts, reducing excessive collagen accumulation. It suppresses the abnormal proliferation of hyperactive fibroblasts by activating autophagy and programmed cell death [apoptosis] pathways, acting primarily through the PI3K/Akt/mTOR signaling pathway [101].

Desatinib is a chemotherapy drug belonging to the class of tyrosine kinase inhibitors [originally approved for chronic myeloid leukemia] that has gained immense significance in longevity medicine as one of the most potent senolytic agents. Senolytics are compounds capable of selectively inducing apoptosis [programmed cell death] in senescent cells—also known as "zombie

cells"—which accumulate with age and secrete toxic inflammatory molecules (SASP) responsible for tissue aging [102].

The combination of dasatinib and quercetin is the most extensively studied senolytic regimen [102]. Dasatinib alone does not eliminate all types of senescent cells; for this reason, it is used in combination with quercetin for anti-aging purposes: dasatinib primarily eliminates senescent adipocyte progenitors, whereas quercetin targets endothelial cells [103]. Naturally, given that dasatinib is a potent oncology drug associated with the typical side effects of chemotherapy, extending its use for senolytic purposes requires great caution. Furthermore, while quercetin proved effective in males, it showed minimal endothelial benefits and was associated with an increase in inflammatory pathways—specifically in fibroblasts—in females [104].

Pyrroloquinoline quinone [PQQ] is a redox-active molecule that have significant beneficial implications for human health. It acts as an essential cofactor for oxidative enzymes that are fundamental for mitochondrial function and ATP synthesis [105]. PQQ's antioxidant nature mitigates oxidative stress, which is involved in many diseases. Clinical studies have shown many potential benefits of PQQ supplementation, such as improvements of cardiovascular health, cognitive function, insulin sensitivity, and preventive effects towards metabolic syndromes. It exerts anti-aging effects primarily through enhancing mitochondrial biogenesis, exerting antioxidant activity and inhibiting inflammatory pathways [106 – 110].

Discussion

It is well known that, despite the rise in the average age of the population over recent decades, aging is unfortunately very frequently accompanied by chronic multimorbidity—particularly, though not exclusively, of a cardiovascular nature—which diminishes quality of life and places a significant socioeconomic burden on families and healthcare institutions. Moreover, it is also known that, notwithstanding advances in the prevention and treatment of cardiovascular diseases, these conditions remain the leading cause of death in both developed and developing countries [111]. Cardiology in the elderly has long focused on treating frailty and multimorbidity, without delving into the

biology and pathophysiological mechanisms that drive cardiovascular aging itself. Yet, these mechanisms require in-depth investigation to foster understanding and enable the implementation of preventive and therapeutic measures. Ideally, such interventions should take place before old age is reached, specifically to halt or at least slow down age-related changes; however, targeted interventions addressing these mechanisms later in life could likely still mitigate the harmful effects of aging on the cardiovascular system. Among the best-known mechanisms linked to accelerated aging—particularly regarding the cardiovascular system—is insulin resistance accompanied by hyperinsulinemia; this condition now has a rather high global prevalence, ranging from 25% to 50% depending on the region in question [112].

Unfortunately, we have observed that insulin resistance is increasingly affecting younger age groups—even children—largely due to unhealthy lifestyles that often go unnoticed [113]. Therefore, early diagnostic and preventive measures regarding insulin resistance should be implemented at a young age, primarily to address and modify the unhealthy lifestyle habits driving the condition [115-117]. Above all, we need to re-educate young people on portion sizes and food choices [and, naturally, discussions about food must also include what they drink]. Carbohydrate and ultra-processed food intake must be significantly reduced to prevent excessive insulin spikes, which are harmful in their own right and exacerbate insulin resistance [118]. On the other hand, it is also well known that a large part of the population has become sedentary, having progressively reduced their physical activity due to a lack of time and laziness. This is the worst possible approach, whether one is young or older.

Regular physical activity is a fundamental pillar for maintaining a healthy body and preventing numerous diseases. Staying active does not merely help control weight; it also triggers a range of biological and psychological benefits that improve both the quality and length of life [119].

We have seen that physical exercise improves many pathological mechanisms associated with aging, a key one being insulin resistance. Skeletal muscle is one of the organs richest in insulin receptors; physical exercise activates these receptors, which in turn regulate the

translocation of GLUT4 from the cell cytoplasm to the cell membrane surface, thereby enhancing glucose uptake and utilization by the cells [120]. Physical exercise is fundamental for young people, but it is perhaps even more important in old age—primarily for preventing the development of sarcopenia [121].

Sarcopenia—defined as the progressive and generalized loss of muscle mass, strength, and quality—is closely linked to increased morbidity [the incidence of diseases and complications] and mortality within the population, particularly among the elderly [122]. Muscle is not merely an organ for movement but a true metabolic and endocrine organ; when it deteriorates, the entire body becomes more fragile.

We have, in fact, seen how it has been discovered, in recent years, that contracting muscle secretes and releases myokines into circulation—hundreds of small proteins with endocrine, paracrine, and autocrine actions [123].

They have shown anti-inflammatory action, to improve metabolic health, to improve insulin sensitivity and to promote fat oxidation. They promote brain protection, stimulating neurotrophic factors such as brain-derived neurotrophic factor (BDNF), improving memory and mood, while protecting against cognitive decline. Furthermore, they reduce the risk of cardiovascular disorders, type 2 diabetes, and cancer [34, 35, 123].

Conclusions

This narrative review of the scientific literature on the role of insulin resistance and myokines in cardiovascular aging highlights the importance of further investigating the biological mechanisms underlying the pathophysiology of cardiovascular aging, with the aim of identifying interventions for prevention and, potentially, the reversal of aging-related pathological processes. Understanding the role of insulin resistance in the development of cardiovascular aging suggests that counteracting it could slow down the associated age-related organ damage. Furthermore, the discovery that physical exercise stimulates the secretion of myokines—and the recognition of their beneficial effects in counteracting insulin resistance and impacting many of our organs—highlights the fundamental importance of consistent physical exercise tailored to the capabilities of

individuals of all ages, from the young to the elderly.

Declarations

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The authors contributed equally to the conception, the collection of works to be reviewed, and the drafting of the manuscript.

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