Identification of Putative Causal Relationships between Blood-Based Biomarkers and Prediabetes-Induced Senescence: A Comprehensive Review

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Abstract: Prediabetes, a pivotal phase in glucose metabolism between normalcy and diabetes, exerts a profound influence on the aging process and the risk of age-related diseases. This comprehensive review delves into the intricate web of blood-based biomarkers that collectively expedite senescence, marking the transition from a state of health to age-related complications. Key findings underscore the significance of diverse biomarkers, such as telomere length, p16INK4a, senescence-associated secretory phenotype (SASP) factors, DNA methylation clocks, advanced glycation end products (AGEs), inflammatory and oxidative stress markers, circulating hormones, and additional factors such as folate, B12, and osteocalcin. Not only do these biomarkers serve as indicators of senescence but they also actively fuel chronic inflammation, oxidative stress, and metabolic dysregulation, all of which contribute to accelerated aging. The implications of this understanding are profound, as prediabetes emerges as a critical period in an individual's life, influencing various physiological systems, including the vascular and neural systems, metabolic functions, hormonal regulation, and bone health. Recognizing the profound influence of prediabetes on senescence provides a foundation for personalized intervention strategies to mitigate age-related complications and promote healthy aging. Future research directions call for a more diverse array of biomarkers, the in-depth exploration of their roles, and the development of tailored precision medicine strategies to ensure a holistic understanding and effective management of prediabetes-induced senescence and its implications for aging. This knowledge has far-reaching implications for public health and clinical practice, emphasizing the need for early detection and intervention in prediabetic individuals to enhance the quality of life in an aging population with diverse needs.

Keywords: prediabetes; senescence; blood-based biomarkers; aging; chronic inflammation; glucose metabolism

1. Introduction

The global prevalence of prediabetes, a metabolic state characterized by insulin resistance and elevated blood glucose levels below the threshold for diabetes diagnosis, has emerged as a significant public health concern [1]. Prediabetes is a critical precursor to type 2 diabetes (T2D); however, it often remains undiagnosed, and individuals with prediabetes are at a heightened risk of transitioning to T2D [2]. It is also associated with a range of adverse health outcomes and age-related complications, including cardiovascular diseases, neurodegenerative disorders, and frailty [3]. Given the growing aging population worldwide, a comprehensive understanding of how prediabetes impacts senescence is of great significance.

The relationship between aging and chronic illnesses such as diabetes has drawn significant attention in the field of public health as the world's population ages [4]. Between normoglycemia and overt diabetes, prediabetes, which is defined by increased blood glucose levels, is a critical stage in the continuum of glucose dysregulation [5]. It is critical to comprehend the many mechanisms by which prediabetes affects the aging process. The realization that prediabetes contributes to an accelerated aging phenotype and predisposes people to diabetes is the driving force behind this extensive research [6]. The evaluation of blood-based biomarkers, which act as markers of the underlying physiological and molecular processes connecting prediabetes and senescence, is a crucial component of this study [7].

Assessing blood-based biomarkers within the framework of prediabetes-induced senescence provides a comprehensive viewpoint on the complex interplay between metabolic dysregulation and aging [8]. This is especially important because aging-related diseases and prediabetes share many pathophysiological pathways [9]. This review is important because it could provide researchers and physicians with the resources, they need to identify people who are at risk of developing prediabetes, as well as premature aging. By facilitating early intervention and preventive steps to lessen age-related issues, it provides a proactive approach to healthcare [10]. Furthermore, identifying the biomarkers linked to senescence brought on by prediabetes is crucial for deciphering the molecular causes of aging, and presents opportunities for focused interventions that can lessen the negative effects of prediabetes on the health of older persons [11].

In addition to improving our understanding of the aging process, the scientific investigation of blood-based biomarkers in prediabetes-induced senescence holds enormous promise for enhancing the health and well-being of prediabetic individuals [12]. We can identify new treatment targets and preventive measures by dissecting the relationships between particular biomarkers and accelerated aging [13]. With a deeper understanding of the relationship between metabolic health and senescence, and, ultimately, develop guidance for the development of interventions to promote healthy aging and lessen the burden of age-related diseases among prediabetic individuals, these insights could have far-reaching implications for the fields of gerontology and diabetes care [14].

This comprehensive review investigates the relationship between prediabetes and age-related changes, with a specific focus on blood-based biomarkers. This study will delve into the impact of prediabetes on telomere length, p16INK4a expression, senescence-associated secretory phenotype (SASP) factors, DNA methylation clocks, advanced glycation end products (AGEs), inflammatory markers, and oxidative stress markers. This study will further explore the influence of prediabetes on circulating hormones, growth factors, and metabolic markers. This study provides a thorough exploration of these various blood-based biomarkers that are associated with both prediabetes and senescence by synthesizing existing knowledge on these biomarkers. Understanding this connection is of paramount importance in the context of contemporary healthcare, as it has the potential to shed light on the mechanisms underlying accelerated biological aging in prediabetic individuals and provide valuable insights into the pathogenesis of age-related chronic diseases. This analysis will contribute to our understanding of the complex relationship between prediabetes and the aging process, ultimately facilitating the development of targeted interventions and strategies for mitigating the adverse effects of prediabetes-induced senescence.

2. Age-Related Changes in Plasma Biochemistry and Vascular Dynamics in Prediabetes

2.1. Prediabetes as a Precursor of Age-Related Vascular Changes

A key prelude to age-related vascular alterations is prediabetes, which is defined by high blood glucose levels that do not fulfil the criteria for diabetes [15]. The circulatory system, which includes the arteries and veins, undergoes structural and functional changes because of the complex and diverse process of vascular aging [16]. It is essential for the emergence of hypertension and associated problems, and age-related cardiovascular illnesses [17]. Prediabetes can dramatically accelerate vascular aging, increasing

the risk of cardiovascular morbidity and mortality in patients with it. Prediabetes affects approximately one in three persons in many countries [18].

Oxidative stress is one of the main ways that prediabetes affects the aging of blood vessels [19]. Increased oxidative stress, which is defined as an imbalance between reactive oxygen species (ROS) and antioxidant defences, is common in prediabetic patients [19]. This oxidative load may eventually contribute to vascular aging by causing oxidative damage to the walls of blood vessels [20]. A chronic rise in blood glucose and variations in insulin resistance in prediabetes intensify oxidative stress and foster an environment favorable for the oxidative alteration of lipids and proteins in the vascular system [21]. This accelerates these vascular alterations and increases the risk of age-related cardiovascular problems such as endothelial dysfunction and atherosclerosis [21].

Furthermore, prediabetes is closely associated with chronic low-grade inflammation, often referred to as "meta-inflammation" [22]. Prediabetes intensifies inflammatory processes, which primarily cause vascular aging [19]. The pro-inflammatory condition of prediabetes can encourage immune cells within the vascular wall to become activated, triggering an inflammatory response that hastens the aging process of the vessels [23]. As a result, blood vessel stiffening, atherosclerotic plaque development, and decreased vascular reactivity occur [23]. The significance of prediabetes as a prelude to vascular alterations associated with aging is noteworthy, emphasizing the need to comprehend these mechanisms and determine pertinent blood-based indicators to oversee and address this metabolic disorder [24]. This review explores the role of such biomarkers in tracking the progression of vascular aging in prediabetes and their potential for mitigating the adverse outcomes associated with this accelerated aging process.

2.2. Altered Plasma Biochemistry and Implications for Senescence

Prediabetes significantly impacts the biochemical makeup of blood, creating conditions for accelerated senescence [25]. A vital factor in determining general health, plasma biochemistry affects many physiological functions [26]. Blood plasma composition is altered in prediabetic individuals because of the dysregulated glucose and lipid metabolism in the systemic environment [27]. Elevated levels of circulating inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are one of the major biochemical alterations linked to prediabetes (see Figure 1) [28]. Pro-inflammatory signals play a role in the persistent low-grade inflammation that is frequently observed in prediabetes, a condition that is sometimes called "Inflammaging" [29]. Since inflammation is a major factor in senescence, a persistently inflammatory environment speeds up the aging of many organ systems [30].
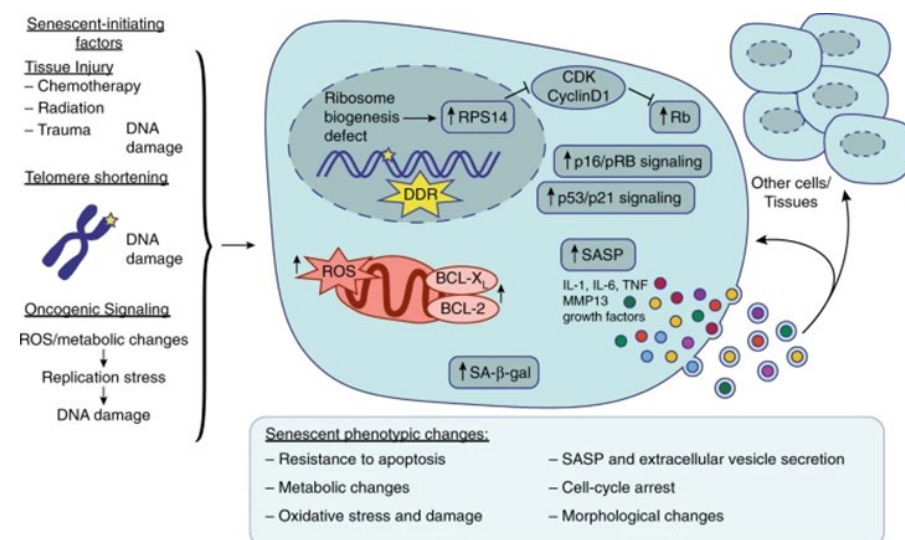

Figure 1. Overview of prediabetes-induced vascular senescence as adapted from source and redrawn from Bio Render. Several factors can induce senescence in different tissues, such as tissue injury,

telomere shortening, and oncogenic signaling, which all lead to DNA damage, the DNA damage response (DDR), and consequent cell cycle arrest by the activation of p16/pRB signaling and/or p53/p21 signaling. Nucleolar stress and ribosome biogenesis defects can also induce RPS14 accumulation in the nucleus and activate Rb by inhibiting the CDK4/cyclin D1 complex, leading to cell cycle arrest. Senescent cells also exhibit increased senescence-associated β-galactosidase (SA-β-gal) production, reactive oxygen species (ROS) accumulation, and anti-apoptotic factors such as BCL-XL and BCL-2. Senescent cells exhibit several phenotypic changes such as resistance to apoptosis, oxidative stress and damage, metabolic changes, morphological changes, cell cycle arrest, and extracellular vesicle secretion containing SASP factors such as IL-1, IL-6, TNF, MMP13, and various growth factors. This SASP can either feedback in an autocrine manner to the senescent cell, or, in a paracrine manner, influence and promote senescence and inflammation in the surrounding cells and tissues [31].

Moreover, abnormal lipid profiles, such as elevated triglyceride and decreased high-density lipoprotein (HDL) cholesterol levels, are linked to prediabetes [32]. Due to its pro-atherogenic nature, dyslipidemia encourages the build-up of cholesterol in blood vessel walls and the onset of atherosclerosis, a disease generally associated with advanced age [33]. Atherosclerosis raises the risk of cardiovascular events such as heart attacks and strokes by limiting blood flow and encouraging the formation of blood clots [34]. The combined effect of these changes in parameters related to plasma biochemistry speeds up the aging process of organ and vascular systems [7].

Prediabetes causes hyperglycemia by upsetting glucose homeostasis and going beyond inflammation and dyslipidemia [35]. Elevated blood glucose levels promote the glycation of proteins, including those essential for vascular health [36]. This process results in the formation of advanced glycation end products (AGEs), which promote oxidative stress and arterial wall stiffening [37]. AGEs have broad implications for age-related complications such as renal dysfunction and neurodegenerative diseases, in addition to their association with vascular senescence [38]. Examining the interaction between these biochemical alterations and the aging process in prediabetes is essential because the altered plasma biochemistry in prediabetes is a critical link in the chain of events that accelerates senescence.

2.3. Role of Biomarkers in Plasma Biochemistry Changes

As a metabolic state that lies between normoglycemia and diabetes, prediabetes is characterized by a complex interplay of biochemical factors, many of which are important biomarkers for changes in plasma biochemistry [39]. These biomarkers are essential for understanding the pathophysiological changes linked to prediabetes, and how they affect senescence [40]. Several important biomarkers have emerged in the context of changes in plasma biochemistry, providing insight into the biochemical dysregulations that underlie accelerated aging and age-related vascular dynamics [41].

2.3.1. Telomere Length

Genomic stability depends on telomeres, which are protective caps that sit at the ends of chromosomes [42]. Since telomere shortening is a sign of cellular aging and senescence, their length is a crucial factor in determining cellular lifespan [43]. Telomere shortening occurs at a significantly faster rate in prediabetes, a disorder characterized by oxidative stress, low-grade inflammation, and chronic metabolic disruptions [44]. These environmental factors, frequently associated with prediabetes, hasten the attrition of telomeres [45]. Telomere length thus functions as a biomarker reflecting the accelerated aging of cells in prediabetic subjects. This phenomenon has broader implications because, in addition to indicating cellular aging, short telomeres also contribute to the general senescence observed in prediabetic people [44]. Deciphering the complex interplay between prediabetes and accelerated senescence, which will illuminate the molecular mechanisms underlying this condition's effects on aging and age-related illnesses, requires an understanding of the dynamics of telomere length.

2.3.2. p16INK4a

In the context of cellular senescence, p16INK4a functions as a critical regulator. This biomarker regulates senescence-related irreversible cell growth arrest, functioning as a sentinel [46]. The expression of p16INK4a is generally higher and more prominent in prediabetic than in non-prediabetic individuals [47]. This upregulation, which is a result of the inflammatory and metabolic environment linked to prediabetes, indicates a higher frequency of senescent cells [48]. The high frequency of p16INK4a expression in prediabetics highlights the harmful effects of this metabolic disorder on the integrity of cells [49]. A state of cellular stress and dysfunction, indicated by elevated p16INK4a levels, is linked to prediabetic individuals' age-related health conditions, as well as the general aging process [50]. The function of p16INK4a is crucial for unravelling the connection between prediabetes and cellular senescence, providing insights into the molecular processes that underpin the condition's impact on the aging process [51].

2.3.3. Senescence-Associated Secretory Phenotype (SASP) Factors

SASP is a broad category of substances secreted by senescent cells, which includes growth factors chemokine and proinflammatory cytokines [52]. These elements have a significant impact on nearby cells and tissues and the microenvironment in which senescent cells are located [52]. Chronic low-grade inflammation, a characteristic feature of prediabetes, primarily drives the production of SASP factors [53]. Consequently, increased blood levels of SASP factors are linked to prediabetes [54]. These biomarkers demonstrate how senescent cells actively promote inflammation and modify plasma biochemistry [55]. Elevated SASP factor levels in prediabetes serve as indicators of the role of senescence in systemic changes in plasma biochemistry and the overall inflammatory milieu [56]. The senescence process in prediabetes and its consequences for age-related health conditions are further complicated by the interaction between senescence and inflammation, which is reflected by SASP factors [57]. The functions of SASP factors in modifications to plasma biochemistry are essential for clarifying how prediabetes hastens senescence and influences aging [58].

2.3.4. DNA Methylation Clocks

Epigenetic modifications, specifically DNA methylation, are essential for controlling gene expression and are crucial in the aging process [59]. DNA methylation clocks have become useful biomarkers for determining the rate of aging because they quantify the epigenetic age of cells or tissues [60]. These epigenetic clocks frequently exhibit an accelerated aging pattern in the context of prediabetes [60]. Metabolic and oxidative stress linked to prediabetes disrupts DNA methylation patterns, explaining the acceleration of this process [61]. As a result, prediabetic individuals show changes in their epigenetic landscape that correspond to an older biological age [60]. These biomarkers provide important clues about the epigenetic modifications that accelerate senescence in prediabetes, and shed light on the underlying mechanisms and consequences of age-related disorders [62].

2.3.5. Advanced Glycation End Products (AGEs)

Advanced glycation end products, commonly known as AGEs, serve as critical biomarkers in prediabetes-induced senescence [63]. Prediabetes is often associated with elevated levels of AGEs, which stem from the persistent hyperglycemia and oxidative stress characteristic of the condition [19]. AGEs are formed through a non-enzymatic reaction between sugars and proteins, and their accumulation is indicative of glycation and oxidative damage [64]. In prediabetes, the heightened levels of AGEs underscore the accelerated aging of tissues and systems, with profound implications for age-related complications [65]. These biomarkers reflect the complex biochemical changes that drive senescence, and contribute to age-related alterations in vascular dynamics and other physiological processes [66]. The functions of DNA methylation clocks are crucial for clarifying the ways in

which prediabetes affects the epigenetic control of aging and its wider consequences for health conditions associated with aging [67].

3. Circulating Hormones and Growth Factors Associated with Aging in Prediabetes

3.1. Hormonal Shifts in Prediabetes and Their Influence on Senescence

A complex interplay of hormonal changes with significant implications for the senescence process characterizes prediabetes [25]. An interruption in the insulin-like growth factor (IGF) axis is one of the primary hormonal changes linked to prediabetes [68]. Changes in the levels and bioavailability of insulin-like growth factor 1 (IGF-1), a hormone essential for tissue repair, cell growth, and differentiation, are frequently observed in prediabetic individuals [69]. Insulin resistance, a defining feature of prediabetes, can hinder IGF-1 signaling and exacerbate systemic metabolic abnormalities [70]. This disturbance of the IGF axis causes the accelerated aging of cells and is associated with the senescence of different tissues, which affects the ability of tissues to regenerate and their overall physiological function [71]. Furthermore, prediabetics have different hormonal profiles for other growth factors, such as brain-derived neurotrophic factor (BDNF), which is important for neuronal health and cognitive function [72]. Particularly in older adults, altered BDNF levels in prediabetes patients can have an impact on cognitive health [73]. The complex relationships between hormonal changes in prediabetes and their effects on aging are highlighted by disruptions in BDNF signaling, which can cause cognitive decline and intensify the senescence process [74].

Moreover, changes in leptin and adiponectin, which are secreted by adipose tissue, are part of the hormonal landscape of prediabetes [75]. Lower levels of adiponectin, a hormone that has anti-inflammatory and insulin-sensitizing qualities, are frequently observed in prediabetic people [76]. Decreased levels of adiponectin can exacerbate aging-related metabolic alterations and insulin resistance [77]. However, because of modifications in adipose tissue, prediabetes is also associated with changes in leptin, a hormone involved in appetite regulation and energy expenditure [21]. These changes in hormones can affect body weight, metabolism, and general health, which can further accelerate the aging process [78]. Deciphering the complex hormonal changes associated with prediabetes and how they affect senescence is essential to understand the wider effects of metabolic conditions on aging and age-related health issues [79].

3.2. Growth Factors and Their Role in Age-Associated Processes

Growth factors play a particularly important role in prediabetes-induced senescence [63]. Growth factors are essential for the coordination of several physiological processes. Examples of these include vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and insulin-like growth factor-binding proteins (IGFBPs) [80]. The hormonal milieu in prediabetic individuals frequently involves changes in the IGF-1 and IGFBP system [81]. These alterations affect tissue healing, cell division, and growth, and are intimately related to insulin resistance and metabolic dysregulation [82]. The IGF-1 signaling axis is disrupted, which speeds up senescence and reduces the ability of cells and tissues to regenerate [83]. Moreover, prediabetes is associated with alterations in VEGF levels, which are crucial regulators of angiogenesis and vascular homeostasis [84]. Changes in VEGF levels can affect tissue perfusion and vascular dynamics, which can lead to age-related vascular alterations that are frequently observed in people with prediabetes [85].

Clarifying the intricate interactions between hormonal changes and senescence requires an understanding of the roles played by these growth factors in age-related processes [86]. Changes in growth factors, such as bone morphogenetic proteins (BMPs) and brain-derived neurotrophic factor (BDNF), are accompanied by modifications in IGF-1, IGFBPs, and VEGF, which in turn affect different physiological systems [87]. The regulation of cellular growth, tissue repair, angiogenesis, and neuroprotection depends on these growth factors, and their disruption in prediabetes highlights the complex effects of this metabolic disorder on the aging process [88]. Gaining insight into how growth factor dysregulation

in prediabetes affects age-related physiological changes and the emergence of age-related health conditions requires an understanding of the complexities of this condition (see Table 1) [89].

Table 1. Circulating hormones and growth factors associated with aging in prediabetes.

Circulating Indicators of Aging	Dynamics during Aging	Function/Risk Factor	Reasons for the Condition	Lifespan Influence	Ref.
Growth hormone (GH)	Altered levels	Impact on muscle mass and bone density	Insulin resistance	Influence on aging	[90]
Insulin-like growth factor 1	Variations during aging	Regulation of cell growth and repair	Metabolic changes	Potential lifespan influence	[91]
Dehydroepiandrosterone sulphate (DHEA-S)	Decreased levels	Hormonal changes	Prediabetes	Aging effect	[92]
Testosterone (in men)	Changes in aging	Impact on muscle and bone health	Hormonal alterations	Potential influence on the lifespan	[93]
Estrogen (in women)	Hormonal shifts during aging	Effects on bone density and cardiovascular health	Menopause and prediabetes	Aging impact	[94]
Circulating growth factors	Alterations with age	Role in cell growth, repair, and regeneration	Aging process	Lifespan variations	[95]
Brain-derived neurotrophic factor (BDNF)	Age-related changes	Cognitive health in aging	Prediabetes and aging	Potential influence on the lifespan	[96]
Insulin-like growth factor-binding proteins	Age-related alterations	Modulation of IGF-1 effects	Metabolic changes	Aging and lifespan	[97]
Additional factors in aging	Dynamics during aging	Various influences on aging	Prediabetes and aging	Lifespan variations	[98]
Telomere Length	Shortening with age	Cellular aging indicator	Oxidative stress and inflammation	Influence on aging	[99]
p16INK4a	Increased levels with age	Cellular senescence regulator	Prediabetes and aging	Accelerated aging	[100]
Senescence-Associated Secretory Phenotype (SASP) Factors	Elevated levels with age	Impact on inflammation and biochemistry	Chronic inflammation	Aging implications	[101]
DNA methylation clocks	Accelerated aging with age	Epigenetic changes indicator	Metabolic and Oxidative Stress	Influence on aging	[102]
Advanced Glycation End Products (AGEs)	Increased levels with age	Age-related complications indicator	Glycation and oxidative stress	Accelerated aging	[64]
Inflammatory Markers	Elevated with age	Indicators of chronic inflammation	Prediabetes and aging	Aging and inflammation	[103,104]
Oxidative stress markers	Increased with age	Oxidative damage indicators	Prediabetes and aging	Influence on aging	[105]
Red blood cell distribution width (RDW)	Increased with age	Inflammation and metabolic changes	Prediabetes and aging	Influence on aging	[106]
Hemoglobin A1c (HbA1c)	Elevated with age	Impact of hyperglycaemia on tissues and systems	Chronic hyperglycaemia	Aging and diabetes	[107]
Serum Albumin	Decreased with age	Nutritional status indicator	Prediabetes and aging	Influence on aging	[108]

3.3. Role of Biomarkers in Hormonal Changes

3.3.1. Circulating Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1)

Variations in GH and IGF-1 levels are common in prediabetic individuals because of insulin resistance and metabolic changes, which are characteristics of prediabetes [70]. The insulin resistance seen in prediabetes is closely associated with these hormonal alterations, which indicate the endocrine system's influence on the disease and its function in mediating senescence [109].

3.3.2. Dehydroepiandrosterone Sulfate (DHEA-S)

A significant decrease in the levels of the steroid hormone dehydroepiandrosterone sulfate (DHEA-S), which is generated by the adrenal glands, is frequently observed in prediabetic individuals [110]. This hormonal change plays a crucial role in the context of senescence caused by prediabetes because it adds to the range of hormonal aging changes [57]. The synthesis of sex hormones, such as estrogen and testosterone, which are essential for many physiological functions, begins with the production of DHEA-S [111]. The complex relationship between prediabetes and senescence is further highlighted by the decrease in DHEA-S levels in prediabetes, which indicates a significant hormonal shift that affects the aging process [112].

3.3.3. Testosterone (In Men)

Changes in testosterone levels are frequently noted in male prediabetic individuals, affecting various aspects of the aging process [98]. These alterations may significantly affect bone density, muscle mass, and other aging-related factors [98]. The essential male sex hormone testosterone is essential for preserving bone health, muscle mass, and general vigour [113]. The hormonal changes associated with prediabetes underscore the impact of the illness on the endocrine system and its role in determining the course of aging in men.

3.3.4. Oestrogen (In Women)

Changes in estrogen levels in prediabetic women can have a substantial effect on different aspects of aging [114]. These hormonal shifts may have an impact on cardiovascular health, bone density, and many other aging-related factors [114]. The main female sex hormone estrogen has a significant impact on preserving cardiovascular health, bone health, and general well-being [115]. Changes in estrogen levels in people with prediabetes highlight the impact of the disease on the endocrine system and how it affects how women age [116].

4. Age-Associated Inflammatory Factors in Prediabetes

4.1. Inflammatory Mediators in Prediabetes-Induced Senescence

Chronic low-grade inflammation, a hallmark of prediabetes, significantly influences age-associated senescence [117]. A range of inflammatory mediators are prominent in this context. Notably, prediabetic individuals frequently have elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP), and others [19]. These mediators of inflammation play a pivotal role as biomarkers reflecting the chronic inflammatory state associated with prediabetes [19]. For example, CRP is a sensitive indicator of systemic inflammation, and IL-6 is essential for controlling inflammation and immune responses [118]. Their increased risk of prediabetes is an essential component of the disease's pathophysiology, rather than just a side effect [118]. The existence of these inflammatory mediators indicates how chronic inflammation contributes to senescence and how it speeds up aging in prediabetic individuals [119].

Furthermore, there is a strong correlation between prediabetes and elevated oxidative stress, which amplifies the influence of inflammatory mediators on senescence [19]. Reactive oxygen species (ROS) and oxidative damage are caused by the proinflammatory state associated with prediabetes, which is characterized by the release of factors such as tumour necrosis factor-alpha (TNF-α) [120]. These molecular events highlight the complex interplay between oxidative stress and inflammation in prediabetes-induced senescence [121]. Understanding how inflammatory mediators contribute to prediabetes-induced senescence offers important new understandings of the processes that underlie the condition's acceleration of aging and its consequences for age-related medical disorders (see Table 2).

Table 2. Age-associated inflammatory mediators in prediabetes-induced senescence.

Circulating Biomarker	Dynamics during Aging	Function and Risk Factors in Aging	Molecule Longevity Influence	Ref.
Inflammatory Mediators	Changes during aging	Role in chronic inflammation and aging	May influence lifespan	[122]
Pro-inflammatory Cytokines (e.g., IL-6)	Increased levels	Chronic inflammation and aging	May shorten the lifespan	[30,123]
Chemokines (e.g., MCP-1)	Altered dynamics	Recruitment of immune cells and aging	May impact lifespan	[124]
Growth factors (e.g., TGF-β1)	Variation with age	Modulation of cell growth and aging	Influence on the lifespan	[125]
Senescence-Associated Secretory Phenotype (SASP) Factors	Increased with age	Promotion of inflammation and aging	May influence lifespan	[126]
Inflammatory markers (e.g., CRP)	Elevated with age	Indicators of chronic inflammation	May impact lifespan	[56]
Oxidative stress markers (e.g., ROS)	Increased with age	Indicators of oxidative damage	May influence lifespan	[127]
Endothelial markers (e.g., vWF)	Altered dynamics	Indicators of endothelial dysfunction	May impact lifespan	[128]
DNA damage markers (e.g., 8-OHdG)	Increased levels	Indicators of DNA damage and aging	May influence lifespan	[129]
Mitochondrial dysfunction markers (e.g., mtDNA)	Changes during aging	Indicators of impaired mitochondrial function	May impact lifespan	[130]
Immune system biomarkers (e.g., CD4+ T cells)	Altered dynamics	Immune system indicators of aging	May influence lifespan	[56,123]

4.2. Chronic Inflammation and Its Implications for Senescence

In prediabetes, chronic inflammation is at the forefront of age-associated senescence and significantly affects multiple physiological systems [19]. Chronic low-grade inflammation, a feature of prediabetes, largely promotes senescence [117]. In this context, prediabetic individuals frequently have elevated levels of various inflammatory mediators, including interleukin-1 beta (IL-1β), interleukin-18 (IL-18), and high-sensitivity C-reactive protein (hs-CRP) [131]. These inflammatory factors are largely responsible for the systemic inflammation that accelerates aging [132]. Pro-inflammatory cytokines that can worsen immune responses and inflammatory pathways include IL-1β and IL-18 [133]. The persistent inflammatory state in prediabetes is reflected in hs-CRP, a sensitive marker of systemic inflammation [134]. The increased levels of these mediators indicate the critical role that chronic inflammation plays in the senescence brought on by prediabetes, which impacts multiple physiological systems and hastens age-related health issues [135].

Moreover, oxidative stress and the inflammatory milieu in prediabetes are tightly linked, which further complicates the senescence process [136]. Tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators in prediabetes frequently contribute to the production of reactive oxygen species (ROS) and oxidative damage [120]. These molecular interactions increase the level of oxidative stress in prediabetic individuals, which strengthens the influence of chronic inflammation on aging [19]. The interaction between oxidative stress and inflammation highlights the complex processes underlying the senescence observed in prediabetes [137]. It also emphasizes the necessity of investigating therapeutic approaches that address oxidative stress and inflammation to lessen the effects of prediabetes on age-related health issues and premature aging [138].

4.3. Role of Biomarkers in Inflammatory Factors
4.3.1. Senescence-Associated Secretory Phenotype (SASP) Factors

Higher than normal levels of SASP factors, a set of secreted factors linked to senescent cells, are frequently observed in prediabetic individuals [139]. The chronic inflammation frequently seen in prediabetes is the cause of this increase in SASP factors [140]. SASP

factors are important indicators that highlight the proactive function of senescent cells in promoting inflammation and modifying the inflammatory environment in people with prediabetes [141].

4.3.2. Inflammatory Markers

Elevated levels of well-known inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), are frequently used to diagnose prediabetes [142]. These markers indicate the presence of the low-grade chronic inflammation commonly observed in prediabetic patients [19]. A sensitive indicator of systemic inflammation, CRP, captures the persistent proinflammatory milieu linked to prediabetes [143]. Similarly, IL-6, an important modulator of inflammation and immune responses, is crucial in mediating the inflammatory processes associated with prediabetes [144]. These inflammatory markers demonstrate the active role that chronic inflammation plays in determining the course of senescence and its role in the accelerated aging observed in prediabetic individuals. The mechanisms underlying senescence in prediabetes and its implications for age-related health conditions are clarified by these markers, which also serve as important indicators of inflammation.

5. Vascular and Neural System Aging in Patients with Prediabetes

5.1. Prediabetes-Induced Vascular Changes and Senescence

Prediabetes has a major impact on the vascular system's aging process, initiating a series of alterations that greatly accelerate senescence [145]. The accelerated progression of atherosclerosis and endothelial dysfunction are two of the main characteristics of vascular aging in prediabetes [146]. Specifically, endothelial dysfunction is a major factor in aging because it indicates a decline in the endothelium's ability to control vascular tone, preserve homeostasis, and avoid blood clot formation [147]. Chronic hyperglycemia and inflammation cause endothelial dysfunction in prediabetic patients, which speeds up vascular senescence [19]. The existence of these vascular alterations highlights the complex interplay among prediabetes, endothelial dysfunction, and senescence, underscoring the diverse effects of prediabetes on the aging process of the vascular system [148].

Moreover, age-related changes in prediabetes can also affect the neural system, which is intricately linked to the vascular system [85]. The illness affects overall neurological health and cognitive function by accelerating neural senescence [85]. A common feature of aging is cognitive decline, which is more likely to occur in people with prediabetes [149]. Vascular alterations associated with prediabetes, such as decreased cerebral blood flow and microvascular dysfunction, contribute to neurodegenerative processes. Together, these elements cause the aging of neural tissue to occur more quickly (see Table 3) [150]. Deciphering the connection between vascular alterations caused by prediabetes and their consequences for the aging of the neural system is essential to understand the larger influence of this metabolic disorder on aging and its consequences for neurological and cognitive health [151].

Table 3. Biomarkers of prediabetes-induced vascular and neural system aging.

Biomarker	Role in Aging	Implications for Senescence	Ref.
Telomere length	Reflects cellular aging and senescence	Accelerated aging and cellular senescence	[152]
p16INK4a	Regulates cellular senescence	Increased cellular senescence	[153]
Senescence-associated secretory phenotype (SASP) Factors	Reflect senescent cell secretions	Promote inflammation and senescence	[154]
DNA methylation clocks	Epigenetic aging indicators	Accelerated epigenetic aging	[155]
Advanced glycation end products (AGEs)	Reflect glycation and oxidative stress	Contributions to accelerated aging and age-related complications	[156]

Table 3. *Cont.*

Biomarker	Role in Aging	Implications for Senescence	Ref.
Inflammatory markers	Indicators of inflammation	Contributions to inflammation associated with aging	[157]
Oxidative stress markers	Indicators of oxidative damage and stress	Exacerbation of age-related oxidative damage	[156]
Endothelial dysfunction	Indicators of vascular dysfunction	Exacerbation of endothelial dysfunction and impact on vascular health	[158]
Mitochondrial dysfunction	Reflect mitochondrial function and health	Impairment of mitochondrial function associated with aging	[159]
Red blood cell distribution width (RDW)	Reflect changes in erythrocytes	Indicate inflammation and metabolic changes affecting aging	[160]
Haemoglobin A1c (HbA1c)	Reflects long-term blood glucose levels	Accelerating aging due to chronic hyperglycaemia	[161]
Serum albumin	Reflects nutritional status and frailty	Affecting nutritional status and frailty	[159]
Circulating Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1)	Reflect hormonal changes	Influence of insulin resistance and metabolic changes	[162]
DHEA-S	Reflects hormonal changes	Contributions to hormonal changes associated with aging	[163]
Testosterone (in men)	Reflects hormonal changes in men	Impact of muscle mass, bone density, and aging	[63,164]
Estrogen (in women)	Reflects hormonal changes in women	Affects bone density, cardiovascular health, and aging	[165]
Brain-derived neurotrophic factor (BDNF)	Reflects changes in neurotrophic factors	Influence on cognitive health, particularly in aging	[156]
IGF-binding proteins	Reflect changes in IGF-1 bioavailability	Contributions to metabolic and aging-related effects	[166]
Folate and B12 levels	Reflect nutritional deficiencies	Impact of DNA methylation and repair essential for aging	[167]
Osteocalcin	Reflect changes in bone health	Affecting bone health, a key consideration in aging	[168]
Adiponectin	Reflects changes in metabolic health	Impact of insulin resistance and metabolic changes	[167]
Leptin	Reflects changes in adipose tissue	Impact of metabolism and aging	[155]
Homocysteine	Reflects cardiovascular risk	Maybe more prevalent in prediabetic individuals	[156,169]
Insulin resistance markers	Reflect insulin resistance	May worsen with age in prediabetic individuals	[170,171]

5.2. Neural System Aging and Cognitive Implications in Prediabetes

Prediabetes affects not only the aging of the vascular system, but also the aging of the neural system, which has important implications for cognition [172]. An inevitable aspect of aging is cognitive decline, which is more likely to occur early in prediabetic people [173]. Vascular changes linked to prediabetes are intimately linked to neurodegenerative changes that are observed in the condition [174]. Through processes such as decreased cerebral blood flow and microvascular dysfunction, chronic hyperglycemia and inflammation in prediabetes directly affect neural tissue. Together, these elements cause the aging of neural tissue to occur more quickly [175]. Prediabetic individuals exhibit more severe cognitive

deficits, especially in areas linked to memory, executive function, and information processing speed [172]. Gaining an appreciation of the full impact of this metabolic condition on aging and cognitive health requires an understanding of the relationship between prediabetes-induced neural system aging and its cognitive implications [176].

Furthermore, prediabetes can impact neural senescence through pathways involving oxidative stress, inflammation, and metabolic alterations [137]. Neuroinflammation, a defining feature of neurodegenerative diseases such as Alzheimer's disease, can result from these processes [137]. Proinflammatory mediators in the central nervous system, activated by chronic inflammation and oxidative stress in prediabetes, exacerbate neural senescence [177]. The complex interactions among these variables highlight the significance of treating cognitive health in people with prediabetes and creating plans to lessen the effects of neural system aging on cognition [178].

5.3. Role of Biomarkers in Vascular and Neural Aging

5.3.1. Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are important biomarkers in the context of vascular and neural system aging in prediabetes [179]. Elevated levels of AGEs are a common feature of prediabetes and have significant implications for the development of age-related complications and the acceleration of aging [85]. A class of molecules known as AGEs is produced when proteins and lipids undergo non-enzymatic glycation and oxidation. The increased production and accumulation of AGEs is a result of prediabetes' chronic hyperglycemia and oxidative stress [179]. These molecules actively contribute to the vascular and neural system aging observed in prediabetic individuals, in addition to reflecting the biochemical changes that drive senescence [7]. The increased levels of AGEs in prediabetes indicate that this biomarker plays a crucial role in determining the course of aging, emphasizing the significance of addressing AGEs-related mechanisms so as to lessen the effects of prediabetes on the brain and vascular systems.

5.3.2. Endothelial Dysfunction

The vascular system ages significantly because of prediabetes, and endothelial dysfunction is emerging as a critical biomarker [180]. A common feature of vascular aging is endothelial dysfunction, which is worsened by this condition [180]. Endothelial cells are essential for controlling blood flow and preserving vascular homeostasis [181]. Chronic inflammation and hyperglycemia aggravate endothelial dysfunction in prediabetic individuals, indicating a crucial phase of vascular senescence [19]. A more noticeable effect on endothelial markers, such as von Willebrand factor (vWF), a vital mediator of blood clotting and vascular health, is linked to endothelial dysfunction [182]. To lessen the effects of aging on prediabetic people, it is important to address endothelial markers, as the existence of endothelial dysfunction in the condition highlights the complex relationship between vascular aging and prediabetes [183].

6. Systemic Inflammation in Prediabetes

6.1. Link between Prediabetes and Systemic Inflammation

The long-term, low-grade inflammation associated with aging is markedly worsened in prediabetic patients, resulting in a complex interaction between the metabolic disorder and aging [56]. Prediabetes, via various interrelated mechanisms, plays a major role in the promotion of inflammation [19]. The enduring proinflammatory condition associated with prediabetes, which is fuelled by oxidative stress and chronic hyperglycemia, is crucial to this connection [184]. Systemic inflammation is facilitated by these factors, which also activate proinflammatory pathways and release proinflammatory cytokines. Interestingly, elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), and other inflammatory markers are frequently observed in prediabetic individuals, supporting the link between prediabetes and systemic inflammation (see Figure 2) [185]. These inflammation biomarkers show the complex relationship between prediabetes and the accelerated aging process,

which ultimately results in the systemic inflammation seen in this population. They also serve as indicators of the elevated inflammatory state in prediabetic individuals [186].
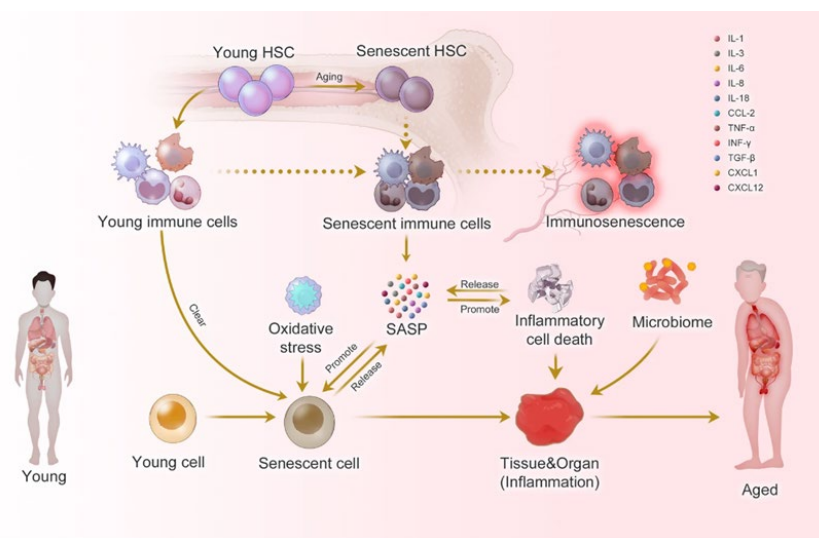

Figure 2. Prediabetes-induced systemic Inflammaging (focusing on immunosenescence, which is immune system aging) as adapted from source and BioRender: Inflammaging at the molecular, cellular, and organ levels. During the aging process, almost all cells in the body undergo senescence, a state characterized by dysfunction and a senescence-associated secretory phenotype (SASP). SASP affects immune cells, impairing their ability to recognize and eliminate senescent cells, thereby contributing to immunosenescence. Immunosenescence can impair the immune response to infections and diseases, making the organism more vulnerable to illnesses. Moreover, the accumulation of senescent cells can trigger inflammation in organs, leading to organ damage and an increased risk of age-related diseases. This process is intensified by positive feedback loops that drive the accumulation of inflammation and organ damage, leading to further inflammation and an even higher risk of aging-related diseases [30].

Prediabetes also affects the endocrine system, causing hormonal changes that feed inflammation, which further contributes to systemic inflammation [78]. For example, prediabetes is frequently associated with altered levels of adipokines, such as adiponectin and leptin, which promote a proinflammatory milieu [187]. This hormonal imbalance also intensifies inflammation by affecting the delicate balance between pro- and anti-inflammatory components of the body [188]. The complex interaction of inflammatory markers, hormonal changes, and prediabetes highlights the complexity of systemic inflammation in this metabolic condition [189]. The connection between prediabetes and systemic inflammation is crucial in understanding the wider influence of this illness on the aging process and its consequences for health issues associated with aging.

6.2. Inflammatory Factors and Their Contribution to Senescence

Chronic inflammation, a hallmark of systemic inflammation in prediabetes, largely contributes to the aging of various physiological systems [190]. Several important inflammatory markers, including interleukin-6 (IL-6) and C-reactive protein (CRP), are frequently elevated in prediabetics. These markers indicate a chronic proinflammatory condition that accelerates aging by substantially contributing to senescence [19]. A sensitive measure of systemic inflammation, CRP is a good way to determine whether prediabetes is still linked to a proinflammatory state [28]. Similarly, IL-6 plays a major role in coordinating the inflammatory processes associated with prediabetes. It is a central regulator of immune responses and inflammation [191]. The existence of these inflammatory markers emphasizes the crucial role they play in encouraging senescence and the faster aging seen in prediabetic people.

Moreover, oxidative stress, which increases the effect of inflammatory factors on senescence, is intimately linked to chronic inflammation in prediabetes [119]. Reactive oxygen species (ROS) and oxidative damage are fostered by the proinflammatory state associated with prediabetes, which is marked by the release of factors such as Tumor necrosis factor-alpha (TNF-α) [192]. These molecular events highlight the complex interplay between oxidative stress and inflammation in driving senescence induced by prediabetes [192]. The coexistence of oxidative stress and chronic inflammation in prediabetes, as well as their combined effect on senescence, provide a thorough understanding of the mechanisms through which the condition speeds up aging, and emphasize the significance of treating inflammation in prediabetic individuals to manage age-related health conditions.

6.3. Role of Biomarkers in Systemic Inflammation
6.3.1. Inflammatory Markers (Continued)

Interleukin-6 (IL-6) and C-reactive protein (CRP) are two inflammatory markers that play a significant role in the context of systemic inflammation in prediabetes [193]. Elevated levels of these inflammatory markers are often associated with prediabetes, indicating a persistent proinflammatory state that is commonly seen in prediabetes [19]. As a sensitive measure of systemic inflammation, CRP is an important window into the persistent proinflammatory environment linked to prediabetes [194]. Similarly, IL-6, an important modulator of inflammation and immune responses, is crucial in mediating the inflammatory processes associated with prediabetes [19]. These inflammatory markers are important markers of inflammation and play a major role in the chronic inflammation that occurs with aging in people with prediabetes [137]. Understanding the mechanisms by which prediabetes accelerates systemic inflammation and its implications for age-related health conditions depends on the identification of these biomarkers.

6.3.2. Oxidative Stress Markers

The role of elevated oxidative stress in the context of systemic inflammation in prediabetes cannot be underestimated [195]. Elevated oxidative stress is frequently linked to prediabetes, which can worsen the age-related rise in reactive oxygen species (ROS) and oxidative damage [137]. Oxidative stress is closely associated with the chronic proinflammatory state that characterizes prediabetes, which fosters the production of reactive oxygen species (ROS) and subsequent oxidative damage [196]. The intricate relationship between prediabetes, inflammation, and oxidative stress is highlighted by the presence of oxidative stress markers, which further highlights the complex web of factors that contribute to systemic inflammation [197]. Understanding the wider effects of prediabetes on aging and its consequences for age-related health issues, especially considering systemic inflammation, requires an understanding of the role of oxidative stress markers in this metabolic condition [198].

Furthermore, the immune system's inflammatory reactions are triggered by the interaction of advanced glycation end products (AGE) and their associated Receptor for AGEs (RAGE) [199,200]. The non-enzymatic glycation of proteins, lipids, and nucleic acids produces AGEs, which attach to RAGE and start signaling cascades, which lead to inflammation and oxidative stress [200]. Tissue damage and dysfunction are the consequences of this interaction, which induces the release of pro-inflammatory cytokines and chemokines. With potential benefits for reducing age-related disorders and fostering healthy aging, targeting the AGE–RAGE axis has emerged as a viable therapeutic approach for preventing senescence and inflammation carried on by AGEs [201]. A particular strategy for tackling the harmful consequences of aging and age-related diseases is the use of therapeutic interventions targeted at AGE–RAGE signaling disruption [202]. These interventions have the potential to reduce inflammation and maintain tissue homeostasis.

7. Regeneration and Metabolic Disorders in Prediabetes

7.1. Impaired Regeneration Mechanisms in Patients with Prediabetes

The body's ability to regenerate itself is greatly impacted by prediabetes, and this ability is crucial for preserving tissue integrity and fending off the consequences of aging [203]. Several variables, such as oxidative stress, metabolic dysregulation, and chronic inflammation, are associated with impaired regeneration mechanisms in prediabetes [136]. Chronic inflammation, a hallmark of prediabetes, hampers the body's ability to initiate and sustain regenerative processes [204]. Inflammatory mediators that are activated during a persistent proinflammatory state obstruct the body's regenerative processes, especially regarding tissue repair and cellular turnover [205]. Prediabetic individuals may encounter delayed wound healing and compromised tissue regeneration, particularly in tissues with a high cellular turnover rate, such as the skin and the lining of the gastrointestinal tract. This hindrance to regeneration predominantly affects these tissues [206]. Understanding prediabetes' effects on aging and its consequences for age-related health conditions requires an understanding of the interaction between inflammation and regeneration brought on by the condition [204].

Metabolic dysregulation in prediabetes further compounds the impairment of regeneration mechanisms. A defining feature of prediabetes is insulin resistance, which impairs the body's capacity to use glucose effectively for cellular upkeep and energy production. Because glucose is a necessary fuel for many regenerative mechanisms, such as tissue repair and cell proliferation, this metabolic disruption has a negative impact on the regenerative processes [204–206]. Cellular energy deficiencies impair the body's capacity to mount a strong regenerative response in prediabetes, which is one of the factors contributing to the impaired regeneration seen in prediabetic patients [206]. Gaining an appreciation of the complete influence of prediabetes on the aging process and its consequences for age-related health complications requires an understanding of the connection between impaired regeneration, prediabetes, and related metabolic disorders.

7.2. Metabolic Disorders and Their Impact on Senescence

Prediabetes, a metabolic condition characterized by insulin resistance and dysregulated glucose metabolism, significantly impacts senescence and the body's ability to regenerate itself [119]. One characteristic that sets prediabetes apart is insulin resistance, which impairs the cells' abilities to absorb glucose [136]. The main energy source for cellular processes, including regeneration, is glucose [207]. Metabolic abnormalities in prediabetic people make it difficult for glucose to be used efficiently, upsetting the energy balance required for regenerative processes [208]. This metabolic dysregulation impairs the body's capacity for effective tissue regeneration and repair, which in turn adds to the general senescence observed in prediabetic patients [89]. The complex relationship between senescence and metabolic disorders highlights how critical it is to address metabolic factors in order to lessen the effects of prediabetes on aging.

Moreover, mitochondrial dysfunction, a major contributor to aging, is closely linked to metabolic disorders in prediabetes [209]. Impaired insulin signaling and elevated oxidative stress have a deleterious effect on prediabetic mitochondria, which are the cellular powerhouses in charge of producing energy [196]. Because these mitochondrial disruptions reduce the cell's ability to produce energy for regenerative processes, they worsen cellular aging and senescence [196]. The interplay between metabolic disorders, mitochondrial dysfunction, and senescence highlights the complex mechanisms by which prediabetes accelerates the aging process (see Figure 3) [210]. This underscores the importance of addressing metabolic factors to manage age-related health conditions in prediabetic individuals [210]. Comprehending how metabolic disorders contribute to prediabetes-induced senescence is essential for understanding how this metabolic condition affects aging in general, and what that means for age-related health complications.
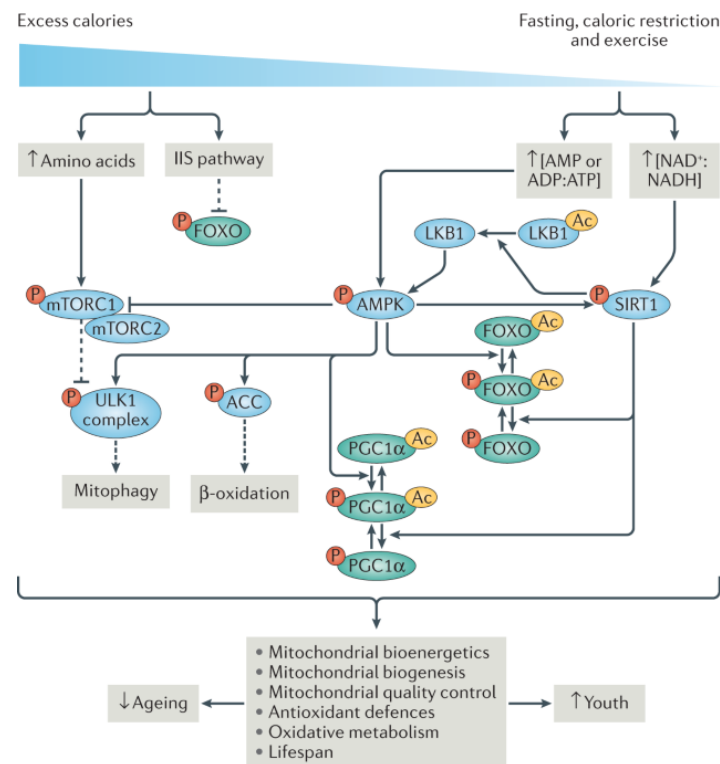
Figure 3. Prediabetes-induced metabolic aging as adapted from source: Signaling pathways linked to longevity govern the maintenance of mitochondrial health. Restricting caloric intake lowers the levels of glucose, amino acids, and lipids, while simultaneously increasing the concentrations of crucial metabolites like NAD+ and AMP. These metabolites play pivotal roles in regulating metabolic sensors such as SIRTs, AMPK, TOR, and insulin–IGF1 signaling pathways. Subsequently, downstream of these metabolic sensors, transcription factors like FOXO and PGC1α coordinate mitochondrial function and equilibrium. Disruption of this intricate regulatory network compromises mitochondrial homeostasis, leading to susceptibility to frailty and various diseases. Noteworthy components of this system include acetyl groups (Ac), acetyl-CoA carboxylase (ACC), liver kinase B1 (LKB1), and UNC51-like kinase 1 (ULK1) [130].

7.2.1. Mitochondrial Dysfunction

Mitochondria are cellular powerhouses responsible for energy production, and their proper functioning is essential for various cellular processes, including regeneration [211]. However, in prediabetes, insulin resistance and metabolic alterations lead to disturbances in mitochondrial function, which manifest as decreased mitochondrial efficiency and increased oxidative stress [212]. The compromised mitochondrial function associated with prediabetes not only affects cellular energy production and exacerbates aging and senescence in prediabetic individuals [213]; mitochondrial dysfunction is also a critical biomarker associated with metabolic changes in prediabetes.

7.2.2. Red Blood Cell Distribution Width (RDW)

Increased red blood cell distribution width (RDW) is a common biomarker of prediabetes, reflecting the condition's associated inflammation and metabolic abnormalities [214]. Red blood cell width variation is a measure of underlying inflammation and metabolic disturbances. These conditions are suggested by an increase in RDW [215]. When elevated RDW is observed in prediabetic patients, it indicates systemic inflammation and metabolic changes that impact aging [216]. The association between RDW, inflammation, and metabolic alterations highlights the necessity of addressing these factors to reduce the risk of age-related health complications in prediabetic individuals [217].

7.2.3. Hemoglobin A1c (HbA1c)

Elevated HbA1c levels in prediabetes can significantly affect how people age [218]. Higher HbA1c values indicate chronic hyperglycemia, whereas lower levels indicate average blood glucose levels over an extended period [219]. In prediabetic people, long-term exposure to high blood sugar levels can hasten the aging process by impacting multiple organs and systems [88]. Advanced glycation end products (AGEs), which can harm proteins and lipids and result in tissue dysfunction, are formed in part by chronic hyperglycemia [88,219]. Because of the critical role that glycation-induced damage plays in the aging of organs and tissues, HbA1c is an important biomarker for understanding how prediabetes affects age-related health conditions, especially regarding diabetes-related aging.

7.2.4. Serum Albumin

Serum albumin levels, a biomarker of nutritional status, may be lower in prediabetic individuals [220]. A drop in serum albumin levels may impact frailty and nutritional deficits [221]. The protein albumin is necessary to keep the colloid osmotic pressure constant and to carry vital nutrients throughout the bloodstream [222]. Reduced serum albumin levels in prediabetes patients may indicate insufficient dietary intake or poor nutrient absorption, which can lead to nutritional deficiencies [223]. These dietary deficits, especially in important vitamins and minerals, can worsen age-related health problems [224]. In addition, decreased serum albumin levels have been linked to frailty in the elderly, which makes this biomarker an important one for assessing the possibility of frailty in people with prediabetes [221]. To effectively manage age-related health complications in this population, it is essential to comprehend the relationship between prediabetes, lower serum albumin levels, and their implications for nutritional status and frailty [225].

7.2.5. Folate and B12

Deficits in certain nutrients, especially folate and vitamin B12, can have a major impact on the metabolic alterations linked to prediabetes [226]. These deficiencies directly impact the processes of DNA methylation and repair, which are crucial for preserving genomic stability and controlling aging [227]. The prevalence of these nutritional deficiencies can be higher in prediabetic individuals, which can accelerate aging [228]. The correct operation of enzymes involved in DNA methylation, a process that regulates gene expression and controls cellular functions, depends on folate and vitamin B12 [225]. Dysregulated DNA methylation can impact aging-related gene expression patterns when it is insufficient [229,230]. Deducing the complete effects of this metabolic condition on aging and its implications for age-related health complications requires an understanding of the role that folate and vitamin B12 deficiencies play in prediabetes-induced metabolic changes and their impact on senescence.

7.2.6. Osteocalcin

Changes in osteocalcin levels are a sign of prediabetes and a biomarker of bone health [231]. Osteoblasts, the cells that form bones, produce a protein called osteocalcin [232]. These changes in osteocalcin levels in prediabetic people have consequences for bone health, which is important for aging people [233]. Osteocalcin is essential for preserving the strength and density of bones [234]. Variations in its concentrations can affect bone turnover and, in turn, bone quality. This change in osteocalcin levels may result in decreased bone mineralization and density, which could put older people at higher risk for fractures and other bone-related problems [235]. It is critical to comprehend the relationship between osteocalcin levels and prediabetes to develop risk-reduction strategies and to comprehend the possible effects on bone health as we age [236].

7.2.7. Adiponectin

Reduced levels of adiponectin, an adipokine with important metabolic and anti-inflammatory properties, can aggravate insulin resistance and age-related metabolic changes in prediabetes [237]. The main function of the protein hormone adiponectin, which is se-

creted by adipose tissue, is to control the metabolism of fats and carbohydrates [238]. These metabolic processes can be disrupted by decreased adiponectin levels in prediabetes, especially regarding the body's inability to properly use insulin, which eventually results in insulin resistance [70]. One of the main causes of aging-related metabolic alterations is deteriorating insulin resistance [239]. Therefore, comprehending the mechanisms underlying metabolic alterations and their implications for age-related health conditions requires an understanding of the relationship between prediabetes and adiponectin levels [240].

7.2.8. Leptin

Because of changes in adipose tissue, prediabetics may have altered leptin levels, which can ultimately impact metabolism and aging [241]. The hormone leptin, which is mostly produced by adipocytes, is essential for controlling metabolism and hunger [242]. These changes in leptin levels in prediabetes can have far-reaching effects [243]. Leptin resistance or decreased sensitivity to leptin may arise from abnormalities in leptin signaling caused by alterations in adipose tissue [244]. Overeating, weight gain, and an unbalanced energy intake are all associated with leptin resistance, and can aggravate metabolic changes and hasten the aging process [78]. Addressing the underlying mechanisms of age-related health issues in prediabetic individuals requires an understanding of the complex relationship between prediabetes, altered leptin levels, and their impact on metabolism and aging [245].

7.2.9. Brain-Derived Neurotrophic Factor (BDNF)

In older adults, altered BDNF levels in prediabetes can have a major impact on cognitive health [246]. A protein called BDNF is essential for the development, upkeep, and plasticity of brain neurons [247]. Changes in BDNF levels in prediabetes patients may impact cognitive function [248]. A higher risk of neurodegenerative diseases and cognitive decline has been linked to decreased BDNF levels [249]. A key component of aging is cognitive health, and abnormalities in BDNF levels can affect memory, learning, and other cognitive processes [250]. Understanding the possible effects on cognitive health in the context of aging and creating strategies to support cognitive well-being in prediabetic individuals require an understanding of the relationship between prediabetes and altered BDNF levels [251].

7.2.10. IGF-Binding Proteins

Metabolic and aging-related effects can be attributed to changes in IGF-binding proteins (IGFBPs) in prediabetes, which can have a major effect on the bioavailability of insulin-like growth factor 1 (IGF-1) [252]. IGFBPs play a crucial role in controlling the availability of IGF-1, a growth factor that is important for metabolism, cell division, and growth. Changes in IGFBPs in prediabetes can affect IGF-1 binding and release, which may affect its signaling pathways [253]. Variations in IGF-1 bioavailability can affect metabolic regulation and tissue maintenance, among other physiological processes [254]. Understanding the relationship between prediabetes and IGFBPs is crucial to understanding the mechanisms underlying the effects related to metabolism and aging in this population [88]. Understanding IGFBPs' function in the context of prediabetes offers valuable information about possible treatment targets for reducing the age-related effects of this illness.

7.2.11. Homocysteine

An amino acid called homocysteine, which is involved in many metabolic processes, has been linked to an increased risk of cardiovascular disease, and may be more common in prediabetic individuals [255]. It is well recognized that homocysteine contributes to the development of atherosclerosis and other cardiovascular diseases [256]. Metabolic abnormalities and changes in folate and vitamin B12 levels can cause elevated homocysteine levels in prediabetes [255]. This homocysteine increase can intensify oxidative stress and endothelial dysfunction, two conditions that hasten the vascular system's aging process [256]. Recognizing the age-related implications of prediabetes, especially regarding the vascular

system, requires an understanding of the relationship between elevated homocysteine levels, cardiovascular risk, and the condition [257].

7.2.12. Insulin Resistance Markers

One of the hallmarks of prediabetes is elevated insulin resistance markers, which can worsen with age [258]. One such marker is the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [258]. One of the main features of prediabetes is insulin resistance, which is typified by the body's decreased sensitivity to the insulin hormone. Insulin resistance markers are frequently elevated in prediabetic individuals, indicating a compromised ability of cells to effectively absorb glucose [259]. Insulin resistance can progress more quickly in older people [260]. The deterioration of insulin resistance is a major factor in the age- and metabolic-related consequences of prediabetes [261]. Inferring the complete impact of prediabetes on the aging process requires an understanding of the role of insulin resistance markers and their potential to intensify age-related metabolic changes.

7.2.13. N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP)

NT-proBNP is produced in the body as a byproduct of BNP breakdown, and functions as a precursor to BNP [262]. The level of NT-proBNP found in the blood is a good indicator of how heart-related diseases, such as heart failure and increased cardiac strain, are developing [262,263]. In clinical contexts, this biomarker is crucial since it provides insightful information for prognostic and diagnostic assessments of cardiovascular diseases [263]. NT-proBNP is a vital tool that helps with the early diagnosis and treatment of heart failure, especially in high-risk populations including the elderly and those with diabetes [264]. It should be noted that decreased renal function and the natural aging process can also cause elevated NT-proBNP levels. The steady increase in NT-proBNP levels in the bloodstream throughout life is acknowledged as a major biological characteristic linked to longer lifespans, emphasizing its potential as a biomarker for evaluating age-related cardiovascular health [265,266]. The breakdown of BNP yields NT-proBNP, which is a dependable marker of increased cardiac strain and the advancement of heart disorders, including heart failure. Its usefulness extends to diagnostic and prognostic assessments, where it is extremely beneficial for the early diagnosis and efficient management of cardiovascular diseases, particularly in susceptible groups such as the elderly and those with diabetes [267]. Additionally, the correlation between increased levels of NT-proBNP and aging and reduced renal function highlights its wider significance in evaluating cardiovascular health in a variety of demographic contexts. The slow increase in circulation levels of NT-proBNP over time indicates a significant biological trait associated with longer life expectancy, highlighting its utility as a biomarker for evaluating cardiovascular health related to aging [268].

7.3. The Negative Effects of Senescence and Pre-Diabetes on Renal Function and Association with Early Stages of Chronic Kidney Disease

Senescence, the physiological aging process, and pre-diabetes, a metabolic condition that occurs before the onset of type 2 diabetes mellitus (T2DM), have deleterious impacts on renal function, and may be involved in the development of chronic kidney disease (CKD) in its early stages [269,270]. Senescence is a broad term for a variety of molecular and cellular changes that upset the homeostatic equilibrium in the renal microenvironment and cause damage to the kidneys' structure and function. These alterations include extracellular matrix remodeling and cellular senescence, which is defined by irreversible cell cycle arrest, and the secretion of pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) [269–271]. These changes ultimately promote renal fibrosis and impaired renal function. Moreover, senescent cells accumulate in the renal parenchyma over time, exacerbating renal inflammation, oxidative stress, and DNA damage, further compromising renal integrity and function [272].

Additionally, the slight impairment of glucose metabolism in prediabetes sets off a series of pathophysiological pathways that have a deleterious effect on renal function [273]. Renal endothelial dysfunction, glomerular hypertrophy, and the increased renal tubular reabsorption of glucose are caused by chronic hyperglycemia and insulin resistance linked to pre-diabetes [273]. These factors promote a pro-inflammatory and pro-fibrotic environment in the kidneys. These changes not only compromise renal hemodynamics, but also facilitate the onset of tubular and glomerular damage, which establishes the foundation for the initial phases of chronic kidney disease [274]. Moreover, renal injury and dysfunction are further aggravated by prediabetes-induced dyslipidemia, oxidative stress, and the activation of the renin–angiotensin–aldosterone system (RAAS), which increases the likelihood of developing overt type 2 diabetes and severe CKD [275]. To slow the progression of CKD and related comorbidities, early intervention strategies targeting metabolic and aging-related pathways, as well as biomarkers like transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and fibroblast growth factor-23 (FGF-23), are crucial. Together, these factors create an environment that is favorable for renal pathology [276].

8. Perspectives for Future Research

8.1. Gaps in Current Understanding and the Need for Further Research

Although this thorough review clarifies the complex interactions among prediabetes, senescence, and blood-based biomarkers, there are still some unanswered questions that underscore the need for a more in-depth study in the future [277]. First, investigating the temporal correlations between these biomarkers and prediabetes-induced senescence is imperative [12]. Examining whether biomarkers are early markers of prediabetes or if the condition only manifests them as it advances could yield important information for prompt diagnosis and treatment [278]. Furthermore, additional investigation is required to clarify the interplay and possible synergies between these biomarkers [278]. It is crucial to understand how various biomarkers may work together to accelerate age-related diseases and senescence in prediabetic patients. This is an area that requires more research [279].

Furthermore, more research is needed to determine how pharmacological and lifestyle interventions affect blood-based biomarkers of prediabetes-induced senescence [280]. It is crucial to find interventions that can adjust these biomarker levels, delay aging and lower the chance of age-related problems in prediabetic patients [60]. Furthermore, it is an exciting direction for future research to investigate the potential of these biomarkers as therapeutic targets [281]. Creating therapies that directly target the identified biomarkers could provide fresh approaches to improving health outcomes and delaying prediabetes-related senescence [282]. All things considered, filling in these knowledge gaps and conducting additional research are essential to improving our comprehension of prediabetes-induced senescence and creating practical plans to lessen its effects on aging and age-related illnesses [283].

8.2. Potential Blood-Based Biomarkers and Intervention Strategies

Future studies should concentrate on finding more blood-based biomarkers that can function as early warning systems for age-related complications linked to prediabetes-induced senescence [6]. The identification of new biomarkers would improve our capacity to identify prediabetes early and to take preventive action [284]. Furthermore, studies should focus on creating customized intervention plans according to the unique biomarker profiles of prediabetic individuals [285]. Customized therapies that focus on each patient's distinct biomarker patterns could offer more accurate and successful methods for slowing aging and averting age-related illnesses [286]. It is crucial to investigate how pharmacological treatments, dietary changes, and exercise routines might affect these biomarkers [286]. These intervention strategies may improve the general health and longevity of prediabetic individuals, while also delaying the onset of senescence.

Subsequent investigations should delve into the complex functions of supplementary blood-based indicators, such as folate and B12, concerning prediabetes-induced senescence [287]. It is crucial to investigate how dietary deficiencies, particularly regarding

important nutrients like folate and B12, affect senescence and the effects of aging in pre-diabetic individuals [288]. Gaining knowledge about how these biomarkers affect DNA methylation and repair—both essential for good aging—can help in identifying the under-lying processes.

Furthermore, future studies should concentrate on the function of biomarkers such as osteocalcin in bone health and aging [289]. The importance of osteocalcin in preserving bone density and general skeletal health is widely established, and in the context of prediabetes-induced senescence, it can provide information about strategies for protecting musculoskeletal integrity in older prediabetic patients [233].

For a more comprehensive understanding of the condition's impact on aging, a thor-ough assessment of these additional biomarkers in prediabetes-induced senescence is imperative. It can reveal novel approaches to addressing nutritional inadequacies and bone health, which are two critical facets of aging well. Future studies examining these biomarkers may lead to better therapeutic and preventive strategies for prediabetic patients to support healthy aging.

9. Conclusions and Insights

9.1. Summarizing the Key Findings on Blood-Based Biomarkers in Prediabetes-Induced Senescence

Several important findings have been highlighted in this thorough review of blood-based biomarkers in prediabetes-induced senescence. Prediabetes is linked to a complex web of biomarkers that interact to speed up aging, increase the chance of developing age-related illnesses, and impact different physiological systems [290]. Telomere length, p16INK4a, advanced glycation end products (AGEs), senescence-associated secretory phe-notype (SASP) factors, DNA methylation clocks, inflammatory markers, oxidative stress markers, circulating hormones, growth factors, and other biomarkers such as folate and B12, osteocalcin, and others, are some of these biomarkers [291]. The review highlights the fact that these biomarkers are active contributors to chronic inflammation, oxidative stress, and metabolic dysregulation—all of which accelerate aging—in addition to acting as markers of senescence. With the potential to improve quality of life and encourage healthy aging, a thorough understanding of these biomarkers and their complex relationships with prediabetes-induced senescence serves as a basis for the development of customized inter-vention strategies aimed at mitigating age-related complications in prediabetic individuals.

9.2. Implications for Understanding Senescence and Aging-related Disorders in Prediabetes

It is critical to comprehend the effects of aging and disorders related to senescence in the context of prediabetes. This thorough analysis emphasizes that prediabetes is a crucial stage that profoundly affects age-related disorders and the aging process; it is not just a stage between normal glucose metabolism and diabetes. In this case, the complex interactions among blood-based biomarkers accelerate senescence, making it essential. The ramifications are extensive and touch on many physiological systems, such as the nervous and circulatory systems, metabolism, inflammation, and hormone control [292]. In addition, the review indicates that the influences of prediabetes on senescence can vary greatly among individuals, emphasizing the necessity of tailored intervention approaches to successfully lessen the effects of aging-related illnesses [293]. These findings highlight the significance of early detection and intervention in prediabetic individuals to promote healthy aging and lower the burden of age-related diseases, with significant implications for public health and clinical practice. In the end, gaining an understanding of the consequences of senescence in prediabetes is essential for improving the well-being and quality of life of an aging population with a variety of needs.

9.3. Future Directions for Research Incorporating Diverse Biomarkers in Prediabetes-Induced Senescence

Future studies on prediabetes-induced senescence should focus on incorporating an even wider range of biomarkers to obtain a thorough grasp of the complex mechanisms

underlying this condition. This strategy may entail both the discovery of novel blood-based biomarkers and a closer examination of their functions. Studies should investigate the interactions among these biomarkers and evaluate how they all contribute to the aging process of physiological systems, which in turn affects age-related illnesses. Future research should also place high priority on creating novel diagnostic instruments and intervention plans that use these various biomarkers for precision medicine. This will enable prediabetic patients to receive individualized care that will delay senescence and encourage healthy aging. A more nuanced understanding of the variability of prediabetes and the complex nature of senescence will be possible through the integration of various biomarkers, thereby opening the door to more efficient and individualized treatments of this illness and its effects on aging.

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