Tables and Figures

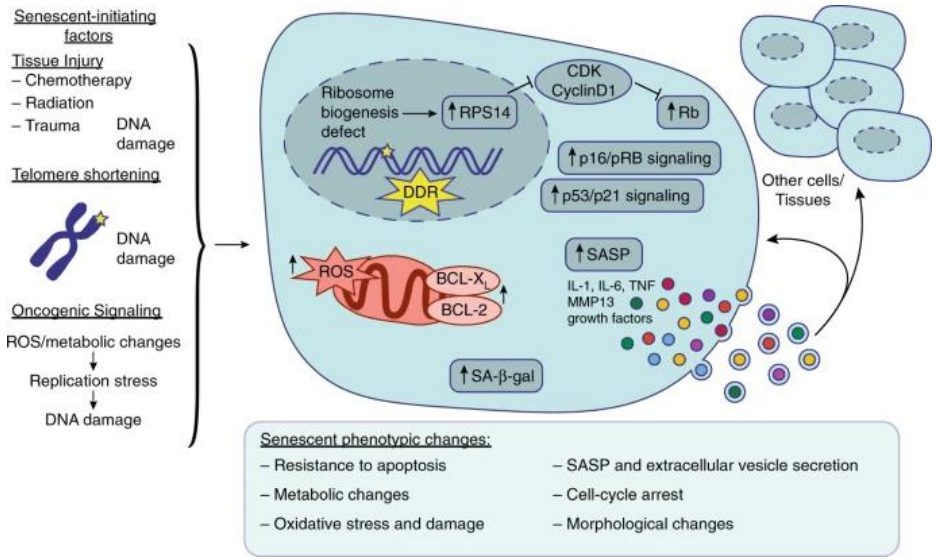

Figure 1: Overview of Prediabetes induced vascular senescence as adapted from source and redrawn from Bio Render: Several factors can induce senescence in different tissues, such as tissue injury, telomere shortening, and oncogenic signalling that all lead to DNA damage, the DNA damage response (DDR), and consequent cell cycle arrest by activation of p16/pRB signalling and/or p53/p21 signalling. Nucleolar stress and ribosome biogenesis defects can also induce RPS14 accumulation in the nucleus and activates 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-X_L and BCL-2. Senescent cells exhibit several phenotypic changes such as a 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]

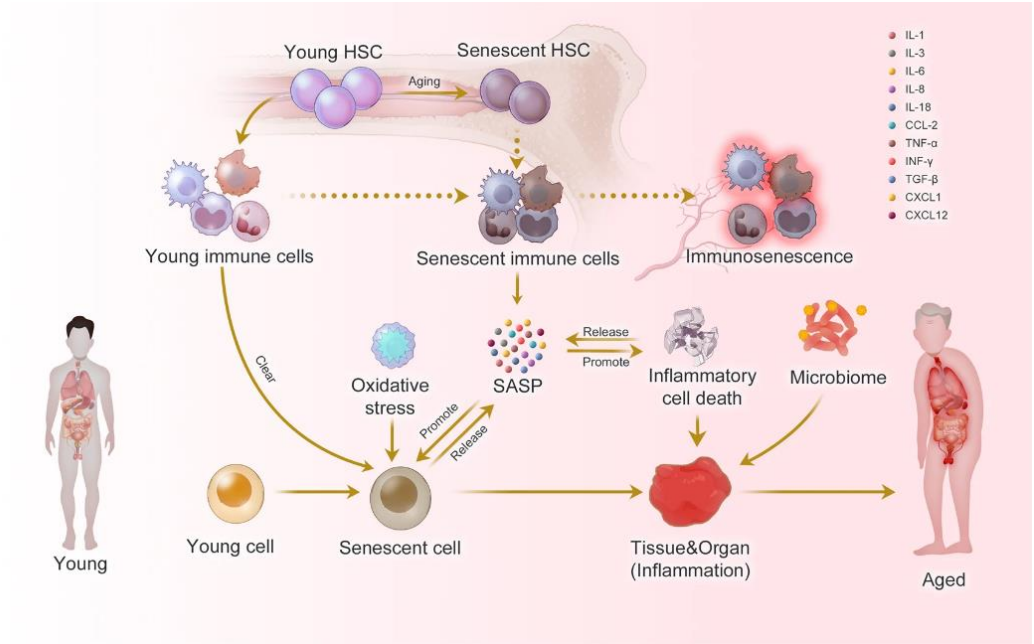

Figure 2: Prediabetes-induced systemic inflammaging (focusing on immunosenescence which is immune system aging) as adapted from source and Biorender: Inflammaging at the molecular, cellular, and organ levels. During the aging process, almost all cells in the body undergo senescence, a state characterized by a dysfunctional state and senescence-associated secretory phenotype (SASP). While immune cells play a crucial role in recognizing and eliminating these senescent cells, they are also affected by SASP, leading to a phenomenon called immunosenescence. Immunosenescence can impair the immunity to respond 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 exacerbated 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].

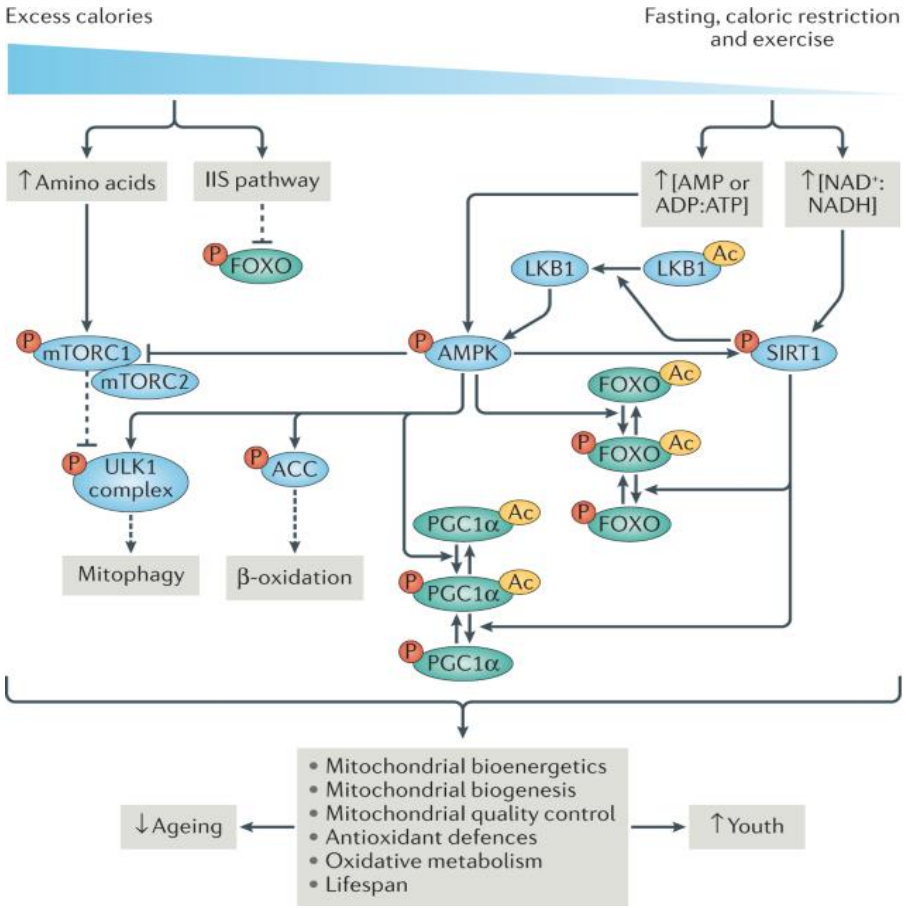

Figure 3: Prediabetes-induced metabolic aging as adapted from source and redrawn from BioRender: The concentrations of important metabolites like NAD+ and AMP rise whereas those of glucose, amino acids, and fats decrease during calorie restriction. A number of metabolic sensors, including insulin-IGF1 signaling (IIS), AMP kinase (AMPK), sirtuins (SIRTs), and the target of rapamycin (TOR), are modulated by these metabolites. Transcription factors like PGC1α and FOXO (peroxisome proliferator-activated receptor-γ coactivator) regulate mitochondrial physiology and homeostasis by acting as a bridge to metabolic sensors. Deficits in mitochondrial homeostasis lead to frailty and illness when this multilayer regulatory mechanism is dysregulated. The abbreviations Ac, ACC, and LKB1 stand for acetyl group, acetyl-CoA carboxylase, and UNC51-like kinase 1, respectively. [130]

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, bone density	Insulin resistance	Influence on aging	[90]
Insulin-like Growth Factor 1 (IGF-1)	Variations during aging	Regulation of cell growth, repair	Metabolic changes	Potential lifespan influence	[91]
Dehydroepiandrosterone Sulfate (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 lifespan	[93]
Estrogen (in women)	Hormonal shifts during aging	Effects on bone density, 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 lifespan	[96]
Insulin-Like Growth Factor-Binding Proteins (IGFBPs)	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, 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 indicator	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]

Table 2: Age-associated Inflammatory Mediators in Prediabetes-Induced Senescence

Circulating Biomarker	**Dynamics during Aging**	**Function/Risk Factor 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 lifespan	[30,123]
Chemokines (e.g., MCP-1)	Altered dynamics	Recruitment of immune cells, aging	May impact lifespan	[124]
Growth Factors (e.g., TGF-β1)	Varied with age	Modulation of cell growth, aging	Influence on 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 in aging	May influence lifespan	[123]

Table 3: Biomarkers in 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	Contribute to accelerated aging and age-related complications	[156]
Inflammatory Markers	Indicators of inflammation	Contribute to inflammation associated with aging	[157]
Oxidative Stress Markers	Indicators of oxidative damage and stress	Exacerbate age-related oxidative damage	[156]
Endothelial Dysfunction	Indicators of vascular dysfunction	Exacerbate endothelial dysfunction and impact vascular health	[158]
Mitochondrial Dysfunction	Reflect mitochondrial function and health	Impair mitochondrial function associated with aging	[159]
Red Blood Cell Distribution Width (RDW)	Reflect changes in red blood cells	Indicate inflammation and metabolic changes affecting aging	[160]
Haemoglobin A1c (HbA1c)	Reflects long-term blood glucose levels	Accelerate aging due to chronic hyperglycaemia	[161]
Serum Albumin	Reflects nutritional status and frailty	Affect nutritional status and frailty	[159]
Circulating Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1)	Reflect hormonal changes	Influence insulin resistance and metabolic changes	[162]
DHEA-S	Reflects hormonal changes	Contribute to hormonal changes associated with aging	[163]

Testosterone (in men)	Reflects hormonal changes in men	Impact muscle mass, bone density, and aging	[63,164]
Oestrogen (in women)	Reflects hormonal changes in women	Affect bone density, cardiovascular health, and aging	[165]