Unraveling the relationship among insulin resistance, IGF-1, and amyloid-beta 1–40: Is the definition of type 3 diabetes applicable in the cardiovascular field?☆

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ARTICLE INFO

Keywords:
Insulin
Insulin resistance
Amyloid-beta
IGF-1
Type 3 diabetes
Atherosclerosis

ABSTRACT

The concept of "type 3 diabetes" has emerged to define alterations in glucose metabolism that predispose individuals to the development of Alzheimer's disease (AD).

Novel evidence suggests that changes in the insulin/insulin-like growth factor 1 (IGF-1)/growth hormone (GH) axis, which are characteristic of Diabetes Mellitus, are one of the major factors contributing to excessive amyloid-beta (Aβ) production and neurodegenerative processes in AD. Moreover, molecular findings suggest that insulin resistance and dysregulated IGF-1 signaling promote atherosclerosis via endothelial dysfunction and a pro-inflammatory state. As the pathophysiological role of Aβ1–40 in patients with cardiovascular disease has attracted attention due to its involvement in plaque formation and destabilization, it is of great interest to explore whether a paradigm similar to that in AD exists in the cardiovascular field. Therefore, this review aims to elucidate the intricate interplay between insulin resistance, IGF-1, and Aβ1–40 in the cardiovascular system and assess the applicability of the type 3 diabetes concept. Understanding these relationships may offer novel therapeutic targets and diagnostic strategies to mitigate cardiovascular risk in patients with insulin resistance and dysregulated IGF-1 signaling.

1. Introduction

Although life expectancy has increased in the last 200 years due to advances in medicine in terms of more precise diagnosis and adequate therapy, the quality of life of geriatric individuals has not improved proportionally [1]. Indeed, the age-related physiological and metabolic changes are risk factors for the development of conditions such as dementia, cardiovascular diseases (CVDs), and metabolic disorders such as obesity and Type 2 Diabetes Mellitus (T2DM) [1,2].

In 2021, it was estimated that 537 million people worldwide were affected by T2DM, and this number is expected to reach 783 million by 2045 [3]. This chronic and complex condition is largely influenced by environmental and genetic factors [4]. In particular, T2DM typically appears in middle or advanced age, along with other conditions such as obesity, hypertension, and altered gut microbiota composition, often coupled with unhealthy lifestyles and smoking [4].

According to the clinical definition, T2DM is characterized by elevated blood glucose levels and altered insulin production by the

☆ The whole or part of this original work has not been previously published in this or a substantially similar form.

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pancreatic β cells usually preceded by a state of insulin resistance in which tissues are less responsive to insulin [4]. It is well-established that processes underlying T2DM result in greater susceptibility to CVDs in older patients [5]. Moreover, insulin resistance has been identified as a pathophysiological mechanism that predisposes to the development of Alzheimer's disease (AD) in patients with T2DM [6]. Proposed molecular basis of the disease consists of the alterations in the insulin/insulin-like growth factor - 1 (IGF-1)/growth hormone (GH) axis, leading to an increase in amyloid-β (Aβ) production [6].

Based on epidemiological and biological observations, some authors have employed the expression "type 3 diabetes" to describe the connection between T2DM and AD [6]. It is important to note that the definition of "type 3 diabetes" does not correspond to a clinical official one, rather it summarizes the hypothesis that the pathological mechanisms of T2DM, such as inflammation, oxidative stress and mitochondrial dysfunction, contribute to AD predisposition.

Given the emerging role of amyloid-β (Aβ) in patients with CVDs [7,8], the purpose of this review is to explore the pathophysiological mechanisms of T2DM and how they may promote an increase in Aβ levels to advance the hypothesis of expanding the definition of type 3 diabetes to cardiovascular aspects.

2. Pathophysiology of diabetes mellitus type 2

2.1. The molecular players: insulin and IGF-1

Insulin is a hormone encoded by a gene located on the short arm of chromosome 11 [9]. The mature peptide is composed of 51 amino acids organized into two chains, the A chain (21 amino acids) and the B chain (30 amino acids), which are held together by two disulfide bonds [9]. The transcription of the insulin gene originates a 110-amino acid peptide, known as prepro-insulin, which consists of a signal peptide, the future A and B chains and the C peptide linker [9]. Finally, excision of the signal peptide leads to the formation of proinsulin, which is converted to insulin after removal of the C peptide via trypsin-like endoproteases [9].

Active insulin is stored in the secretory granules of pancreatic β cells and is immediately released into circulation following an increase in postprandial glucose levels [9]. The liver is the primary site involved in insulin clearance; however other organs such as the kidneys, muscles and adipose tissue also contain receptors and enzymes responsible for its degradation [10]. In particular, insulin-degrading enzyme (IDE) is a metalloprotease that is ubiquitously expressed in both insulin-responsive and non-responsive cells and is a key player in this process [11]. Alterations in insulin degradation can predispose individuals to T2DM or obesity [10] and some polymorphisms of the IDE gene are associated with an increased risk of T2DM in various ethnicities [12].

The gene encoding IGF-1 is located on chromosome 12. IGF-1 is a single-chain polypeptide consisting of 70 amino acids and contains three disulfide bridges, resulting in a structure similar to that of insulin [13]. IGF-1 exerts endocrine function and is mainly produced in the liver following insulin- and GH-mediated stimulation [14]. Moreover, other tissues have also transcriptional capabilities for this anabolic growth factor, such as the heart, kidneys, and cartilage, where it acts in a paracrine manner [14]. The availability of IGF-1 is regulated by the family of insulin-like growth factor binding proteins (IGFBPs) [15], which increase IGF-1 half-life, direct the hormone to target organs and modulate its availability and activity, thus allowing the regulation of apoptosis and cell proliferation [15,16]. Certain polymorphisms are associated with an 18 % reduction in IGF-1 levels compared to the wild-type allele, with a higher risk of developing T2DM [17].

2.2. Insulin and IGF-1 mechanisms of action

Insulin binds with high affinity to the insulin receptor (IR), which is a tyrosine kinase receptor composed of two extracellular α subunits and two transmembrane β subunits. There are two isoforms of IR: IR-A and IR-B, which are obtained through alternative splicing [18]. In particular, IR-B is predominant in the liver, muscle, and white adipose tissue [18], whereas IR-A is expressed in fetal cells, including fetal fibroblasts, renal, liver and muscle cells [19]. Of note, IR-A levels have also been found to be increased in several types of cancers, such as breast and colon cancer [19]. On the other hand, IGF-1 binds with high affinity to the IGF-1 receptor (IGF-1R) and has a lower affinity for IR due to the structural homology between IGF-1 and insulin [20]. The structure of IGF-1R also shows a high similarity to IR consisting of two α subunits and two β subunits [20]. Furthermore, a hybrid receptor resulting from the heterodimerization of half-receptors, namely one α and one β subunit, originating from IR and IGF-1R, has been identified. This hybrid receptor interacts with both insulin and IGF-1 [21].

In the case of IR, IGF-1R, and the hybrid receptor, the interaction with the ligand at the α-subunit level induces autophosphorylation of the β-subunit, which in turn activates the phosphorylation of insulin receptor substrate (IRS) 1 and IRS-2 [22]. The signaling pathways originating from IRS-1 and IRS-2 can be either metabolic or mitogenic, depending on the type of recruited receptor [22]. Metabolic signaling is mediated though the phosphatidylinositol 3-kinase (PI3K), which is composed of the p85 and p110 subunits, the latter of which can promote the transport of glucose. The PI3K catalyzes the addition of a phosphate group to phosphatidylinositol 4,5-bisphosphate (PIP2) resulting in the formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [22]. Subsequently, PIP3 activates Protein Kinase B (PKB or Akt), which effects on a range of substrates such as mTOR regulating protein synthesis and GSK-3 controlling glycogen formation and autophagy suppression [14,18]. Other molecular actions of Akt include inhibition of FOXO, which affects oxidative stress and apoptosis, and RAC that is involved in the migration process [14]. Finally, Akt promotes the activation and expression of endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO), which is essential for endothelial function and vasodilation [23].

In the mitogenic signaling pathway, IRS-1 recruits the GRB2-SOS complex, whose SOS subunit facilitates the replacement of guanosine diphosphate (GDP) with guanosine triphosphate (GTP) on Ras near the plasma membrane [24]. Consequently, Ras activates a signaling cascade that leads to activation of the MAPK/ERK pathway, thus mediating the promotion of cell growth, division, migration, and apoptosis [24] (Fig. 1).

Insulin and IGF-1 are involved in many physiological processes necessary for maintaining metabolic homeostasis and the previously mentioned processes through an axis that relates these two molecules and includes GH [25]. Under physiological conditions, food intake stimulates the release of insulin from the secretory granules of pancreatic β cells into the bloodstream [9]. In contrast, GH is produced in a pulsatile manner in the pituitary gland under the control of the hypothalamus and is influenced by other signals such as the glycemic state, neurotransmitters, and hormones [26]. Insulin and GH stimulate the hepatic secretion of IGF-1, which exerts a negative feedback on the production of both insulin and GH to maintain the balance of the axis that controls energy storage and utilization and lipid synthesis [25].

The insulin/IGF-1/GH axis can be compared with a sensor capable of detecting the nutritional status of the body, thereby regulating both metabolism and cellular growth. The primary function of insulin is to regulate glucose homeostasis by stimulating its uptake into target tissues [9]. Additionally, insulin inhibits gluconeogenesis in the liver and lipolysis in adipocytes [21]. However, the role of insulin is not limited to metabolic homeostasis, as it regulates cell growth and survival, vascular health and inflammation [26]. IGF-1, in addition to its well-known role in cell growth and differentiation, can also promote glucose uptake in some peripheral tissues either directly or by enhancing the action of insulin [26]. Moreover, there is evidence suggesting that IGF-1 is significant in the homeostasis of cardiovascular physiology as it regulates cardiac apoptosis, autophagy, and inflammatory response, controls

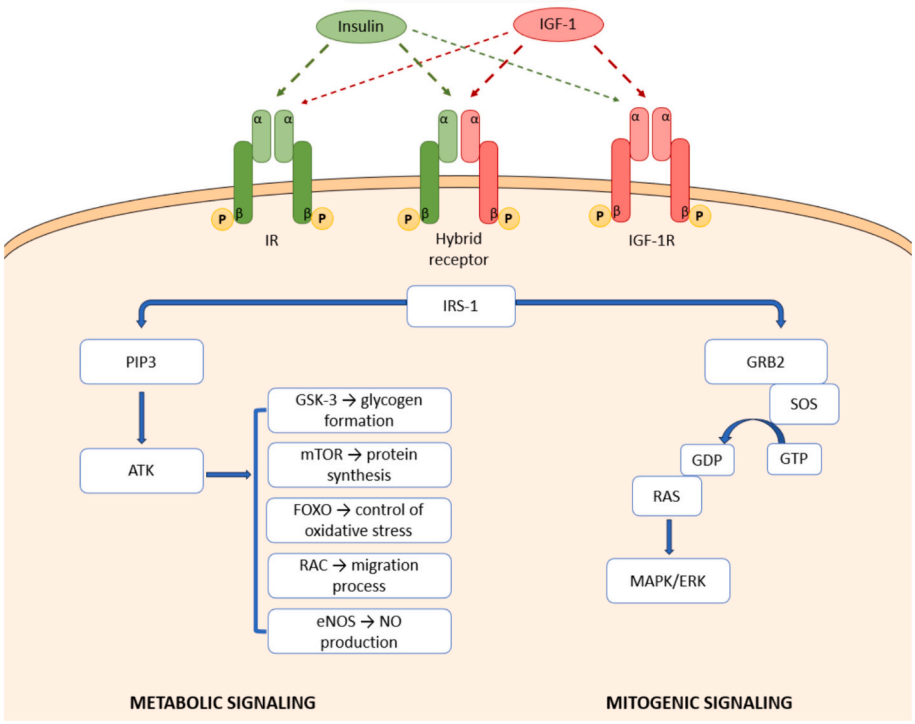

Fig. 1. Metabolic and mitogenic signaling triggered by insulin and IGF-1. AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; IGF-1, insulin-like growth factor-1; IGF-1R, insulin like growth factor-1 receptor; IR, insulin receptor; IRS-1, insulin receptor substrate1; NO, nitric oxide.

oxidative stress and the formation of atherosclerotic plaque and promotes angiogenesis [20].

2.3. *From insulin resistance to diabetes*

For several years, the model for the pathogenesis of T2DM consisted of the development of insulin resistance as a trigger for the onset of hyperinsulinemia and the consequent dysfunction of the pancreatic β-cells [20]. In particular, there are situations in which defects in IR or post-receptor level compromise signal transduction, leading to insulin resistance that evolves into glucose intolerance [27]. Moreover, maintenance of high blood glucose levels promotes an increase in insulin secretion. An alternative hypothesis for the pathogenesis of T2DM has been proposed based on new scientific evidence obtained through genome-wide association studies (GWAS) [25]. In particular, an initial alteration in the insulin/IGF-1/GH axis causes hypersecretion of insulin, followed by the development of insulin resistance and β-cells exhaustion [25]. This new dogma explains why signs of hyperinsulinemia can be observed in individuals with optimal glucose levels [25]. Numerous factors such as aging, obesity, calorie excess, physical inactivity, and inflammation may cause major changes in the insulin/IGF-1/GH axis, thus predisposing patients to T2DM [26] (Fig. 2).

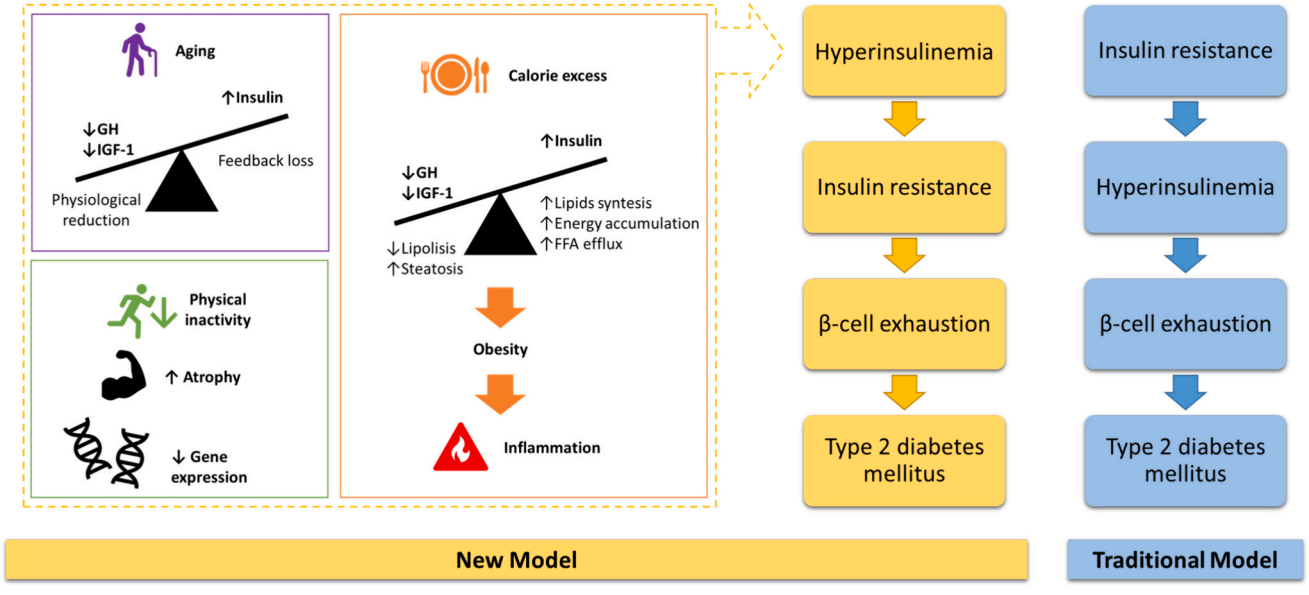

Fig. 2. Comparison between traditional and new models of T2DM pathogenesis.

In particular, aging causes an imbalance in the equilibrium between insulin and GH due to the reduction in physiological levels of GH and IGF-1 [28]. Therefore, low levels of IGF-1 do not provide adequate negative feedback on insulin production, predisposing to the development of hyperinsulinemia and insulin resistance [25]. Moreover, aging is associated with lower self-renewal of pancreatic β cells and the impairment of their functionality [29].

In modern society, continuous food intake leads to a state of overnutrition in which obesity promotes the development of insulin resistance and the establishment of local and systemic inflammation [30]. Moreover, a dynamic trend was observed when considering the influence of body mass index (BMI) on GH and IGF-1 concentrations. In particular, BMI greater than 24 kg/m^2 is associated with a substantial increase in the synthesis of IGF-1 due to GH increase [31]. In the overweight range or first-degree obesity (BMI 30–34.9 kg/m^2), the two molecules reach a plateau up to a BMI of 36 kg/m^2 (massive obesity) and from this level onwards the levels of both GH and IGF-1 decrease [31].

Insulin and GH have complementary and opposing roles in the regulation of fat metabolism. In particular, the former stimulates lipid synthesis and energy storage, whereas the second normally promotes lipolysis both in adipose tissue and in hepatocytes [25,26]. Although mature adipocytes do not respond to stimulation by IGF-1, fatty acid metabolism is strongly affected by the imbalance in this hormone [26]. It has been described that changes in IGF-1 levels contribute to the accumulation of free fatty acids (FFAs) in tissues other than adipose tissue, particularly skeletal muscle and liver, triggering insulin resistance due to the phosphorylation of serine residues in IRSs [26]. This leads to a blockade of the activation of IRSs mediated by IR and IGF-1R on tyrosine residues [26].

Normally, insulin accelerates the breakdown of ApoB, a structural protein necessary for the assembly of FFAs into very low-density lipoprotein (VLDL) [30]. In cases of insulin resistance, an increase in FFAs and an insufficient ApoB degradation lead to hypertriglyceridemia, elevated VLDL, and a modified transfer between high-density lipoprotein (HDL) and low-density lipoprotein (LDL), with the latter being preferred [32]. An impaired antilipolytic effect of insulin on visceral adipose tissue may promote liver steatosis, which promotes changes in metabolic homeostasis [26].

From an inflammatory perspective, visceral adipose tissue is a secretory organ that produces tissue-specific cytokines known as adipokines such as leptin and adiponectin, in addition to pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [33]. In particular, TNF-α inhibits the receptors for insulin signaling reducing glucose transporters on the membrane of target cells, whereas IL-6 is capable of inhibiting the insulin pathway through the activation of the STAT3 pathway and the subsequent transcription of SOCS3 [33]. Studies have highlighted that obesity leads to an increase in the activity of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in the liver, which leads to inflammation and elevated expression of TNF-α, interleukin-1β (IL-1β), and IL-6, thus contributing to the development of insulin resistance [33]. The development of inflammation plays an important role in the alteration of the insulin/IGF-1/GH axis, as pro-inflammatory cytokines decrease the levels of circulating IGF-1 [34].

Lastly, it has been shown that impaired insulin sensitivity can result from a sedentary lifestyle [35]. A single day of reduced physical activity, corresponding to approximately 260 steps per week, is sufficient to alter insulin action through mechanisms that are still unclear [36]. Severe physical inactivity has been suggested to contribute to intracellular lipid accumulation, which alters skeletal muscle insulin signaling and mitochondrial bioenergetics. On the other hand, physical inactivity can lead to a reduction in protein synthesis, which can explain the muscle atrophy that is often associated with insulin resistance. Therefore, physical exercise is a pivotal strategy to prevent and treat insulin resistance because of its significant improvement in insulin-independent glucose uptake.

3. Type 3 diabetes

Currently, over 50 million patients suffer from AD and this number is estimated to double every five years, reaching 152 million cases by 2050 [37]. AD is a degenerative illness characterized by memory loss and cognitive impairment that can lead to changes in behavior and personality [37]. From a neuropathological standpoint, changes in individual behaviors are due to neural atrophy and synaptic loss, which are caused by the cytotoxic action of the extracellular accumulation of Aβ in insoluble plaques and neurofibrillary tangles of hyperphosphorylated tau protein [38].

AD is a multifactorial disease, and advanced age, genetic and environmental factors, presence of CVDs, poor diet and metabolic syndromes such as T2DM and obesity are among the main associated risk factors [37]. Indeed, there is increasing evidence of close relationship between metabolic syndrome and the development of various neurodegenerative disorders. In particular, patients with T2DM have been found to have 65 % increased risk of developing AD [39]. The association between these two diseases is becoming increasingly significant, leading to the coining of the definition of “type 3 diabetes” [6].

According to recent observations, T2DM influences cognitive function through changes in cerebrovascular functionality, hyperphosphorylation and accumulation of tau protein, and altered balance between Aβ synthesis and clearance [40]. T2DM contributes to impaired vascular reactivity and reduced cerebral perfusion, which lead to cerebrovascular lesions and a reduction in brain volume in areas including the hippocampus, and the gray and white matter [41]. Neuronal loss negatively affects cognitive functions such as memory, attention, and information processing [42]. Interestingly, studies have shown that the brain structure is similarly altered in both T2DM and AD, with the hippocampus being the most affected region [43].

Moreover, it has been found that tau protein phosphorylation is pronounced in murine models with T2DM [40]. In addition, experiments conducted in mice have demonstrated that insulin resistance is associated with an increase in Aβ production and a reduction of over 50 % in its degradation [44–46]. Miklossy and colleagues described that Aβ and hyperphosphorylated tau can accumulate in the pancreas of patients with T2DM [47]. However, the actual association between these deposits in the pancreas and brain remains unknown [47]. Moreover, several studies have reported that relatively small soluble oligomeric species exhibit higher toxicity compared to larger protein aggregates, causing cell membrane damage and resulting in cell death [48]. Abnormal protein aggregation triggers the formation of self-propagating complexes, that expand through the interaction of similar or different proteins [48]. Indeed, Aβ deposits may often be favored by the presence of other pro-amyloidogenic proteins such as amylin, TDP43 and alpha-synuclein [49,50]. Interestingly, it has been observed that in brain of patients with AD and T2DM there was the colocalization of Aβ aggregates with amylin, which is a hormone secreted by pancreatic β-cells along with insulin to control glycemia [51]. The accumulation of amylin in the central nervous system and cerebrospinal fluid contributes to the alterations in microvasculature and brain structure, further corroborating the role of amylin in the pathogenesis of AD [51].

Furthermore, excess of Aβ reduces the cerebral uptake of both insulin and IGF-1, which play significant roles in synaptic and glial functions [52]. In addition to its role in glucose homeostasis, insulin is necessary for neurotrophic and neuroendocrine functions [53]. Although insulin is primarily of pancreatic origin, it has been discovered that some neural cells can also produce this hormone [54]. In contrast, IGF-1 is also produced in all cell types in the central nervous system, exerting numerous functions such as proper brain development, neuroprotection, the neurotransmitter release and Schwann cells survival, migration, proliferation, and myelination [55].

Finally, numerous studies support the hypothesis that a deficit of both insulin and IGF-1 or their receptors can lead to imbalances in neuronal homeostasis [6,56]. In particular, Rivera et al. reported that

decreased insulin and IGF-1 levels are associated with the progression of AD owing to the reduction in acetylcholine in the brain, which is a neurotransmitter critical for maintaining memory and cognitive functions [56].

Lastly, insulin resistance, alterations in IGF-1 signaling and increased production of Aβ seem to share other pathophysiological mechanisms such as, inflammation, oxidative stress, mitochondrial dysfunction and production of advanced glycation end products (AGEs) [6,55].

4. Amyloid β synthesis and degradation

Aβ is generated by proteolytic processing of the amyloid precursor protein (APP), which is a type 1 transmembrane protein obtained by alternative splicing of the homonymous gene located on chromosome 21 [57,58]. APP is highly expressed in numerous organs, including the brain, kidney, heart, spleen, and weakly expressed in the liver [57]. In neurons, APP is involved in several biological processes including synapse formation, repair, and anterograde neuronal transport [59,60], while in other cell the function and role of APP is still not fully understood. However, it is noted that APP play a role in blood coagulation and cell adhesion [61].

The proteolytic processing of APP is a key regulatory step in the generation of the Aβ peptide, which, when impaired, leads to the onset of AD [62]. APP cleavage can be mediated by two different proteases, α- and β-secretase. Regardless of which protease cleaves APP first, the subsequent cleavage of the remaining fragment is mediated by the γ-secretase. Aβ is formed when the β-secretase cleaves APP leading to the release of soluble APPβ (sAPPβ) and the C99 fragment, which remains bound to the membrane and is cleaved by the γ- secretase complex [58]. This pathway is called the "amyloidogenic pathway" as it leads to the production of two possible isoforms of Aβ, namely Aβ1–40 and Aβ1–42, and the amyloid precursor protein intracellular C domain (AICD) fragment in the cytosol [58]. Alternatively, APP can be cleaved by α-secretase at the plasma membrane, leading to the release of soluble APPα (sAPPα) and generation of the membrane-tethered C83 fragment [58]. The C83 is consequently cleaved by γ-secretase that generates two peptide products: p3 and AICD [48]. These two products are known to have no implications in the development of AD and this pathway is usually referred to as the "non-amyloidogenic pathway" [58].

Velliquette and colleagues found that in transgenic mice, impaired energy production, as seen in metabolic diseases, leads to increased levels and activity of β-secretase, which in turn contributes to the overproduction of Aβ and may drive AD pathogenesis [63]. Other studies in animal models have also reported that β-secretase plays a key role in regulating metabolism [64,65]. Specifically, excess β-secretase reduces insulin sensitivity and predisposes to obesity in cases of chronic overnutrition [65]. Therefore, the metabolic role of β-secretase could be a promising approach to understanding the link between AD and T2DM. Hyperactivation of β-secretase may promote T2DM as the enzyme regulates the cleavage of IR [66]. Notably, inhibiting β-secretase partially restores insulin signaling by increasing IR availability on the cell surface of hepatocytes [66] and substantially improves systemic glucose homeostasis in a diabetic mouse model [67].

Under normal conditions, the production and clearance of Aβ is regulated by several processes. Aβ can be phagocytosed by white blood cells equipped with enzymes capable of using it as a substrate [68]. Alternatively, circulating Aβ can be enzymatically degraded at the renal or hepatic level, allowing for its excretion [68]. Approximately 20 enzymes responsible for Aβ degradation have been identified [46]. Among these, the zinc-dependent enzymes neprilysin (NEP) and IDE have recently been compared for their proteolytic activity against Aβ isoforms [46]. It has been found that while NEP can form fragments of 2–11 amino acids by acting on 17 possible cleavage sites, the proteolytic activity of IDE leads to the formation of longer fragments, ranging from 6 to 33 amino acids, by acting on 15 sites [46]. However, only NEP has an active site that is capable of using fragments of Aβ previously obtained by other enzymes as substrates. As neither enzyme can degrade Aβ aggregates, it can be hypothesized that their role is pivotal in preventing their accumulation and subsequent aggregation [46].

5. Consequences of diabetes and the emerging role of Aβ in cardiovascular field

AMI is generally considered to be the cause of 30 % of all deaths in patients with T2DM [69]. This is largely explained by the fact that insulin resistance predisposes individuals to the development of coronary artery disease (CAD) [30]. In specifics, in patients with T2DM, impaired insulin response and hyperglycemia have an additive effect in causing endothelial dysfunction, establishment of a pro-inflammatory state, and increased oxidative stress [6]. More precisely, insulin insensitivity in endothelial cells prevents adequate production of NO through the PI3K/Akt pathway [70]. Furthermore, hyperglycemia promotes the activity of protein kinase C (PKC) which induces the phosphorylation of eNOS at Thr497, reducing its activity and stimulating a proinflammatory environment [70]. Therefore, individuals with T2DM tend to have a higher risk of developing micro and macrovascular complications, due to the chronic exposure of endothelial cells to high glucose concentrations [14].

Impaired NO production has numerous effects, including altered vascular contractility and endothelial integrity [69], thus increasing susceptibility to the development of atherosclerotic plaques though the accumulation of LDL in the tunica intima of blood vessels [71]. Furthermore, endothelial activation mediates the expression of adhesion molecules and release of cytokines for the recruitment of monocytes and their subsequent differentiation into macrophages [72]. The phagocytosis of lipids by macrophages results in their appearance as foam cells, which are fundamental in the formation of atherosclerotic plaques [69].

Moreover, insulin resistance promotes the mitochondrial production of reactive oxygen species (ROS) [36]. The physiological production of ROS is essential because it regulates processes such as cell growth, differentiation, senescence, apoptosis, and autophagy [73]. However, excessive ROS production, if not adequately neutralized at antioxidant levels, supports endothelial dysfunction due to NO degradation [73]. Additionally, oxidative stress contributes to the activation of the NF-kB pathway, which promotes the production and secretion of inflammatory cytokines and reduces insulin signaling [70]. Thus, oxidative stress controls mechanisms that explain the persistence of insulin resistance and endothelial dysfunction and plays a significant role in the pathogenesis of vascular alterations [74].

In contrast, IGF-1, which is expressed at the vascular level by macrophages, endothelial cells, and VSMCs, has been reported to have a protective role against atherosclerosis. In particular, studies in animal models have reported that low levels of IGF-1 are associated with extensive plaque formation. Moreover, an inverse correlation between IGF-1 concentration and the risk of myocardial infarction (MI) was reported in patients with CAD, which could be explained by the role of IGF-1 in counteracting the instability of atherosclerotic plaques, modulating the phenotype of VSMCs, and anti-apoptotic properties [17,20]. Therefore, the reduction in the levels of this protective hormone in a state of insulin resistance explains the increased risk of MI observed in patients with this condition.

Finally, regarding Aβ peptides and MI, emerging evidence indicates that Aβ1–40 is involved in atherosclerotic processes, such as plaque formation and destabilization, inflammation and oxidative stress [8,68]. In particular, the Aβ1–40 isoform is of considerable interest in the cardiovascular field as it is produced not only in the central nervous system but also peripherally, leading to vascular lesions, arterial stiffness, and progression of atherosclerosis [75,76].

In addition, it is worth mentioning here that previous studies have reported that Aβ1–42 is present at a significantly lower concentration in aortic atherosclerotic plaques than Aβ1–40 [7]. Moreover, Aβ1–42 is less present in plasma compared to the other isoform as it has a higher

tendency to aggregate, which explains the lower availability in blood and cerebrospinal fluid [7]. The role of Aβ1–42 in the cardiovascular field remains largely unexplored. On the one hand, observations on mice suggest that higher levels of Aβ1–42 are present in animals with obesity and T2DM [77]. On the other hand, a clinical study including patients with no signs of neuropsychological impairment disclosed that only Aβ1–40 had an association with T2DM and CAD [77]. Similarly, a recent study on a cohort of 65 patients with acute myocardial infarction described a trend of higher levels of Aβ1–42 in those with T2DM, which was not statistically significant [78]. Therefore, more studies are needed to assess the role of Aβ1–42 in the cardiovascular field.

More precisely, during the initiation phase of atherosclerotic plaque formation, there is an increase in transcription factors such as hypoxia-inducible factor-1α (HIF-1α), NF-kB, GATA-1, and GATA-4, which are involved in the transcription of β-secretase, thereby promoting the production of Aβ [68]. Aβ is additionally involved in the evolution of atherosclerotic plaque by promoting the accumulation of LDL and macrophages in the tunica intima of blood vessels, supports a pro-inflammatory state during progression, and ultimately establishes a prothrombotic condition that contributes to the obstruction of the vessel following plaque degeneration [79]. Moreover, it is worth mentioning here that Aβ, which is not degraded in the brain, can cross the blood-brain barrier, and enter the bloodstream [7] and that in the context of multiorgan syndromes, the accumulation of Aβ in the hearts of patients with AD has been described in association with increased diastolic dysfunction [76]. Furthermore, the literature suggests that excess Aβ has pro-atherosclerotic properties as well as in the cerebral vessels and aorta [75]. Therefore, based on what has been described so far, it is possible to outline a certain degree of analogy between the pathophysiological mechanisms of CAD mediated by T2DM, due to altered levels of IGF-1, insulin, and Aβ1–40 (Fig. 3).

Lastly, regarding the Aβ peptide and its involvement in the development of atherosclerosis and MI event, it is also important to mention that this molecule plays an important role in tissue damage after the restoration of blood flow. Although restoring blood flow after a MI is the most effective strategy for reducing the infarct size, it is also associated with potentially harmful effects, collectively termed ischemia-reperfusion injury (IRI) [80]. Cardiomyocytes are particularly sensitive to intracellular changes caused by variations in oxygen availability before and after reperfusion. In a hypoperfused state, cardiomyocytes rely on anaerobic metabolism, which causes a reduction in pH and triggers the activation of Na^{+}/H^{+} channels to counteract the excess protons [81]. As a result, the increased influx of sodium reduces the reuptake of calcium into the sarcoplasmic reticulum, thus leading to calcium overload and increased oxidative stress [81]. The abrupt increase in oxygen availability and the reversal of intracellular pH caused by reperfusion are triggering factors of the irreversible opening of the mitochondrial permeability transition pore (mPTP) that together with oxidative stress and calcium overload are responsible for the IRI [81,82]. In particular, the structure of mPTP comprises three elements: a channel on the outer mitochondrial membrane, one on the inner mitochondrial membrane and the cyclophilin D connecting element in the mitochondrial matrix [82]. The activation of mPTP is responsible for the connection between cytosol and mitochondrial matrix through cyclophilin D, thus leading to the reduction of membrane potential, the uncoupling of oxidative phosphorylation and the alteration of adenosine triphosphate synthesis [82]. Moreover, prolonged mPTP opening is responsible for cell death [82].

The mechanisms described so far have also been observed in IRI following stroke events and, interestingly, Aβ appears to play a crucial role in multiple aspects of tissue damage. In addition to Aβ-induced calcium dysregulation and oxidative stress contributing to mitochondrial dysfunction, Aβ oligomers have been found to promote mPTP opening by binding to cyclophilin D, in vitro studies and animal models [82]. Mitochondrial dysfunction causes cellular stress that results in neuronal death and cognition impairment. Of note, Jang and colleagues

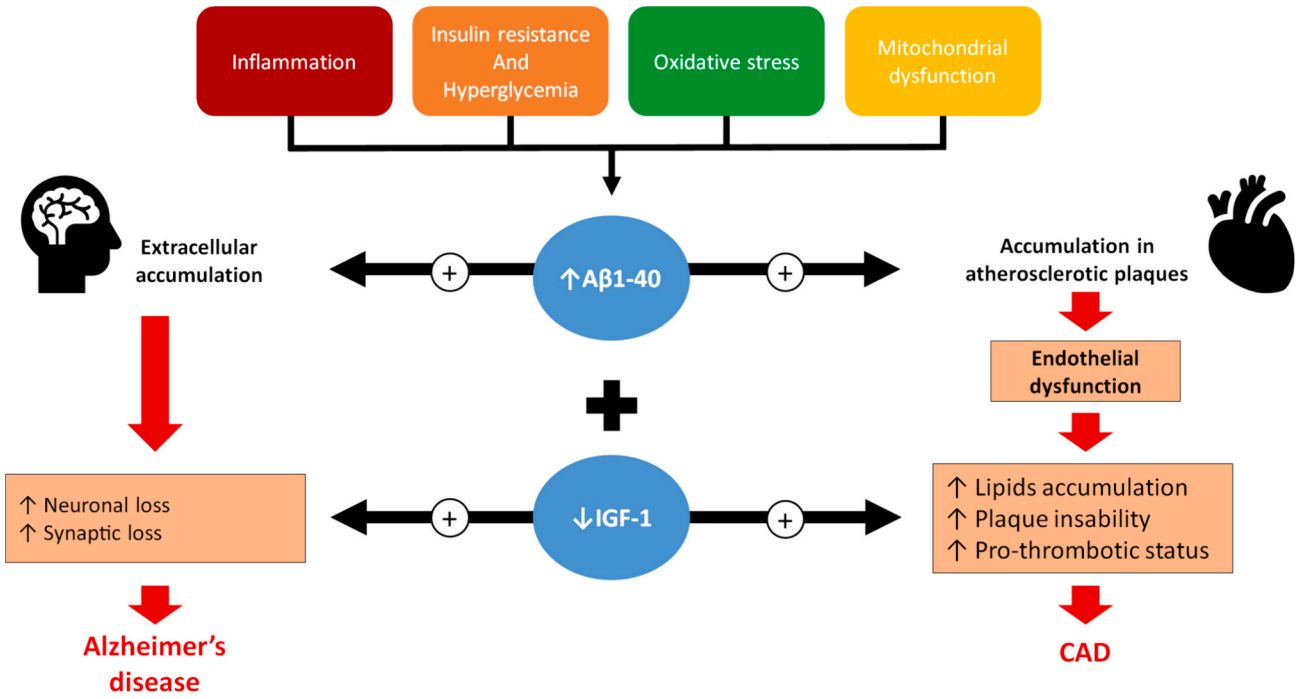

Fig. 3. Interplay among altered levels of insulin, IGF-1 and Aβ1–40 in insulin resistance status in AD and in CVDs. Overall, inflammation, insulin resistance, oxidative stress and mitochondrial dysfunction contribute to the overproduction of Aβ1–40 and reduction of IGF-1 levels. In the brain, Aβ1–40 accumulates together with Aβ1–42 at the extracellular level, causing neuronal and synaptic loss that leads to AD. Moreover, low levels of IGF-1 are not sufficient to maintain its neuroprotective role. On the other hand, the accumulation of Aβ1–40 in atherosclerotic plaques contributes to the establishment of endothelial dysfunction that, combined with reduced levels of IGF-1, aggravates CAD progression, increases plaque instability and favors a prothrombotic state. AD, Alzheimer's disease; Aβ1–40, amyloid beta 1–40; IGF-1, insulin-like growth factor-1.

reported that Aβ1–40 and Aβ1–42 are able to interact with cyclophilin D and induce mPTP activation in isolated cardiac mitochondria and several cultured cell types such as coronary endothelial cells and cardiomyocytes [83]. Thus, these findings suggest the involvement of Aβ1–40 in the detrimental effects following reperfusion in patients with MI. Additionally, the authors observed that treatment with a cyclophilin D inhibitor prevent mitochondrial swelling caused by mPTP activation [83]. Although cyclosporine, a cyclophilin D inhibitor, has shown promising results in counteracting mPTP activation in vitro and in animal models, it was not effective in randomized controlled trials enrolling patients with MI [80,84]. In particular, the treatment did not reduce infarct size, incidence of adverse outcome or prevent left ventricular remodeling [80,84].

6. Conclusion

In conclusion, T2DM is a systemic disease resulting from an imbalance in the insulin/IGF-1/GH axis that affects several physiological processes beyond glucose metabolism. These alterations exacerbate the amyloidogenic process and contribute to an increase in the circulating Aβ isoform. Increased production of Aβ1–40 in patients with T2DM can lead to complications in the nervous and cardiovascular systems. Aβ1–40 has pro-inflammatory, pro-thrombotic and pro-atherosclerotic properties that increase the risk of MI. This finding suggests that Aβ may act as a link between age-related AD, CAD, and T2DM. Therefore, the observations described so far highlight the complex interplay between these conditions, indicating a possible extension of the definition of "type 3 diabetes" to the cardiovascular field. Further exploration of these mechanisms may yield opportunities for preventive interventions such as reducing Aβ synthesis and its pathogenic role.

Funding

None.

Source of funding

None.

CRediT authorship contribution statement

Alessandra Lucia Fluca: Writing – review & editing, Writing – original draft, Visualization. **Beatrice Pani:** Writing – review & editing, Writing – original draft. **Milijana Janjusevic:** Writing – review & editing. **Donna R. Zwas:** Writing – review & editing. **Yosefa Abraham:** Writing – review & editing. **Matteo Calligaris:** Writing – review & editing. **Antonio Paolo Beltrami:** Writing – review & editing. **Flávia Campos Corgosinho:** Writing – review & editing. **Maria Marketou:** Writing – review & editing. **Stefano D'Errico:** Writing – review & editing. **Gianfranco Sinagra:** Writing – review & editing. **Aneta Aleksova:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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