Endocrine, Metabolic & Immune Disorders - Drug Targets, 2019, *19*, 571-579

REVIEW ARTICLE

Focus on the Correlations between Alzheimer's Disease and Type 2 Diabetes

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ARTICLE HISTORY

Received: June 24, 2018
Revised: February 20, 2019
Accepted: February 27, 2019

DOI:
10.2174/1871530319666190311141855

Abstract: ***Background:*** In the last decades, both diabetes mellitus and Alzheimer's disease are constantly increasing. Affected individuals, therefore, represent an enormous problem for the society, governments and global organizations. These diseases are usually considered as independent conditions, but increasing evidence shows that there are links between these two disorders.

Methods: In this review, we analyzed common features present in Alzheimer's disease and diabetes mellitus, showing how these two diseases are strictly correlated to each other.

Results: Some pathogenetic factors are shared by Type 2 Diabetes and Alzheimer's Disease: chronic inflammation, oxidative stress, mitochondrial dysfunction, adiponectin deficiency, different expression of plasma cholinesterase activity and vascular damage could represent a possible explanation for the coexistence of these two conditions in many patients.

Conclusion: A better understanding of this issue and an appropriate management of diabetes by means of physical activity, low fat diet, and drugs to achieve a good glycemic control, avoiding both hyperglycemia and hypoglycemia, can represent a way to prevent cognitive decline and Alzheimer's disease.

Keywords: Alzheimer's disease, Hyperglycemia, Insulin resistance, Type 2 diabetes mellitus, chronic inflammation, neurodegenerative disorder.

1. INTRODUCTION

Alzheimer's Disease (AD) and diabetes mellitus are both frequently encountered conditions [1]. These diseases, representing a very important health problem, are considered as independent diseases, but growing evidence shows that there are many links between these two disorders.

Alzheimer's disease, the most common cause of dementia, is a progressive and limiting neurodegenerative disorder. The two anatomic and histopathological main characteristics of AD are Senile Plaques (SPs) and Neurofibrillary Tangles (NFTs) [2-4]. Memory deficiency first, followed by a steady loss of judgement, verbal fluency, reasoning skills, and other cognitive functions are the most frequent consequences of this illness. Enormous SP deposits in the cerebral cortex induce inflammatory response through astroglial and microglial activation, causing synaptic degeneration, and consequently, cognitive dysfunction [5]. NFTs consist of an intracellular accumulation of the aggregated microtubule-binding protein tau [6-9]. Evidence in the literature shows that hyperphosphorylation of tau protein leads to the formation of NFTs. These deposits are related to synaptic loss and neuronal death, causing cognitive impairment [9]. Although it is scientifically demonstrated that mutations in certain genes cause Familial AD (FAD), more than 90% of AD patients have the sporadic form [10]. This suggests that aging is an important non-modifiable risk factor for AD but not the only one. The aim of this narrative review is to show these links, highlighting the possible role of different factors, such as insulin resistance, inflammation, oxidative stress and mitochondrial dysfunction, which are common to both conditions, explaining their frequent association and mutual influence.

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2212-3873/19 $58.00+.00

2. RISK FACTORS FOR ALZHEIMER'S DISEASE

Most authors claim that AD occurs as a result of complex interactions between genes and other risk factors. Age, a family history of AD and heredity are the most important risk factors that cannot be changed, but emerging evidence suggests that there may be other factors which can be modified.

Genetic variation in Apolipoprotein E (APOE) gene is the most known genetic risk factor for AD [11]. In elderly patients, other risks factors for AD are: obesity, Type 2 Diabetes Mellitus (T2DM), and a long lasting diet high in saturated fat (Table **1**). These risk factors are linked to reduced cognitive function in both humans [12-17] and animal models [18- 25].

Furthermore, insulin resistance has been identified as a major risk factor for the onset of AD.

Table 1. Risk factors.

1	Genetic Variation in Apolipoprotein E (APOE) Gene
2	Obesity
3	Type 2 Diabetes Mellitus (T2DM)
4	Long lasting diet high in saturated fat

3. WHY INSULIN RESISTANCE AND T2DM ARE RISK FACTORS FOR AD

Insulin has a key role in learning and memory, in particular directly regulating ERK, a kinase required for the type of learning and memory compromised in early AD.

In non- pathological situation, insulin binds to the Insulin Receptor (IR) which phosphorylates IR Substrate (IRS) on a tyrosine residue, activating the signaling cascade. In peripheral tissues, this signaling leads to the uptake and sequestration of blood glucose to satisfy cellular energy requirements [26]. In the brain, neuronal cells use glucose with a process that is insulin independent. However, in the brain, insulin plays a key role in neuronal functions by regulating energy metabolism, growth, survival, and differentiation *via* insulin signaling [27-32].

Several hypotheses claim hyperinsulinemia, insulin resistance and T2DM as influence factors for the risk of AD.

According to many scientific studies, hyperinsulinemia and insulin resistance can lead to amyloid extracellular deposition and augmented production of tau proteins, increasing the risk for the brain to develop AD [33]. In the same way, an aberrant insulin signaling can lead to an AD-like pattern of reduced cerebral glucose metabolic rate in the brain [34, 35] possibly evolving in AD [36].

Various studies show that T2DM gets worse [37-48] and induces AD disease [35] in several animal models (rat, mouse).

In addition, T2DM, can lead to small vessel vasculopathy, through various mechanisms such as: accumulation of polyols, non-enzymatic glycosylation of structural proteins (AGE products), oxidative stress, activation of Protein Kinase C (PKC) causing endothelial damage. Small vessels vasculopathy contributes to dementia, independently or in association with AD pathology and causes a disruption of proper function of the brain vasculature [49].

4. TYPE 3 DIABETES: A CONSEQUENCE OF AD

Insulin, produced by pancreas beta cell, crosses the Blood Brain Barrier (BBB) through a carrier -mediated and temperature-sensitive active process [50], and after reaching the brain, it binds to the IR, widespread especially in specific cerebral areas, such as hypothalamus, hippocampus and cortex [51, 52]. Insulin, linking to IR, activates a cascade of intracellular phosphorylation. Through this process, insulin exerts several roles as neuromodulation [53], repairing and neuronal differentiation, and cognitive function [53-58], as shown by studies in animal models [59].

Especially in hyperinsulinemia conditions, insulin has a further role in the formation of SP deposits [58, 60, 61] and phosphorylation of tau protein, component of NFTs. Chronic cerebral hyperinsulinemia in AD brains probably could be caused by a defected IR because its expression is increased in cerebral cells [62].

In the case of SP, consisting of Aβ peptides, some studies demonstrate that high insulin levels promote their deposits after activation of the mitogen activated protein kinase (MAPK) pathways [63]. Other studies give more importance to Insulin-Degrading Enzyme (IDE) [64] in accumulation of SP [60, 64-66]. When insulin levels are normal, IDE degrades insulin and some peptides, included Aβ, but when there are high insulin levels, it promotes only insulin degradation, and in this way, can induce formation of SP deposits [64, 67]. Additionally, hypoglycemia can decrease IDE levels, causing an impairment of SP degradation [58].

Furthermore, SP deposits cause dysregulation of glucose metabolism [62].

Relative to phosphorylation of tau and NFT aggregation, they are promoted by GSK-3β activated by insulin and Insulin-like Growth Factor-1 (IGF-1) stimulation [67, 68-70]. It has been demonstrated that when GSK-3 is inhibited there is an improvement of cognitive functions [71].

Several studies carried out on AD brains showed that in this disease, there are conditions of brain insulin resistance and brain insulin deficiency [32, 71, 72].

These conditions are both consequences of chronic hyperinsulinemia, as already described, a mediator of neurodegeneration, that leads to brain insulin resistance and impaired insulin uptake [72-74]; the latter could lead to brain insulin deficiency [74]. Furthermore, hyperinsulinemia increases SPs and NFT deposits, that can competitively inhibit the binding of insulin to the IR [75-76], causing further insulin resistance. Consequently, it has been termed "type 3 diabetes" [77] (Fig. **1** and Fig. **2**).

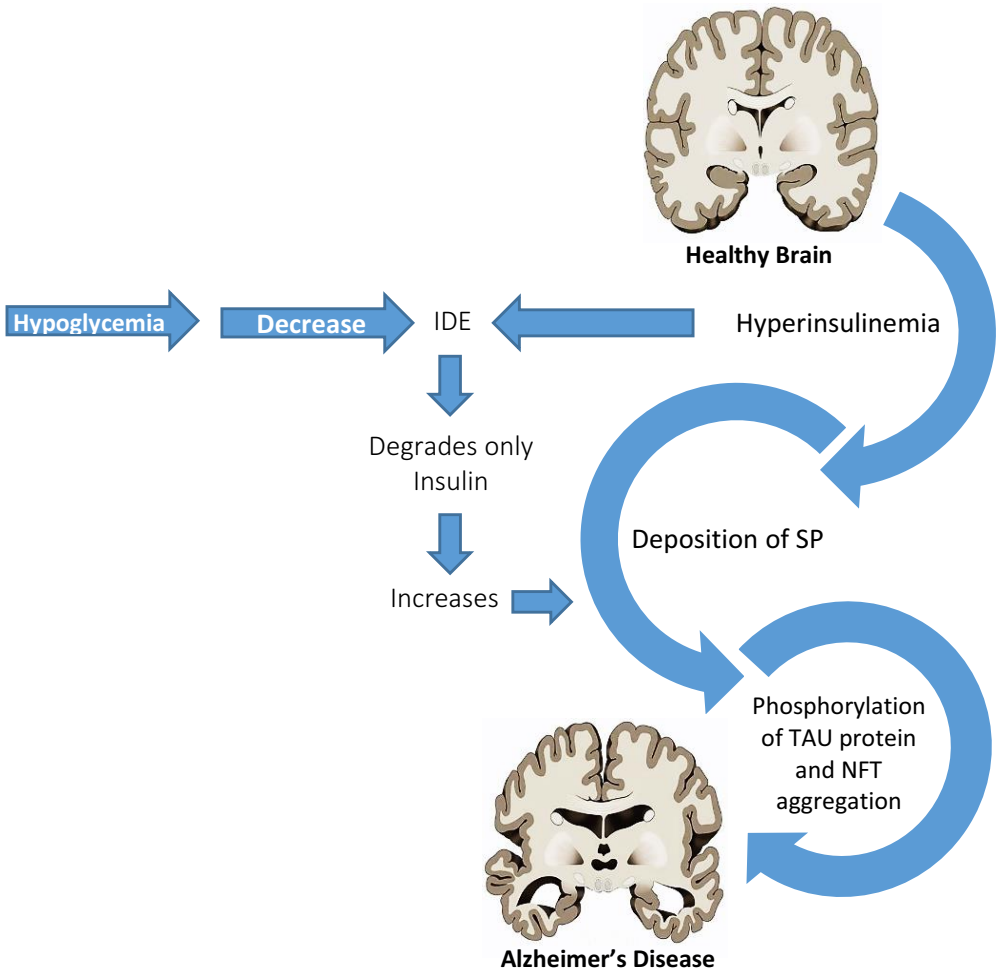

Fig. (1). Type 3 diabetes.

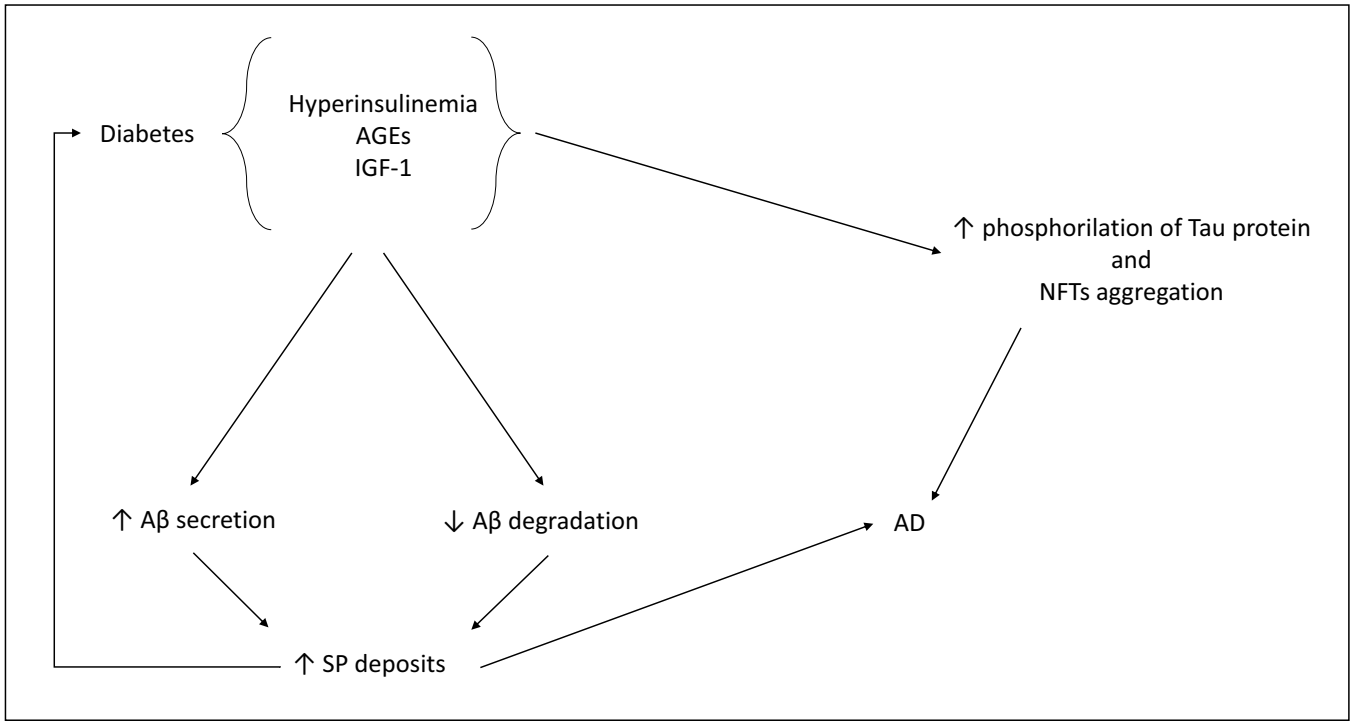

Fig. (2). Possible relationship between diabetes and Alzheimer's disease.

5. PHYSIOPATHOLOGICAL FEATURES COMMON TO T2DM AND AD

It has been observed that there are some pathogenetic factors shared by T2DM and AD (Table **2**) such as: chronic inflammation [78-80], oxidative stress [79, 81], adiponectin deficiency [82], different expression of plasma cholinesterase activity [81, 83] and vascular damage [78], as described in detail below.

Table 2. Physiopathological features common to both T2DM and AD.

1	Chronic Inflammation
2	Oxidative stress
3	Adiponectin deficiency
4	Plasma cholinesterase activity
5	Vascular damage

1) Several studies show that in chronic inflammation process, inflammatory cells, such monocytes and macrophages, produce interleukins, including IL-6 and cytokines, including TNF-α. The latter plays a key role in this process underlying these two diseases [80, 84, 85] as it has been shown by studies on postmortem AD brain in which inflammatory markers have been found [86, 87].

   Particularly, TNF-α is a pro-inflammatory cytokine, produced by macrophages and by microglial cells and when it is activated it can cause inhibition of insulin receptor signaling, promoting phosphorylation of IR, and consequently persistent hyperinsulinemia [78, 80, 88]. It has been demonstrated that when TNF-α is neutralized, insulin sensitivity improves [89, 90].

   Besides hyperinsulinemia, hyperglycemia can cause production and increase of AGEs (Advanced Glycation End-products), identified in SP e NFTs, indicating a further link between hyperglycemia and AD [91].

   Additional production of pro-inflammatory cytokines is stimulated by SP that further activates microglial cells and astrocytes involved in chronic inflammation and consequently in oxidative stress that secondly leads to damage and cellular death, activating moreover inflammatory process [92].

   Additionally, metabolic disorders, such as T2DM, insulin resistance and hyperinsulinemia, set off a chronic low-grade inflammation, causing further production of proinflammatory citokines [78]. This hypothesis is supported by studies conducted both in animal and human models [93, 94].

   So, it is clear that chronic inflammation could be the principal cause of AD and metabolic disorders, such as T2DM [78-80].

   Furthermore, some evidence suggests that bacterial infection could play a key role in inflammatory process, particularly in T2DM [95]. In this case, bacterial infection could start chronic inflammation and then SP deposition, causing the onset of AD [95].

2) Oxidative stress is another link between these diseases, evidenced in animal models [78, 96]. It is a mechanism of cellular damage caused by Reactive Oxygen Species (ROS), produced by high fat diet. They are targeting cellular components, leading to cellular structural alterations, such as an impairment of mitochondrial function [78, 81, 97], and consequently inflammation and Ca2+ dysregulation [81], and following cellular damage and then cellular death [78]. Furthermore, they cause an impairment of insulin secretion and sensitivity [78, 98, 99].

   Increased cytosolic Ca2+ levels are involved in amyloidogenic process and cause a continuous oxidative stress, getting worse the situation [81].

   Additionally, aging is associated with a deficit of antioxidant production and this condition aggravates the pathological situation [100, 101].

3) Another important factor is Adiponectin (APN), an adipocytokine secreted by adipocytes, that is involved in the pathophysiology of these diseases. Indeed, it has been observed that low APN levels are related to hyperinsulinemia, and then APN would have an insulin sensitizing role possibly improving T2DM and AD too [82, 102].

4) Another important component in inflammatory process is represented by plasma cholinesterase activity (pChE). There are two different type of cholinesterase: acetylcholinesterase (AChE) e Butyrylcholinesterase (BuChE). In this case, when we talk about pChE, we refer to BuChE. AD and T2DM are positively related to pChE [83, 103-105]. PChE is also positively correlated to SP deposition [105, 106] and it is also concentrated in cerebral regions involved in AD [106]. Indeed, high levels of BuChE have been found in SP and NFT [59].

   It has been observed that pChE induces AChE downregulation [103], and this happens especially when pChE is hyperactivated [83]. Since AChE arrests inflammation [107, 108], consequently there is an increased inflammation [83].

5) Finally, evidence shows that vascular damage is verifiable in both T2DM e AD but, although it is demonstrated that it is caused by T2DM and that could contribute to dementia [49], the mechanistic link between vasculopathy and AD, independently of the presence of T2DM, has not yet been clarified [56].

6. COGNITIVE DECLINE IN AD

AD is characterized by a particular cognitive decline with specific clinical features such as:

1) Memory impairment: AD patients have a gradual memory impairment, starting with a deficit of episodic memory, especially in the short term, and then semantic (concerning then meaning of words), prospective (regarding their commitments), procedural (regarding the manner in which daily functions are performed), autobiographic (concerning personal experiences) memory.

As a result, at the beginning of this disease, AD patients are aware of this deficit and then they can be depressed.

2) Apraxia: Not capable of carrying out daily life movements.
3) Aphasia: Difficulty in using the word that causes deficit of verbal and written comprehension.
4) Echolalia: Constant repetition of a word or phrase.
5) Agnosia: Inability to recognize objects and their use.
6) Alteration of behavior: Difficulty in speaking, reading and understanding the language, which can cause depression, mutism and isolation. This results in alterations of personality, in contrast with the nature (can suddenly cause aggression) thereby resulting in abrupt humoral changes.
7) Disorientation: Loss of sense of temporal-space orientation.
8) Loss of attention: Inability to focus attention on external inputs and to perform multiple actions at the same time.
9) Urethral and fecal incontinence: Loss of control of anal and urethral sphincters.

Various tests are conducted to examine cognitive decline in this severe illness, but the most used are two:

- Mini-Mental State Examination (MMSE), a point test to evaluate temporal-space orientation, memory, attention, language and spatial visual function.
- The clock drawing test that is used as a screening test to evaluate cognitive functions. It consists to draw a clock and a time indicated by the operator.

7. CONNECTIONS BETWEEN T2DM AND COGNITIVE DECLINE

There are studies that analyzed connections between T2DM and cognitive decline in human models with [80, 109, 110] or without AD [80, 111].

About studies that analyzed connections between T2DM and cognitive decline, a study effectuated in Korean men with T2DM evidenced that T2DM leads to an impairment of cognitive function, even if there is a good metabolic control [111], while another study supposed that a probable cause of cognitive impairment could be a high fat diet that leads to chronic cerebral inflammation and consequently to a cognitive deficit [80, 112, 113].

Many other studies observed connection between AD, T2DM and cognitive impairment. A study focused on the progression of cognitive decline examining a cohort of AD patients divided into two different groups based on the presence or absence of T2DM and the result was that AD patients with T2DM showed less functional cognitive decline over an 18-month period compared with AD patients without T2DM [109].

A review analyzed 10 studies to find connections between diabetes and cognitive impairment in AD patients [110]. It was observed that in 2 of these studies a faster cognitive decline in AD patients was caused by diabetes. Other studies evidenced, however, that in AD patients there was not a correlation between diabetes and cognitive impairment, rather some studies indicated that diabetes could have a protective role [110].

Researchers have speculated that these discordant findings could be caused by the possible role of different causes of cognitive decline, as a cerebral vascular impairment, hyperglycemia (even without diabetes) [114] and frequent episodes of hypoglycemia [72, 110, 115, 116]. Another possible interpretation could be differences in the use of antidiabetic [110, 117], antihypertensive drugs [110, 118], statin or aspirin [110, 119-121], that could have a protective role in cognitive decline in AD.

Another study focused attention on chronic inflammation in both the illnesses. According to a study on post-mortem AD brain, researchers found that patients with a T2DM had more inflammation than patients without T2DM [122]. This hypothesis has been confirmed by another study on post-mortem AD brain that demonstrated that rate of inflammation was correlated to high synapse loss [123].

Furthermore, it has been observed that diabetic retinopathy could be correlated with cognitive impairment and AD [124].

CONCLUSION

There is increasing evidence that diabetes mellitus is associated with depression [125], dementia and AD.

In this review we analyze the close links between diabetes and AD showing how these two diseases are strictly related to each other. It is known that insulin resistance and obesity are risk factors for the development of AD. Notably, a chronic condition of hyperinsulinemia favors the formation of SP deposits and the phosphorylation of tau protein, an important component of NFTs. Furthermore, the increase in SP and NFT deposits may competitively inhibit the binding of insulin to its receptor and this translates into further insulin resistance. In addition to hyperinsulinemia, hyperglycemia can generate the production and increase of AGE (advanced glycation end products) that have been identified in SP and NFT; this indicates a further link between diabetes mellitus and AD.

Therefore, it is well understood how important it is to prevent and treat diabetes through changes in lifestyle (physical activity, low fat diet, *etc.*) as well as achieving a good and stable glycemic control, avoiding both hyperglycemia and hypoglycemia and the administration of antioxidant agents [126] and antidiabetic drugs in order to prevent cognitive decline and then AD. Furthermore, it is really important to accurately evaluate patients to look for the clinical conditions frequently found in the elderly that can precipitate cognitive impairment, such as hypothyroidism [127] and testosterone deficiency in old men [128].

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The study did not receive any funds/grants.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Vincenzo Fiore: project leader, data collection, manuscript writer; Antonia De Rosa: data collection; Paolo Falasca: data collection, manuscript writer; Massimo Marci: data collection; Edoardo Guastamacchia: manuscript reviewer; Brunella Licchelli: manuscript reviewer; Vito Angelo Giagulli: manuscript reviewer; Giovanni De Pergola: manuscript reviewer; Antonella Poggi: data collection; Vincenzo Triggiani: manuscript final revision.

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