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ASSOCIATION TYPE 2 DIABETES MELLITUS AND ALZHEIMER DISEASE : A SYSTEMATIC REVIEW

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Abstract

The International Diabetes Federation (IDF) reports that diabetes affects one in ten people throughout the world, and that insulin-resistant type 2 diabetes mellitus (T2DM) accounts for 90 percent of all cases of diabetes. According to findings from epidemiology research, the pathophysiology and clinical patterns of Alzheimer's disease and type 2 diabetes are similar. Insulin resistance is a hallmark of both illnesses. The pathogenesis differentiates between inflammatory, metabolic, and zinc-deficient variants of the condition. Alzheimer's disease is associated with both type 2 diabetes and prediabetes, often known as metabolic syndrome. Due to the fact that Alzheimer's disease shares many pathophysiological similarities with diabetes, it is sometimes referred to as type 3 diabetes. A primary focus of dementia research is insulin resistance, which impairs cognitive function and contributes to the development of dementia. IGF has an effect on cognition as well. The chance of acquiring T2DM rises with age, much like the risk of developing Alzheimer's disease, and T2DM also raises the risk of developing dementia in general, specifically Alzheimer's disease. Both T2DM and AD are chronic and complex diseases, and both show evidence that oxidative stress and inflammation play a role in the progression of the diseases. Despite the fact that T2DM is primarily a peripheral disorder and AD is a disease of the central nervous system, the two diseases share some similarities.

Keyword: *Alzheimer Disease; Genomic; Neurobehaviour; Type 2 Diabetes Mellitus*

INTRODUCTION

Alzheimer's disease (AD) causes 60–70% of dementia in older persons. The etiology of AD is still unknown, but genetic, environmental, and pathological risk factors have been identified. The brain forms amyloid-β (Aβ) oligomers and fibrils when neuronal cells aggregate and deposit Aβ peptides on their extracellular surfaces.[1] AD patients also have brain hyperphosphorylation of tau protein, which produces neurofibrillary tangles in neuron microtubules. Cytotoxic actions on neuronal cells cause cognitive impairment. Throughout the previous few decades, diabetes mellitus (DM) prevalence has increased.[2]

According to the International Diabetes Federation (IDF), 1 in 10 persons worldwide have diabetes, and insulin-resistant type 2 diabetes mellitus (T2DM) accounts for 90% of all diabetes occurrences. T2DM, like dementia, increases with age, but metabolic disturbances also raise dementia risk.[3,4] T2DM, a peripheral disease, and AD, a central nervous system ailment, share protracted prodromal periods and chronic, complex circumstances. Chronic oxidative stress and inflammation also contribute to disease progression. Age, obesity, poor diet, chronic stress, hereditary profile, and sedentary lifestyle are further risk factors.[4–6]

A meta-analysis of 28 prospective observational studies on 89,708 diabetic patients found a 73% increase in the risk of total dementia, including AD and vascular dementia, and a 56% increase in AD risk. Type 3 diabetes (T3DM), a neurometabolic condition, was coined from these findings that DM increases AD risk. Hyperglycemia causes glutamate-induced excitotoxicity in neuronal cells, and insulin resistance in the brain may cause amyloid-β buildup, tau phosphorylation, oxidative stress, AGEs, and death. AD and T2DM's link is unclear.[4,7,8]

Epidemiology research showed that Alzheimer's and type 2 diabetes overlap pathogenesis and clinical trends. Both disorders have insulin resistance. The pathomechanism distinguishes inflammatory, metabolic, and zinc-deficient forms.[8] Type 2 diabetes and prediabetes/metabolic syndrome are linked to Alzheimer's disease. Alzheimer's disease is nicknamed type 3 diabetes due to its pathophysiological similarities to diabetes. Insulin resistance, which affects cognitive function and promotes dementia, is a focus of dementia research. IGF affects cognition too.[9]
This study wants to assess the association type 2 diabetes mellitus and alzheimer disease.

METHODS

Protocol

The author used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to comply with in order to ensure that this research was carried out in accordance with the referenced standards. This is done to ensure that the results of this investigation are accurate.

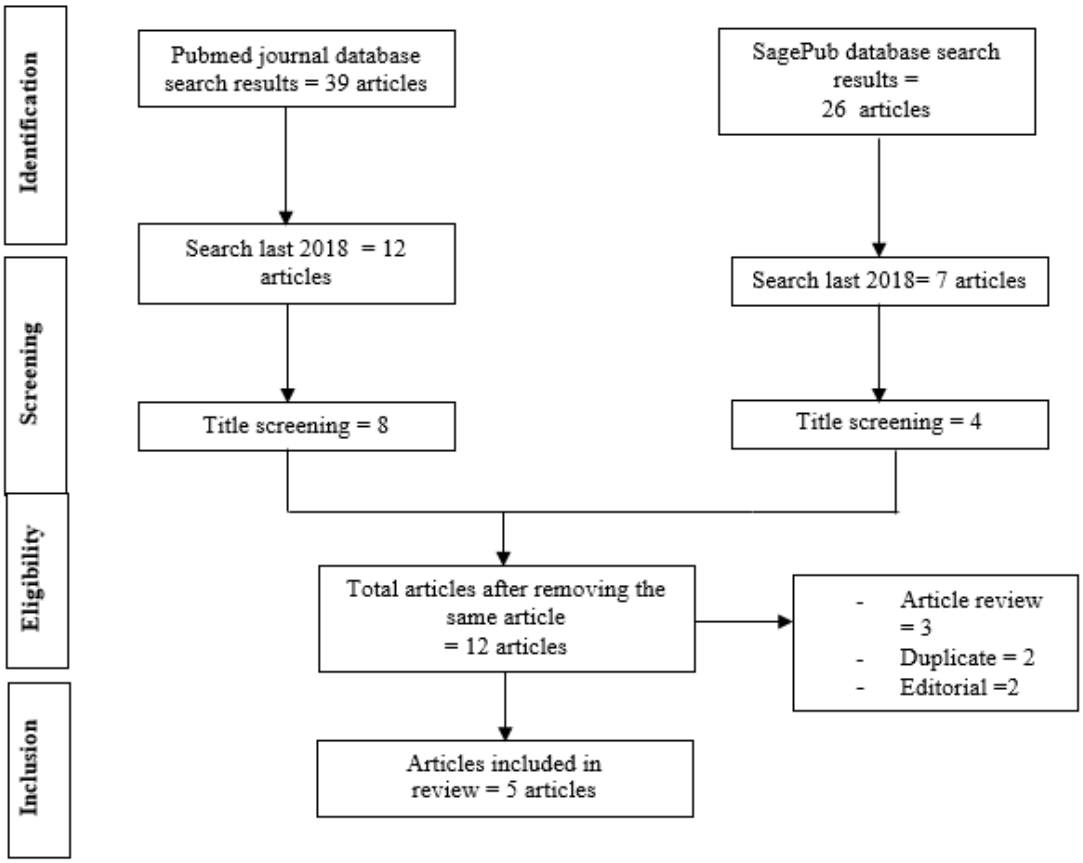

Figure 1. Article search flowchart

Criteria for Eligibility

This literature review aims to assess the association type 2 diabetes mellitus and alzheimer disease by evaluating or analyzing previous studies on the subject. This article is made with a theme in order to show significant problems in the issues raised. Researchers participating in studies met the following criteria: 1) To be considered for publication, the publication must be written in English and focus on the association type 2 diabetes mellitus and alzheimer disease. 2) Articles published after 2018 but before the time period covered by this systematic review were included in this assessment. Editorials, submissions without DOI, previously published review articles, and entries substantially similar to those previously published in journals are examples of research excluded in this article.

Search Strategy

We used "type 2 diabetes mellitus" and "alzheimer disease" as keywords.The search for studies to be included in the systematic review was carried out from February, 17th 2023 using the PubMed and SagePub databases by inputting the words: *("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields])* used in searching the literature.

Data retrieval

After reading the research abstract and title, the writers evaluated the studies to determine whether or not they satisfied the inclusion criteria. The writers then choose a number of previous studies to cite as references for this one. After looking at multiple different research that all followed the same pattern, we have arrived at this conclusion. All of the included studies need to be written in English and can't have a publication date earlier than 2018.

In the systematic review, we only looked at studies that qualified to be included if they satisfied all of the inclusion criteria. This restricts the search to only material that is relevant. We do not consider any research results that do not adhere to the criteria we have outlined. After this step comes the evaluation of the research in its entirety. Throughout the course of the investigation of this study, the following information was discovered: names, authors, publication date, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Before picking which publications to study further, each author conducted their own independent analysis of the individual studies provided in the publication's title and abstract. Thereafter, we will evaluate all papers that match the inclusion criteria and are acceptable for the systematic review. Then, we will pick which publications to include in the review depending on our findings. This criterion is used to select reviewable manuscripts. to simplify as much as possible the procedure of picking papers for review. Which prior studies were undertaken, and what aspects of those research qualify them for inclusion in the review?

RESULT

First study from Kingdom of Bahrain with 12 patients showed 62 proteins were identified as being differently expressed in T2DM compared to healthy controls, and they were categorized into 16 functional protein groups. The biggest category consisted of immuneassociated proteins. In addition, around 25 of these proteins (40%) have been previously related with DM; however, the relationship of the remaining 37 proteins with T2DM was an unique finding. In T2DM, the majority of identified proteins were elevated. The discovered proteins may have a role in the illness's etiology or act as disease biomarkers.[10]

Huth, et al (2019)[11] conducted a study and they showed MASP levels were connected with both incident type 2 diabetes and prediabetes. Incidence of type 2 diabetes was inversely linked with adiponectin. Individual continuous outcomes were linked with MASP, adiponectin, apolipoprotein A-IV, apolipoprotein C-II, C-reactive protein, and glycosyl phosphatidy linositol specific phospholipase D1. The combination of MASP, apolipoprotein E (apoE), and adiponectin enhanced the prediction of diabetes over both reference models, but MASP plus CRP improved the prediction of prediabetes over the HbA1c model.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Abdulwahab, 2019[10]	Bahrain	Case control study	6 patients with T2DM and 6 controls	**Upregulated:** α-1-acid glycoprotein 2, *Ig μ chain C region*, Ig γ-3 chain C region, thrombin light chain, heparin cofactor 2, protein IGKV3-11, *Ig κ chain C region*, serum amyloid P-component, Ugl-Y3 (fragment), Ig γ-2 chain C region, *zinc-alpha-2-glycoprotein*, Ig γ-1 chain C region, *ceruloplasmin*, multiple P DZ domain protein, isoform 2 of *haptoglobin-related protein*, complement component C8 α chain, vitronectin, Ig λ-2 chain C regions, protein PRR C2B, clusterin β chain (fragment), *Ig α-1 chain C region*, plasminogen, isoform 2 of ficolin-3, Ig α-2 chain C region, protein AMBP (fragment), *inter-alpha-trypsin inhibitor heavy chain H2*, uncharacterized protein, pigment epithelium-derived factor, protein IGKV2-28, hemoglobin subunit δ, *apolipoprotein B-100*, eukaryotic translation initiation factor 4E type 3 (fragment), multiple epidermal growth factor-like domains protein 11 (fragment), hemoglobin subunit α, *galectin-3-binding protein*, β-defensin 112, myosin light chain 5, transthyretin, rap guanine nucleotide exchange factor 2, THO complex subunit 3, bile salt export pump, importin-8, V-set and immunoglobulin domain-containing protein 8 **Downregulated:** Ig γ-4 chain C region, ribulose-5-phosphate-3-epimerase isoform CRA_a, isoform 4 of Coiled-coil domain- containing protein 17, protein Njmu-R1, *inter alpha trypsin inhibitor heavy chain H1*, Ig κ chain V-I region AG, procollagen C endopeptidase enhancer 2 (fragment), isoform SH-iPLA2 of 85/88 kDa, calcium-independent phospholipase A2, suppression of tumorigenicity 5 protein, apolipoprotein C II, *apolipoprotein A-I*, Hemoglobin subunit γ-2, intraflagellar transport protein 122 homolog (fragment), hemoglobin subunit β, CD5 antigen-like, Ig γ-3 chain C region, plasma protease C1 inhibitor, Ig γ-2 chain C region, TATA box-binding protein-associated factor RNA polymerase I subunit C, DDB1- and CUL4-associated factor 8, Ig γ-4 chain C region, homeobox protein SIX5
Huth, 2019[11]	Germany	Prospective cohort study	892 participants (123 cases)	**Upregulated:** mannose-associated serine protease, apolipoprotein C-II,a polipoprotein C-III, apolipoprotein E **Downregulated:** adiponectin
Dey, 2019[12]	USA	Case control study	Control (n = 5) and AD patients (n = 6)	**Upregulated:** putative tRNA pseudouridine synthase Pus10, transcription factor IIIB 90 kDa subunit, roquin−2, CAP-Gly domain-containing linker protein 1 **Downregulated:** Phosphoenolpyruvate carboxykinase, adenylate kinase, dihydrolipoyl dehydrogenase, stress−70 protein, cytochrome c, glycine amidinotransferase, estradiol 17-beta-dehydrogenase, 3-hydroxyacyl-CoA dehydrogenase type−2, carnitine O-palmitoyltransferase, enoyl-CoA hydratase domain-containing protein, alanine--glyoxylate aminotransferase, glycine N-acyltransferase, glutathione S-transferase kappa 1, activating transcription factor 7-interacting protein, 60S acidic ribosomal protein, dynein heavy chain 5, dmX-like protein, peflin, noelin−3, isoform 4 of Tumor protein D53, rho-associated protein kinase 1, n-acetylneuraminate lyase, zinc finger protein 862, cingulin, inner centromere protein, isoform 2 of Chordin-like protein
Li, 2018[13]	USA	Case control study	5 patients with AD and 5 controls	**Upregulated:** integrin alpha 2B **Downregulated:** Complement C3, serum amyloid A4, haptoglobin, chemokine (C-X-C motif) ligand 7
Park, 2019[14]	Republic of Korea	Prospective cohort study	147 participants (40 cases)	Downregulated: Galectin 3-binding protein, angiotensin 1- converting enzyme

Dey, et al (2019)[12] study showed TMT-LC/LC-MS/MS technology can analyze 4826 protein components (4368 genes), encompassing at least 6 orders of magnitude in dynamic range, making it one of the most comprehensive serum proteome analyses available. In the AD and control groups, we defined intra- and inter-group variability. A statistical study found that proteins in Alzheimer's disease were differently expressed. Interestingly, these changed proteins are concentrated in mitochondrial, fatty acid beta oxidation, and AGE/RAGE pathways. Lastly, we used the TOMAHAQ technique to validate the reduction in PCK2 and AK2 in our AD samples.

Other study showed ten tryptic peptides that belonged to 5 proteins in plasma lipoproteins had unadjusted p values < 0.05, compared to no peptides in immunodepleted plasma. Furthermore, 27, 32, 17, and 20 tryptic peptides in VLDL, IDL, LDL and HDL, demonstrated overall peptide fold differences > 1.05 or < 0.95, compared to only 6 tryptic peptides in immunodepleted plasma. The overall comparisons, therefore, suggested greater peptide/protein differences in plasma lipoproteome when measured in individual plasma lipoproteins than as total in immunodepleted plasma.[13]

Park, et al (2019)[14] using mass spectrometry (MS)-based proteome analysis to identified five plasma biomarker candidates and confirmed these proteins using an enzyme-linked immunosorbent test. Our integrated models were highly predictive of brain amyloid deposition, with an overall accuracy of 0.871, 79% sensitivity, and 84% specificity, and an accuracy of 0.836, 68% sensitivity, and 90% specificity in patients with MCI. These findings suggested that a combination of proteomic-based blood proteins may be used to predict cerebral amyloid formation.

DISCUSSION

Diabetes mellitus (DM) is a basic metabolic illness in which the metabolism is regularly disrupted and metabolic homeostasis is thrown off due to a lack of or a decrease in insulin activity. Insulin is a key metabolic regulator for all macromolecules, including carbs, lipids, and proteins. Insulin secretion, on the other hand, is controlled by a number of metabolites, including ATP/ADP and NAD/NADH ratios, blood glucose, and amino acids. We hypothesized that a number of proteins would play a role in DM pathogenic alterations and their outcomes.[4,15–17]

The most remarkable discovery was that the immunological protein class was widely represented and significantly elevated in T2DM (15/18 proteins). These proteins mostly consist of Ig chain C regions (γ, α, κ, μ and λ). Ig chain V-I region AG and Protein IGKV2-28, the latter of which was shown to be elevated, were also discovered. These two proteins were previously shown to be related with the autoimmune illness systemic lupus erythematosus.[10,19,20]

Study in Germany showed MASP signal is derived from peptides that are proteotypic for the three isoforms MASP-1, MASP-3, and MAP44, it is presently not viable to distinguish between these isoforms. MASP-1 is the most abundant serine protease of the complement lectin pathway and thus a major player in the complement cascade. This cascade is initiated when a complex consisting of mannose-binding lectin (MBL), MBL-associated serine proteases (MASPs: MASP-1, MASP-2, MASP-3) and MBL-associated proteins (MAP19 and MAP44) binds to its target carbohydrate-containing ligands.[11,21]

Dey, et al found 4826 proteins and showed great proteome coverage, sensitivity, and reproducibility, as well as multiplexed focused tests. Although our pilot work used substantial fractionation and a long instrumentation time, we propose to attain similar findings with 4000 proteins in a suitable time frame. This comprehensive TMT-LC/LC-MS/MS apparatus will be useful for measuring complicated clinical specimens in general. These unique protein signatures may be associated to Alzheimer's disease development and have the potential to be used as biomarkers in a large-scale study, maybe using the TOMAHAQ-based LC-MS3 test.[12]

The 'TGVI' and 'AAGN' peptides were most substantially related with incident diabetes in our peptide-specific sensitivity analysis. In contrast to the 'SLPT' peptide, which is exclusively proteotypic for the MASP-1 isoform, these two peptides may be derived from MASP-1, MASP-3, or MAP44, indicating that MASP-3 or MAP44 are responsible for the observed connection and should be most relevant for prediction purposes. MASP-3 has an unique substrate selectivity and inhibitor profile compared to MASP-1 and MASP-2; for example, it selectively cleaves insulin-like growth factor (IGF) binding protein 5 (IGFBP-5), which binds to IGFs such as IGF-1.[11,17,21]

The function of immunity in T2DM is bimodal, as immunity may contribute to the pathophysiology of T2DM, while the suppression of immunity is one of the disease's most significant repercussions. Several immunological proteins were also elevated in T2DM, including isoform 2 of Ficolin-3, β-defensin 112, Complement component C8 chain, and Serum amyloid P-component. The immunological proteins CD5 antigen-like, Ig γ-4 chain C region, and Ig κ chain V-I region AG were downregulated.[10,19,20]

Recent research indicates that cognitive impairment and dementia are widespread (and underrecognized) consequences of diabetes mellitus (DM). Many studies have demonstrated that phenotypes associated with obesity and/or changes in insulin homeostasis are related with an increased risk of cognitive decline and dementia, including not just vascular dementia but also Alzheimer's disease (AD). Included in this category are prediabetes, diabetes, and the metabolic syndrome.[22]

There is more and more evidence that insulin abnormalities and insulin resistance are more common in people with Alzheimer's disease. This may contribute to the disease's pathophysiology and clinical symptoms. Insulin has been known for a long time to be important for how energy is used in the periphery. Over the past 20 years, a number of different studies have started to show that insulin is also important for energy metabolism and other parts of how the CNS works. Twenty years ago, researchers found that insulin and insulin receptors were expressed densely but selectively in the brain, including in the medial temporal regions that help form memories.[18]

Insulin may also regulate the amyloid precursor protein and its product beta-amyloid (Abeta), which are linked to senile plaques, a neuropathological characteristic of Alzheimer's disease. Insulin has been hypothesized to promote Abeta's intracellular trafficking and inhibit its breakdown. These findings are consistent with the hypothesis that insulin irregularities may impact Abeta levels in the brains of Alzheimer's disease patients. The increased incidence of insulin resistance in Alzheimer's disease and the multiple avenues through which insulin may alter clinical and pathological features of the illness imply that increasing the efficiency of insulin may have therapeutic value for Alzheimer's disease patients.[18]

Diabetes types 1 and 2 are also significant risk factors for worse performance in a number of cognitive skills. Chronic hyperglycemia and hyperinsulinemia largely induce the development of Advanced Glucose Endproducts (AGEs), resulting in an excess of Reactive Oxygen Species (ROS). Protein glycation and increased oxidative stress are the two primary processes involved in biological aging, and both are likely implicated in the etiopathogenesis of Alzheimer's disease.[22]

Alzheimer's disease is characterized by amyloid ß buildup in the brain, hyperphosphorylation of tau proteins, and disruption of neurofibrillary tangles. Amyloid ß is co-secreted with insulin by pancreatic ß-cells. Autopsy revealed the presence of amyloid ß and hyperphosphorylated tau protein in the Langerhans islets. Amyloid deposits in the pancreatic and the brain exhibited comparable characteristics. As a result of hyperglycemia, glycation endproducts stimulate the formation of amyloid plaques, neurofibrillary disruption, and activated microglia, all of which are characteristic of Alzheimer's disease.[23]

Chronic hyperglycemia results in oxidative stress, which formerly had a major role in the development of both illnesses. Low-grade inflammation is an important pathophysiological element in both conditions. Inflammation is generated by proinflammatorical adipocytokines, dysbacteriosis, metabolic endotoxaemia brought on by lipopolysaccharides, and a high-fat diet, which also contributes to insulin resistance. Recent research indicates that microbial amyloid, the primary bacterial byproduct, also contributes to the pathology of the human central nervous system.[23]

Alzheimer's disease is a diverse illness for which there is now no effective treatment. The use of intranasal insulin spray has produced promising outcomes. In animal tests, insulin sensitizers such as metformin and thiazolidines have also improved cognitive functioning. In addition to its insulin-stimulating impact, Glucagon-like peptide-1 possesses central pleiotropic effects. The use of these compounds appears to have yielded promising research outcomes. More recently, glucagon-like peptide-1 and glucose-dependent insulinotropic peptide have been delivered in combination, with encouraging preliminary results. The significant breakthrough has not yet occurred. Now, we must prioritize the prevention of these chronic diseases by a healthier lifestyle.[23]

CONCLUSION

Type 2 diabetes mellitus (T2DM) increases the risk of Alzheimer's disease, as does aging. T2DM, a peripheral problem, and AD, a central nervous system disease, are both chronic and complicated disorders that entail oxidative stress and inflammation.

REFERENCE

[1]. Redulla R. Reminiscence therapy for dementia. Issues Ment Health Nurs. 2020;41(3):265–6.
[2]. Yang S-H. Cellular and Molecular Mediators of Neuroinflammation in Alzheimer Disease. Int Neurourol J [Internet]. 2019 Nov 30;23(Suppl 2):S54-62. Available from: https://doi.org/10.5213/inj.1938184.092
[3]. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract. 2020;162:108072.
[4]. Chen Y, Yu Q, Gong C-X. Molecular connection between diabetes and dementia. Diabetes Mellit A risk factor Alzheimer's Dis. 2019;103–31.
[5]. Kubis-Kubiak AM, Rorbach-Dolata A, Piwowar A. Crucial players in Alzheimer's disease and diabetes mellitus: Friends or foes? Mech Ageing Dev. 2019;181:7–21.
[6]. Tumminia A, Vinciguerra F, Parisi M, Frittitta L. Type 2 Diabetes Mellitus and Alzheimer's Disease: Role of Insulin Signalling and Therapeutic Implications. Int J Mol Sci. 2018 Oct;19(11).
[7]. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig. 2013;4(6):640–50.
[8]. Rorbach-Dolata A, Piwowar A. Neurometabolic evidence supporting the hypothesis of increased incidence of type 3 diabetes mellitus in the 21st century. Biomed Res Int. 2019;2019.
[9]. Peña-Bautista C, Baquero M, Vento M, Cháfer-Pericás C. Omics-based biomarkers for the early Alzheimer disease diagnosis and reliable therapeutic targets development. Curr Neuropharmacol. 2019;17(7):630–47.
[10]. Abdulwahab RA, Alaiya A, Shinwari Z, Allaith AAA, Giha HA. LC-MS/MS proteomic analysis revealed novel associations of 37 proteins with T2DM and notable upregulation of immunoglobulins. Int J Mol Med. 2019;43(5):2118–32.
[11]. Huth C, von Toerne C, Schederecker F, de las Heras Gala T, Herder C, Kronenberg F, et al. Protein markers and risk of type 2 diabetes and prediabetes: a targeted proteomics approach in the KORA F4/FF4 study. Eur J Epidemiol [Internet]. 2019;34(4):409–22. Available from: https://doi.org/10.1007/s10654-018-0475-8
[12]. Dey KK, Wang H, Niu M, Bai B, Wang X, Li Y, et al. Deep undepleted human serum proteome profiling toward biomarker discovery for Alzheimer's disease. Clin Proteomics [Internet]. 2019;16(1):16. Available from: https://doi.org/10.1186/s12014-019-9237-1
[13]. Li D, Huang F, Zhao Y, Villata PW, Griffin TJ, Zhang L, et al. Plasma lipoproteome in Alzheimer's disease: a proof-of-concept study. Clin Proteomics [Internet]. 2018;15(1):31. Available from: https://doi.org/10.1186/s12014-018-9207-z
[14]. Park J-C, Han S-H, Lee H, Jeong H, Byun MS, Bae J, et al. Prognostic plasma protein panel for Aβ deposition in the brain in Alzheimer's disease. Prog Neurobiol [Internet]. 2019;183:101690. Available from: https://www.sciencedirect.com/science/article/pii/S0301008219301194
[15]. Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
[16]. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001;414(6865):799–806.
[17]. Hölscher C. Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease. Biochem Soc Trans. 2011 Aug;39(4):891–7.
[18]. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs. 2003;17(1):27–45.
[19]. Al Kindi MA, Chataway TK, Gilada GA, Jackson MW, Goldblatt FM, Walker JG, et al. Serum SmD autoantibody proteomes are clonally restricted and share variable-region peptides. J Autoimmun. 2015;57:77–81.

[20]. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999 Dec;26(3–4):259–65.
[21]. Thiel S. Complement activating soluble pattern recognition molecules with collagen-like regions, mannan-binding lectin, ficolins and associated proteins. Mol Immunol. 2007;44(16):3875–88.
[22]. S Roriz-Filho J, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves MLF, et al. (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta. 2009 May;1792(5):432–43.
[23]. Halmos T, Suba I. [Alzheimer's disease and diabetes - the common pathogenesis]. Neuropsychopharmacol Hungarica a Magy Pszichofarmakologiai Egyes lapja = Off J Hungarian Assoc Psychopharmacol. 2016 Mar;18(1):5–19.