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REVIEW

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Alzheimer's disease and type 2 diabetes mellitus: A systematic review of proteomic studies

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Abstract

Similar to dementia, the risk for developing type 2 diabetes mellitus (T2DM) increases with age, and T2DM also increases the risk for dementia, particularly Alzheimer's disease (AD). Although T2DM is primarily a peripheral disorder and AD is a central nervous system disease, both share some common features as they are chronic and complex diseases, and both show involvement of oxidative stress and inflammation in their progression. These characteristics suggest that T2DM may be associated with AD, which gave rise to a new term, type 3 diabetes (T3DM). In this study, we searched for matching peripheral proteomic biomarkers of AD and T2DM based in a systematic review of the available literature. We identified 17 common biomarkers that were differentially expressed in both patients with AD or T2DM when compared with healthy controls. These biomarkers could provide a useful workflow for screening T2DM patients at risk to develop AD.

KEYWORDS

Alzheimer's disease, peripheral biomarkers, Proteomics, type 2 diabetes mellitus

1 | INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among older people accounting for about 60%–70% of cases (World Healthy Organization, 2020). The etiology of AD is not yet completely elucidated, although significant advances have been achieved in the knowledge of genetic and environmental risk factors, as well as in relation to the pathological findings associated with this neurodegenerative disorder. One of the main hallmarks of AD is the aggregation and deposition of amyloid-β (Aβ) peptides on the extracellular surface of neuronal cells, leading to the formation of Aβ oligomers and fibrils in the brain. Moreover, AD patients present hyperphosphorylation of tau protein in the brain, which accumulates in the microtubules of neurons and forms neurofibrillary tangles. These events promote cytotoxic effects on neuronal cells inducing cognitive decline (Yang, 2019).

At the same time, the prevalence of diabetes mellitus (DM) has increased during the last decades. According to the International Diabetes Federation (IDF), 1 in 10 people are living with diabetes around the world (IDF, 2020) and type 2 diabetes mellitus (T2DM) accounts for almost 90% of all diabetes cases (IDF, 2020), which is characterized by insulin resistance. Similar to dementia, the risk for developing T2DM increases with age; on the other hand, this metabolic disturbance also increases the risk for dementia (Chen, Yu, & Gong, 2019).

Although T2DM is primarily a peripheral disease and AD is a disorder of the central nervous system, both share some common features, such as long prodromal phases, in addition to being chronic and complex conditions (Kubis-Kubiak, Rorbach-Dolata, & Piwowar, 2019). In addition, both show involvement of chronic oxidative stress and inflammation in the disease progression. Besides age, other common risk factors include poor dietary habits, obesity, chronic stress, genetic profile, and sedentary lifestyle (Chen et al., 2019).

A meta-analysis of DM cases and the risk of all types of dementia, including AD and vascular dementia, based on 28 prospective

observational studies conducted on 89,708 patients with DM, reported an increase of 73% in the risk of all types of dementia and 56% in the risk of AD in diabetic patients (Gudala, Bansal, Schifano, & Bhansali, 2013). These data suggest that DM induces greater susceptibility to AD, which gave rise to a new term, type 3 diabetes (T3DM), a neurometabolic disorder (Rorbach-Dolata & Piwowar, 2019).

There are some hypotheses to explain the connection between AD and T2DM, as the hyperglycemia, which leads to glutamate-induced excitotoxicity in neuronal cells; in addition to insulin resistance in the brain, which may contribute to amyloid-β accumulation, tau phosphorylation, oxidative stress, advanced glycation end products (AGEs) formation, and apoptosis (Rorbach-Dolata et al. 2019). However, there is no clear explanation for the relationship between AD and T2DM.

The expansion of omics platforms have allowed advances in the knowledge of AD and DM, as identification of new biomarkers for diagnosis or prognosis, knowledge of possible pathophysiological mechanisms, and development of different therapeutic strategies (Peña-Bautista, Baquero, Vento, & Cháfer-Pericás, 2019). Among the omics technologies, proteomics is the characterization of the proteome, including expression, structure, function, interaction, and modification of overall proteins present in a cell, tissue, or organism at any stage. Proteomics is considered one of the most important methodologies for understanding the function of the gene, but more complex when compared with genomic technology (Aslam, Basit, Nisar, Khurshid, & Rasool, 2017).

Several studies have used proteomic techniques in order to characterize AD and T2DM, but as far as we know, no study investigated the proteomic profile in diabetic patients with AD. Therefore, this study aimed to systematically review the studies using proteomic methodologies for the identification of plasma/serum proteins in AD and to compare with a database of all plasma proteomic biomarkers identified for T2DM. The identification of common biomarker proteins for both diseases could facilitate greater understanding of the pathophysiological mechanisms linking AD and T2DM.

2 | MATERIAL AND METHODS

We used the key terms: "(((((plasma) OR serum) OR blood) AND proteomic analysis) OR proteome) AND Alzheimer's disease AND Humans; (((((plasma) OR serum) OR blood) AND proteomic analysis) OR proteome) AND type 2 diabetes AND Humans", to search PubMed, SCOPUS and Cochrane databases, without language or date restriction. Original research articles and case-control studies, published until January 2020 were included. Three authors carried out the search strategy independently (JDP, VGF, ALMS). Systematic reviews and meta-analysis were excluded, but a previous manual search was conducted in these studies in order to identify other relevant references. Studies based on cell lines, animal model or other samples than plasma or serum, were also excluded. Initially, we performed a screening of database results through reading of titles and abstracts. After, the selection was based on a complete reading of each preselected article.

The quality of the studies was determined using the QUADOMICS methodology (Table 1), and it was evaluated independently by two authors (JDP and KBG) (Galazis, Afxentiou, Xenophontos, Diamanti-Kandarakis, & Atiomo, 2013; Lumbreras et al., 2008; Parker, GómezSaez, Lumbreras, Porta, & Hernández-Aguado, 2010). QUADOMICS is an adaptation of QUADAS - a quality evaluation tool for use in systematic reviews of diagnostic accuracy studies, which takes into account the technical particularity presented by omics methodologies (Lumbreras et al., 2008; Parker et al., 2010). Studies that reached at least 9/14 queries of the QUADOMICS were classified as high quality (HQ), whereas those that scored less were classified as low quality (LQ). None of the studies explicitly stated that the index test results were interpreted without knowledge of the results

TABLE 1 QUADOMICS criteria to evaluate the quality of the -omics research reports included in a systematic review (Lumbreras et al., 2008; Parker et al., 2010)

Study phase
1. Were selection criteria clearly described?
2. Was the spectrum of patients representative of patients who will receive the test in practice?
3. Was the type of sample fully described?
4. Were the procedures and timing of biological sample collection with respect to clinical factors described with enough detail? 4.1. Clinical and physiological factors 4.2. Diagnostic and treatment procedures.
5. Were handling and pre-analytical procedures reported in suficiente detail and similar for the whole sample? and, if differences in procedures were reported, was their effect on the results assessed?
6. Is the time period between the reference standard and the index test short enough to reasonably guarantee that the target condition did not change between the two tests?
7. Is the reference standard likely to correctly classify the target condition?
8. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?
9. Did patients receive the same reference standard regardless of the result of the index test?
10. Was the execution of the index test described in suficiente detail to permit replication of the test?
11. Was the execution of the reference standard described insufficient detail to permit its replication?
12. Were the index test results interpreted without knowledge of the results of the reference standard?
13. Were the reference standard results interpreted without knowledge of the results of the index test?
14. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
15. Were uninterpretable/intermediate test results reported?
16. Is it likely that the presence of overfitting was avoided?

of the reference standard, consequently the 12th and 13th criteria of the QUADOMICS were not applied (Galazis et al., 2013).

In order to develop an integrated understanding of the overlapped proteins observed in the studies to AD and T2DM, we applied a network biology approach using STRING software (https://string-db.org/) and the pathway analysis performed according to Kegg. p-value <.05 was considered significant.

3 | RESULTS

The initial search on databases returned 432 articles about proteomics in AD and 317 in T2DM. We considered only original articles, which resulted in 340 studies about AD and 279 about T2DM. After screening by titles and abstracts, 42 studies to AD and 19 to T2DM were maintained. Following, the complete reading of each article resulted in 14 exclusions of studies on AD and seven on T2DM: a) AD – five studies did not identify the proteins (only the molecular mass); three evaluated only the protein glycosylation profile, or novel Aβ peptides species and one of them evaluated the lipidomic profile; two studies failed to include a control group or investigated only patients with mild cognitive impairment (MCI); one study evaluated the proteomics by machine learning without describing the relevant proteins; two studies applied the proteomic methodology in brain tissue or cerebrospinal fluid (CSF); and proteomic techniques were not used in the last study; b) T2DM – two studies failed to identify the proteins or to include a healthy control group; four investigated only the glycosylation profile or proteins turnover, or protein post-translational modification; one study applied proteomic approaches in mononuclear peripheral cells. Thirty-four of the 40 studies were classified as HQ by fulfilling at least 9/14 criteria of QUADOMICS (Abdulwahab, Alaiya, Shinwari, Allaith, & Giha, 2019; Chiu et al., 2018; Cocciolo et al., 2012; Craig-Schapiro et al., 2010; Dayon et al., 2017; Dey et al., 2019; Dincer et al., 2009; Fania et al., 2017; Gómez-Cardona et al., 2017; González-Sánchez et al., 2008; Hu et al., 2012; Huth et al., 2019; Hye et al., 2006; IJsselstijn et al., 2011; Jensen et al., 2013; Kitamura et al., 2017; Li et al., 2008, 2018; Liu et al., 2006, 2009; Llano, Devanarayan, & Simon, 2013; Meng et al., 2017; Muenchhoff et al., 2017; Nazeri et al., 2014; Nowak et al., 2016; Park et al., 2019; Ray et al., 2007; Riaz, Alam, & Akhtar, 2010; Sattlecker et al., 2014; Shen et al., 2017; Soares et al., 2009; Zabel et al., 2012; Zhang et al., 2008; Zhao et al., 2015). The six remaining studies were classified as LQ, reaching less than 9/14 queries (Bennett et al., 2012; Johnstone, Milward, Berretta, Moscato, & Initiative, 2012; Kang et al., 2016; Long, Pan, Ifeachor, Belshaw, & Li, 2016; Yang, Lyutvinskiy, Soininen, & Zubarev, 2011; Yang et al., 2012), consequently these articles were excluded from the review. Finally, a total of 22 studies about AD and 12 about T2DM were included (Figure 1), resulting in 1,185 AD cases versus 1,678 controls (one study did not specify the classifications of the groups, total = 292); and 834 T2DM cases versus 2,500 controls (Table 2).

The main proteomic technique used was liquid chromatography–tandem mass spectrometry (LC-MS), observed in 13 studies; followed by matrix-assisted laser desorption time-of-flight (MALDI-TOF) – S in seven studies; Luminex® in 4; isobaric tags for relative and absolute quantitation (iTRAQ) – LC/MS, nano-electrospray ionization (ESI) – MS and SOMAscan® in two studies each; and orbitrap-MS, ultra performance liquid chromatography (UPLC) – MS, OLINK®, ion trap – MS, and MAPTM® in one study each. Some authors used two techniques for best quality of the identification (Table 2).

The present systematic review resulted in 205 proteomic biomarkers for AD and 149 for T2DM. Variants of the same protein because of post-translational modifications or splicing were then considered as the same entity (Galazis et al., 2013).

A crosschecking was carried out in the two databases and 17 proteomic biomarkers were simultaneously and differentially

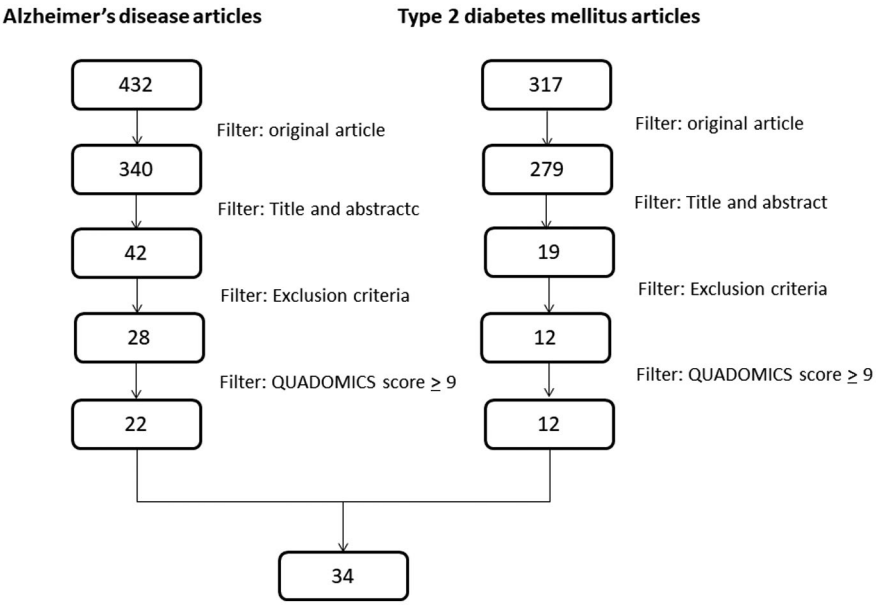

FIGURE 1 Flowchart with the description of systematic search in the literature

TABLE 2 Characteristics of the studies included with their respective proteins identified

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Alzheimer's Disease studies					
Cocciolo et al. (2012)	Italy	10	10	Upregulated: *alpha2-macroglobulin*, fibrinogen gamma chain Downregulated: *haptoglobin beta chain*, fibrinogen alpha chain, *apolipoprotein A-I*, serotransferrin, beta2-glycoprotein	Nanomate Orbitrap XL MS/MS
Craig-Schapiro et al. (2010)	USA	292 total (not specified AD number)	Not specified	-Upregulated: Chitinase-3-like protein 1	LC-MS/MS
Dayon et al. (2017)	Switzerland	48	9	Upregulated: insulin-related binding *protein* 2, CO7, NOE1, Selenoprotein P1, angiotensinogen, apolipoproteim M Downregulated: pregnancy zone *protein*, *apolipoprotein E*	LC-MS/MS
Dey et al. (2019)	USA	5	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	LC/LC/MS/MS
Fania et al. (2017)	Italy	12	36	Upregulated: *apolipoprotein A-I*	MALDI-TOF/MS
González-Sanchez et al (2018)	Spain	49	74	Upregulated: talina, RHO GDP, Platelet APP, Platelet amyloid-β 1–40, Platelet amyloid-β 40 secreted, Platelet amyloid-β 1–42, Platelet amyloid-β 42 secreted. Downregulated: vinculin, Moesin, complement C3b	MALDI-TOF/TOF
Hu et al. (2012)	USA	368	88	Upregulated: brain natriuretic peptide, cortisol, tumor necrosis factor receptor superfamily member 6, IL-3, IL-10, IL-12p40, osteopontin, IL-13, IL-15, *pancreatic polypeptide*, resistin, stem cell factor Downregulated: *apolipoprotein E*, c-reactive protein, E-selectin, serum amyloid protein	Multiplex Human Discovery MAPTM Luminex xMAP platform

(Continues)

TABLE 2 (Continued)

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Hye et al. (2006)	UK	50	50	Upregulated: desmoplakin, *Ig kappa chain C region*, Ig kappa chain V-II region, serum amyloid P-component, serum albumin, galectin-7, complement factor H (CFH), *alpha-2 macroglobulin*, *ceruloplasmin*, Ig lambda chain C regions, Ig lambda chain V-III region, CFH related protein 2 precursor, Ig lambda chain V-II region, Ig kappa chain V-I region, Ig kappa chain V-IV region; *Ig alpha-1 chain C region* Downregulated: inter-alpha-trypsin inhibitor heavy chain H4, *complement C4*, Ig gamma-I chain C region, histone H2B.a/g/h/k/l, CD5 antigen-like, *Ig μ chain C region*	LC-MS/MS
IJsselstijn et al. (2011)	Netherlands	43	43	Upregulated: Pregnancy zone protein	LC-MS
Kitamura et al. (2017)	Japan	10	9	Upregulated: *apolipoprotein A-IV*, fibrinogen gamma chain Downregulated: *apolipoprotein A-I*, kininogen-1, alpha-2-HS glycoprotein, afamin, plasminogen	MALDI-TOF/TOF/MS
Li et al. (2018)	USA	5	5	Upregulated: integrin alpha 2B Downregulated: Complement C3, serum amyloid A4, *haptoglobin*, chemokine (C-X-C motif) ligand 7	LC-MS/MS
Liu et al. (2006)	Taiwan	74	59	Downregulated: *apolipoprotein A-I*	MALDI-TOF/TOF/MS
Llano et al. (2013)	USA (Alzheimer's Disease Neuroimaging Initiative Database - ADNI)	58	109	Upregulated: alpha1-microglobulin, *alpha2-macroglobulin*, brain natriuretic peptide, betacellulin, eotaxin 3, heparin-binding EGF-like growth factor, myeloperoxidase, *pancreatic polypeptide*, receptor for advanced glycosylation end products, tenascin-C Downregulated: apolipoprotein A-II, *apolipoprotein E*, c-reactive protein, immunoglobulin M, interlukin-16, placenta growth factor, serum glutamic oxaloacetic transaminase, *transthyretin*, vitronectin	Luminex xMAP platform
Muenchhoff et al. (2015)	Australia	411	24	Upregulated: fibrinogen beta chain, fibronectin Downregulated: complement factor B, *apolipoprotein B-100*, vitamin D binding protein, *ceruloplasmin*	iTRAQ LC-MS/MS
Nazeri et al. (2014)	USA	49	85	(*no information about fold-change between case/control groups*): apolipoprotein A-II, brain natriuretic peptide, placenta growth factor, *apolipoprotein E*, alpha-1-microglobulin, interleukin-16, serum glutamic oxaloacetic transaminase, immunoglobulin M, peptide YY, eotaxin-3, tenascin-C, *alpha-2-macroglobulin*, receptor for advanced glycosylation end, *transthyretin*, *pancreatic polypeptide*, vitronectin, pregnancy-associated plasma protein A, thyroxine-binding globulin	Luminex xMAP platform
Park et al. (2019)	South Korea	107	40	Downregulated: *Galectin 3-binding protein*, angiotensin 1-converting enzyme	LC-MS/MS

(Continues)

TABLE 2 (Continued)

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Ray et al. (2007	EUA, Italy, Sweden, Poland	79	85	Upregulated: angiopoietin−2, CCL18, IL−8, intercellular adhesion molecule 1, insulin-like growth factor binding protein 6, IL−11, tumor necrosis factor receptor superfamily member 10d Downregulated: regulated upon activation normal t cell Expressed, and secreted, monocyte-chemotactic protein 3, macrophage inflammatory protein 1δ, epidermal growth factor, colony stimulation factor 3, glial cell neutrophic factor, IL−1α, IL−3, colony stimulating factor 1, platelet-derived growth factor beta polypeptide, TNF	LC/LC/MS/MS
Sattlecker et al. (2014)	UK	211	331	Upregulated: prostate-specific antigen complexed to serine protease inhibitor alpha-1 antichymotrypsin, *pancreatic polypeptide*, trypsin Downregulated: calmodulin-dependent protein kinase	SOMAscan
Shen et al. (2017)	China	15	15	Upregulated: gelsolin, fibrinogen alpha chain, afamin, fibulin-1, fibrinogen beta chain, fibrinogen gamma chain, Downregulated: SERPINA3, *apolipoprotein A-I*, *apolipoprotein B-100*, zinc alpha-2-glycoprotein, complement factor B, *ceruloplasmin*, *inter-alpha-trypsin inhibitor heavy chain H1*, *inter-alpha-trypsin inhibitor heavy chain H2*, SERPINA1, inter-alpha-trypsin inhibitor heavy chain H4, fibronectin, platelet basic protein, plasma protease C1 inhibitor, thrombospondin-1, Von willebrand factor	iTRAQ LC-MS/MS
Soares et al. (2009)	USA	22	19	Upregulated: IL-3, regulated upon Activation Normal T cell Expressed and secreted, IL-8, TNF, Downregulated: intercellular Adhesion Molecule 1	Luminex xMAP platform
Zabel et al. (2012)	USA	6	12	Upregulated: *Complement C4*, *alpha2-macroglobulin*	LC-MS/MS
Zhao et al. (2015)	USA (Alzheimer's Disease Neuroimaging Initiative Database - ADNI)	46	76	Upregulated: calgranulin B Downregulated: allograft inflammatory factor 1, endothelial cell-selective adhesion molecule, signaling lymphocytic activation molecule 5, CD226 antigen	SOMAscan
Diabetes mellitus studies					

(Continues)

TABLE 2 (Continued)

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Abdulwahab et al. (2019)	Kingdom of Bahrain	6	6	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	LC-MS/MS
Chiu et al. (2018)	USA	15	25	Upregulated: glucosepane, N-fructosyl-lysine, N-formylkynurenine Downregulated: methylglyoxal-derived hydroimidazolone, alpha-amino adipic semialdehyde protein carbonyl	LC-MS

(Continues)

TABLE 2 (Continued)

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Dincer et al. (2009)	Turkey	63	61	Upregulated: haptoglobin alpha-2, haptoglobin Hp2, *transthyretin*, chain A Downregulated: thiol-specific antioxidant protein, tertiary structures of three amyloidogenic transthretin variants, *haptoglobin-related protein*	Nano-LC-ESI-MS
Gómez-Cardona et al. (2017)	Mexico	23	62	Upregulated: visfatin, leptin, resistin↑↓ (dependent of BMI), PAI-1, insulin, C-peptide, glucose dependent insulinotropic polypeptide ↑↓ (dependent of BMI), glucagon-like peptide 1 Downregulated: ghrelin	UPLC-MS/MS
Huth et al. (2019)	Germany	660	123	Upregulated: mannose-associated serine protease, apolipoprotein C-II,a polipoprotein C-III, *apolipoprotein E* Downregulated: adiponectin	LC-MS
Jensen et al. (2013)	UK	195	85	Upregulated: *pancreatic polypeptide*, calcitonin, monocyte chemotactic protein 4, leukotactin-1, glucagon-like peptide 2, apolipoprotein C-II, apolipoprotein C-III	MALDI-TOF/MS
Li et al. (2008)	China	5	5	Upregulated: hemopexin, *apolipoprotein E*, serum amyloid A4, apolipoprotein C-III, *apolipoprotein A-I*, apolipoprotein A-II, apolipoprotein C-II, serum amyloid A, complement component C4B, complement component 4A, *complement C4*, complement C3, C4B1, C4b-binging protein alpha chain, splice isoform 1 of complement factor B, complement C1q subcomponent A chain, complement component C8 gamma chain, ficolin 3, ficolin2, complement component C8 alpha chain, Downregulated: serum paraoxonase/arylesterase 1, vitamin D binding protein, *haptoglobin related protein*, serotransferrin, splice isoform 2 of inter alpha trypsin inhibitor heavy chain H4, *apolipoprotein A-IV*, complement component C6, adipsin/complement factor D	Ion trap MS/MS
Liu et al. (2009)	China	15	17	Upregulated: galectin-1 Downregulated: *apolipoprotein A-I*	MALDI-TOF
Meng et al. (2017)	China	200	206	Upregulated: kininogen 1 isoform 1 precursor Downregulated: Complement C3	MALDI-TOF Nano-LC/ESI–MS/MS
Nowak et al (2026)	Sweden	1,256	111	Upregulated: IL-1ra, tissue plasminogen activator	Olink Proseek Multiplex®
Riaz et al. (2010)	Pakistan	50	125	Upregulated: *apolipoprotein E*, leptina, C reactive protein Downregulated: *apolipoprotein A-I*	MALDI-TOF

(Continues)

TABLE 2 (Continued)

Study (year)	Population	Control (n)	Case (n)	Proteins identified	Technique
Zhang et al. (2008)	EUA	12	8	Upregulated: *alpha-2-macroglobulin*, albumin, *apolipoprotein A-I*, apolipoprotein A-II, *apolipoprotein B-100*, complement C4-A, isoform 1 of complement factor B (fragment), isoform 1 of complement factor H, *ceruloplasmin*, Isoform 1 of fibrinogen alpha chain, fibrinogen beta chain, isoform 2 of extracellular matrix protein fras1, vitamin D-binding protein, *haptoglobin*	LC-ETD-MS/MS

Note: Upregulated or downregulated in Alzheimer's Disease (AD) or Diabetes mellitus (T2DM) compared to controls. *Italic*: overlapping between AD and T2DM.

expressed in patients with AD or T2DM, when compared to healthy controls. These proteins were alpha-2-macroglobulin, apolipoprotein A-I, apolipoprotein A-IV, apolipoprotein B-100, apolipoprotein E, ceruloplasmin, complement C4, galectin-3–binding protein, haptoglobin, Ig α-1 chain C region, Ig μ chain C region, Ig κ chain C region, inter-alpha-trypsin inhibitor heavy chain 1, inter-alpha-trypsin inhibitor heavy chain 2, pancreatic polypeptide, transthyretin, and zinc alpha 2-glycoprotein (Figure 2).

The level of expression showed variable consistency when evaluated in different studies. However, their association with AD or T2DM was corroborated with animal model studies or genoma wide association studies (GWAS) (Table 3).

Protein–protein interactions showed that, among the 17 proteins selected, 14 were identified in the software database (except Ig α 1 chain C, Ig μ 1 chain C and Ig κ 1 chain C region). The interaction was observed between 13 of them ($p < 1.0\ e^{-16}$), with 56 edges, since pancreatic polypeptide was not related to other proteins. The significant pathways identified, which involved the inter-related proteins, were cholesterol metabolism ($p = 7.68\ e^{-07}$), vitamin digestion and absorption ($p = 6.84\ e^{-06}$), fat digestion and absorption ($p = 1.78\ e^{-05}$) and complement and coagulation cascades ($p = 9.73\ e^{-05}$) (Figure 3).

4 | DISCUSSION

In this systematic review, we identified a panel of 17 proteins detected by proteomic technology, which were differentially expressed in both T2DM and AD patients when compared to control individuals. These findings may help to establish a link between these diseases and to identify promising biomarkers. Contradictory results about protein expression levels, when compared to control group, were observed mainly in AD studies, probably because of different diagnostic criteria applied or to different disease stage, since differently from T2DM that presents laboratory markers, AD diagnosis is basically clinical.

Biomarkers obtained from peripheral blood samples, as the proteins evaluated in the present review, are particularly desired over other types of costly or invasive procedures, and could be indicative of brain pathology (Kim et al., 2014; Mapstone et al., 2014). However, accurate blood biomarkers to AD diagnosis are still under investigation. In fact, it is unknown the ability of a set of peripheral markers to link alterations in the blood to those in the brain, where accumulation of distinct pathological features is believed to trigger symptom onset. Moreover, as is common in progressive diseases, there are many alterations in the markers because of chronic comorbidities that may be reflected in peripheral blood concentrations (Varma et al., 2018). Thereby, the results obtained from blood samples should be evaluated with caution in central diseases evaluation.

The islet of Langerhans in T2DM is characterized by cell loss related to amyloid polypeptide (AP) deposits, a protein co-expressed and secreted with insulin. Such as Aβ protein in AD, AP spontaneously forms into amyloid aggregates in an aqueous environment. The alignment analysis revealed an important overlap (90%) in

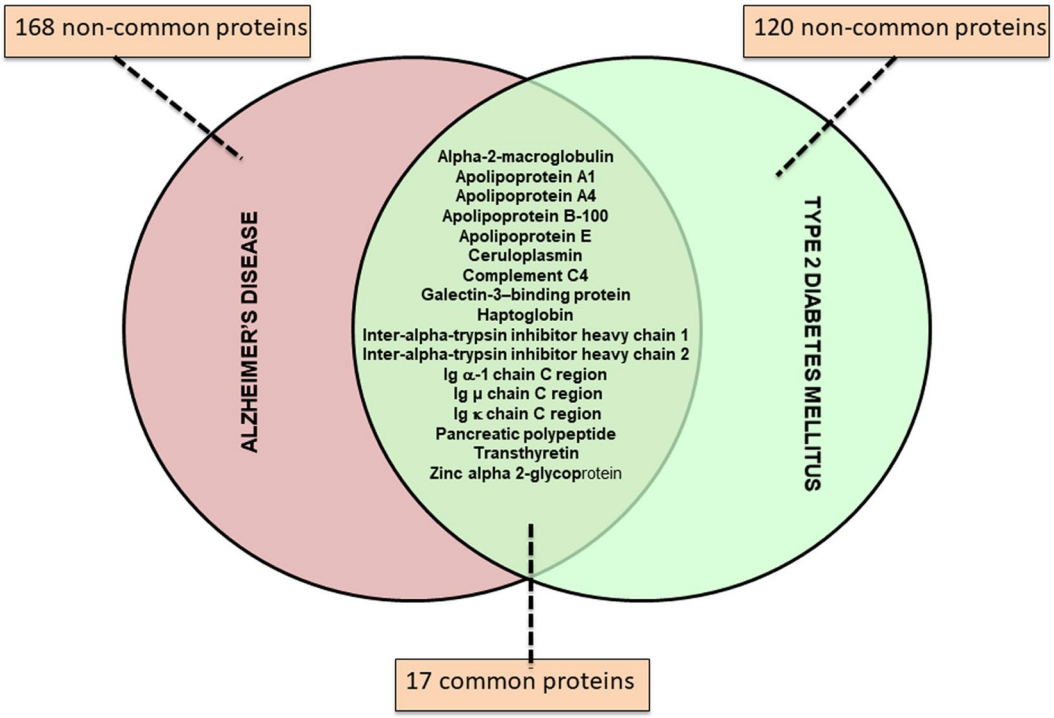

FIGURE 2 Common proteins differentially expressed in Alzheimer's disease or Type 2 diabetes mellitus patients when compared to controls

structural properties of these proteins. In both diseases, a locally amyloid expressed protein is deposited with a gradual decline in the number of cells. These cytotoxic mechanisms include the chaperone protein pathway, a system for protein trafficking, which bind nascent proteins and facilitate their transport within the cell (Janson et al., 2004). Curiously, an increased frequency of islet amyloid in patients with AD was observed, nevertheless, brain amyloid was not increased in patients with T2DM versus normoglicemic group, but the density of neuritic plaques was associated with the duration of diabetes (Janson et al., 2004).

Although tauopathies are associated with degenerative disorders as AD, microtubule-associated protein tau is also present in human islets of Langerhans with biophysical similarities to the pathology in the brain. Maj et al. (2016) showed that a protein tau is over-expressing in beta-cell derived rodent with significantly decreased insulin transcription, translation, and secretion, indicating the importance of balanced tau-phosphorylation and dephosphorylation for adequate insulin action. Interestingly, cytoplasmic tau and Aβ protein deposits were detected in pancreatic β cells of subjects with AD similarly to observe in T2DM individuals with normal neuropathological examination (Martinez-Valbuena et al., 2019).

Beyond amyloid precursor protein metabolism and phosphorylation of tau protein, many biochemical processes affect similarly both AD and T2DM, including oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, lipid metabolism, and membrane lipid deregulation (Toledo et al., 2017). In is known that impaired cerebral glucose uptake occurs decades before the onset of cognitive dysfunction in AD (Chen & Zhong, 2013), and neurotoxicity is associated to mitochondrial dysfunction and release of reactive oxygen species, as seen in diabetic condition. Several studies have shown that insulin resistance can contribute to AD pathology, and consequently, AD could be considered as a metabolic disease mediated by brain insulin resistance (de la Monte & Tong, 2014). Moreover, peripheral metabolism, diet, and gut microbiome have suggested impacting the metabolic impairment in both AD and T2DM (Toledo et al., 2017).

Among the proteins identified, alpha-2-macroglobulin (A2M) was increased in both AD and T2DM groups when compared to controls in all studies (Table 3). A2M is the major non-immunoglobulin molecule among the most abundant proteins in the peripheral blood circulation, which can inhibit a broad spectrum of proteases and pro-inflammatory cytokines, in addition to inducing the transcriptional activation of various genes related to cell proliferation/hypertrophy and atherosclerosis (Yoshino et al., 2019). The relationship between plasma A2M and DM has been known for a long time (James, Merriman, Gray, Duncan, & Herd, 1980), but a correlation between salivary levels of A2M and blood levels of HbA1c, triglycerides, fasting, and postprandial blood sugar in T2DM subjects has been described (Chung et al., 2016; Rastogi, Kalra, & Gowda, 2019). Seddighi et al. (Seddighi, Varma, & Thambisetty, 2018) showed that plasma A2M levels were also significantly correlated with total-tau and phosphorylated tau concentrations in CSF, and that higher serum levels of A2M in cognitively normal individuals were associated with a higher risk of progression to clinical AD in men. They hypothesized that A2M, a chaperone protein and an acute phase protein, may be involved in the inflammation and in the pathogenesis of preclinical

AD because of its capacity to facilitate the aggregation of misfolded Aβ peptide (Seddighi et al., 2018; Varma et al., 2017). Hence, α2M seems to show importance in both AD and T2DM pathophysiology.

Apolipoprotein A-I (APOA1) plays a diversity of roles in human physiology, such as cholesterol transport and regulation of inflammation. Through the ATP-binding cassette protein A1 (ABCA1), APOA1 serves as the primary lipid acceptor protein for lipids, such as cholesterol and phosphatidylcholine, and it also acts as part of the high density lipoprotein (HDL) carrying the excess of cholesterol from tissues (Keeney et al., 2013). In addition, APOA1 has been reported to present antioxidant and anti-inflammatory properties. Some studies have reported decreased serum APOA1 during inflammation, but increased levels in CSF after brain injury (Keeney et al., 2013), which justify different results observed in the proteomic studies (Table 3). APOA1 is highly expressed in glial and neuronal cells playing a homeostatic role by promoting cholesterol and phospholipid efflux to ApoE (Aguilar Salinas et al., 2007). Association of APOA1 with MCI conversion to AD was also observed, as well as a tendency toward an association with high amyloid burden assessed by [18F]-flutemetamol PET, as well as cognitive decline, brain atrophy, and protection of hippocampal neuronal cultures from Aβ-induced neurodegeneration (Westwood et al., 2018). Although two proteomic studies have shown higher APOA1 expression in T2DM group (Table 3), reduced APOA1 levels have been observed in diabetic group, and consequently HDL levels, which triggers cholesterol accumulation in beta cells resulting in decreased insulin secretion. Moreover, cholesterol accumulation in the adipocyte may facilitate additional deposition of lipids and alter the fat cell physiology, a factor involved in T2DM development (Aguilar Salinas et al., 2007).

Apolipoprotein A-IV (APOA4) is the major component of HDL and chylomicrons, and occurs in a lipoprotein-free form. It has been proposed to play a role in reverse cholesterol transport, activation of lecithin cholesterol acyltransferase (LCAT), and promotion of cholesterol efflux from cholesterol-preloaded cells across binding to various cells. APOA4 may act in the brain and was detected in astrocytes of rats (Császár, Kálmán, Szalai, Janka, & Romics, 1997). Császá et al. (Császár et al., 1997) reported that APOA4-2 allele might confer higher susceptibility to AD, which corroborate the proteomic findings, but Cui, Huang, He, Zhang, and Luo, (2011) observed that APOA4 deficiency increases Aβ deposition and results in cognitive damage in a mouse model. Ji, Urakami, Adachi, and Nakashima,(1999) did not find association between APOA4 genotypes and late-onset AD in the Japanese population, suggesting that the APOA4 role in AD is not completely elucidated. In animal model, APOA4 reduced fasting blood glucose in obese diabetic mice and enhanced glucose uptake in the cardiac muscle and adipose tissue of wild-type mice. In addition, APOA4 enhanced glucose uptake in mouse adipocytes via the PI3K-Akt/GLUT4 translocation (Li, Wang, Xu, Howles, & Tso, 2017). The higher expression of APOA4 in T2DM group according to proteomic study (Li et al., 2008) should be elucidated.

Apolipoprotein B-100 (APOB) was observed to be decreased in AD and increased in T2DM groups compared to controls in the proteomic studies (Table 3). APOB is a glycoprotein that circulates in the plasma as the major protein component of low-density lipoprotein (LDL). It is synthesized in the liver and is required for the formation and secretion of triglyceride-rich very low-density lipoproteins (VLDL) for plasma cholesterol transport (Bereczki et al., 2008). Consequently, high levels of APOB are associated with elevated LDL concentrations and higher atherogenic profile (Sabbagh et al., 2004). Significantly higher levels of APOB were found in AD patients when compared to controls (Caramelli et al., 1999). Over-expressed human APOB protein was also related to cerebrovascular lesions, apoptosis, and neurodegeneration (Bereczki et al., 2008), as well as impairment of the episodic-like memory, associated with disorganization of the neuronal microtubule network, increase in astrogliosis, and lipid peroxidation in the brain regions associated with AD in transgenic mice (Ramírez et al., 2011). Higher levels of APOB were also associated with increased glucose levels in Finnish men (Fizelova et al., 2015). Indeed, several studies have demonstrated the superiority of APOB measurement when compared to LDL to establish cardiovascular risk in T2DM, and improvement of outcomes after lipid-lowering drug therapy in these patients (Hermans, Ahn, & Rousseau, 2013). There are controversial findings in proteomic analyses, however, APOB seems to play an important role both in AD and T2DM.

Apolipoprotein E (APOE), especially the isoform E4 encoded by ε4 allele, is the strongest genetic risk factor related to sporadic AD. Inheritance of one copy of *APOE* ε4 is associated with a threefold increase in AD risk and two copies are related to over 10-fold increased risk (Hesse et al., 2019). APOE shows a role in Aβ production and clearance, and causes more synaptic loss around plaques in mouse models of familial AD (Hesse et al., 2019). In addition, a meta-analysis of 59 studies, comprising 6,872 T2DM cases and 8,250 controls, showed that E4 was associated with the increased risk for the development of T2DM (Ren et al., 2019). Differentially, a 15-year follow-up study with 436 patients from a Southern European primary prevention cohort showed increase in T2DM incidence in E2 isoform carriers, which has revealed a protective effect on AD (Santos-Ferreira et al., 2019). Although the isoform and alleles involved in T2DM are not completely elucidated, ApoE is an important connection between AD and T2DM. The proteomic studies showed reduced APOE expression in AD, but increased in T2DM group, which suggest that the results could be influenced by the different APOE isoforms in different diseases.

Although two proteomic studies [Hye et al. (2006) and Abdulwahab et al. (2019)] have shown increase expression in ceruloplasmin (CP) in AD and T2DM groups, respectively, its reduction have been associated to oxidative stress observed in both diseases. The ion copper (Cu) is an essential nutrient involved in electron and oxygen transport. The imbalance of Cu homeostasis has been attributed to the increased levels in the fraction of serum Cu not bound to ceruloplasmin (non-CP), or free Cu (Squitti et al., 2018). Non-CP Cu is redox active and its toxicity is related to its ability to accelerate oxidative stress and AGEs formation, a hallmark of T2DM, resulting in extracellular matrix damage in tissues, including the brain (Squitti,

TABLE 3 Final overlapping proteins in Alzheimer's Disease and type 2 diabetes mellitus

Protein	Alzheimer's disease studies	Evidence of significance	Other studies involving AD	Diabetes mellitus studies	Evidence of significance	Other studies involving diabetes
Alpha−2-macroglobulin (A2M)	Hye et al. (2006) Nazeri et al. (2014) Llano et al. (2013) Cocciolo et al. (2012) Zabel et al. (2012)	↑ $p = .006$ $p = .0196$ (not informed ratio AD x control) ↑ $p < .05$ ↑ Ratio 2.17 ↑ $p < .06$	Polymorphisms in the *A2M* gene is associated with AD and result in increased accumulation of amyloid plaques [Kovacs (2000)]; A2M is associated with preclinical AD, and tau phosphorylation in the brain [Varma et al. (2017)].	Zhang et al. (2008)	↑ Ratio 2.0	*A2M* gene is associated with diabetic retinopathy [Wang et al. (2017)]
Apolipoprotein A-I (APOA1)	Kitamura et al. (2017) Shen et al. (2017) Fania et al. (2017) Cocciolo et al. (2012) Liu et al. (2006)	↓ $p < .01$ ↓ Average ratio 0.55 ↑ $p < .05$ ↓ Ratio 1.7 ↓ $p < .0002$	Two genome wide association studies (GWAS) identified *APOA1* gene as a lipoprotein metabolism and HDL component associated with AD risk [Button et al. (2019)]	Li et al. (2008) Riaz et al. (2010) Liu et al. (2009) Zhang et al. (2008) Abdulwahab et al. (2019)	↑ $p = 2.14e^{-7}$ ↓ $p < .001$ ↓ Ratio 4.2 ↑ Ratio 3.0 ↓ $p = .0283$	Increased ApoA-I truncated form in serum of animal model of diabetes [Cubedo et al. (2015)]
Apolipoprotein A-IV (APOA4)	Kitamura et al. (2017)	↑ $p < .05$	ApoA-IV deficiency increases Aβ deposition and results in cognitive damage in mouse model of AD [Cui et al. (2011)]	Li et al. (2008)	↓ $p < .05$	ApoA-IV promotes glucose uptake in mouse adipocytes and suppresses hepatic gluconeogenesis. ApoA-IV-/- mice showed reduced insulin secretion and impaired glucose tolerance [Qu, Ko, Tso, and Bhargava (2019)]
Apolipoprotein B−100 (APOB)	Muenchhoff et al. (2015) Shen et al. (2017)	↓ $p < .05$ ↓ Average ratio 0.6	Rare coding variants in *APOB* gene were associated to early-onset AD [Wingo et al. (2019)]; transgenic mouse model overexpressing APOB had significant memory impairment and increased β-amyloid levels [Löffler et al. (2013)]	Zhang et al. (2008) Abdulwahab et al. (2019)	↑ Ratio 1 ↑ $p = .0008$	*ApoB* variants related to cis-eQTLs in subcutaneous adipose tissue [Cirillo et al. (2018)]

(Continues)

TABLE 3 (Continued)

Protein	Alzheimer's disease studies	Evidence of significance	Other studies involving AD	Diabetes mellitus studies	Evidence of significance	Other studies involving diabetes
Apolipoprotein E (APOE)	Dayon et al. (2017) Nazeri et al. (2014) Llano et al. (2013) Hu et al. (2012)	↓ $p = .04$ $p = .0013$ (not informed ratio AD x control) ↓ $p < .05$ ↓ OR = 0.955	Strongest genetic risk factor for AD [Belloy, Napolioni, and Greicius (2019)]	Li et al. (2008) Riaz et al. (2010) Huth et al. (2019)	↑ $p = 3.28\ e^{-10}$ ↑ $p < .001$ ↑ $0.003 < p < .099$	Controversal: ε2 polymorphism increase the susceptibility to T2DM [Lin et al. (2014)]; ε3/ε4 genotype carriers increase risk of T2DM [Guan et al. (2009)]
Ceruloplasmin (CP)	Muenchhoff et al. (2015) Hye et al. (2006) Shen et al. (2017)	↓ $p < .05$ ↑ $p = .0155$ ↓ Average ratio 0.3	Characterized as a copper (Cu)-containing protein binding, which enhances dimerization of amyloid precursor protein (APP) and increase extracellular release of Aβ [Noda et al. (2013)]; *CP* gene deletion increase memory impairment, iron accumulation, reactive oxygen species (ROS) levels and leads to cell apoptosis in AD mouse model [Zhao et al. (2018)]	Zhang et al. (2008) Abdulwahab et al. (2019)	↑ Ratio 2.0 ↑ $p = .0071$	Streptozotocin-diabetic model rats had higher plasma ceruloplasmin levels compared to control rats [Uriu-Adams, Rucker, Commisso, and Keen (2005)]
Complement C4 (C4A and C4B)	Zabel et al. (2012) Hye et al. (2006)	↑ $p < .01$ ↓ $p = .0206$	High *C4A* and *C4B* copy numbers in AD patients leading to increased C4 protein expression [Zorzetto et al. (2017)]	Li et al. (2008)	↑ $p = 3.06\ e^{-69}$	Higher *C4A* copy numbers is associated with the protection of residual beta-cell function in new-onset type 1 diabetes; lower *C4B* is correlated with the end of disease remission post diagnosis [Kingery, Wu, Zhou, Hoffman, and Yu (2012)]

(Continues)

TABLE 3 (Continued)

Protein	Alzheimer's disease studies	Evidence of significance	Other studies involving AD	Diabetes mellitus studies	Evidence of significance	Other studies involving diabetes
Galectin 3-binding protein (LGALS3BP)	Park et al. (2019)	↓ Ratio = −0.26	Galectin−3 upregulated in the brains of mice - familial AD animal model - and expressed in microglia associated with Aβ plaques. Gal3 deletion decreased the Aβ burden and improved cognitive behavior [Boza-Serrano et al. (2019)]	Abdulwahab et al. (2019)	↑ $p = .0086$	Galectin−3 decreases the response of innate and adaptive immunity to overnutrition which leads to adipose tissue inflammation and oxidative stress in T2DM animal model, thus protecting against the obesity-associated type 2 diabetes [Pejnovic et al. (2013), Menini et al. (2016)]
Haptoglobin (HP)	Cocciolo (2012) Li (2018)	↓ Ratio = 0.6 ↓ $p = .0407$	Compared with subjects with Hp 2–2 genotype, Hp 1–1 subjects performed significantly worse in semantic categorization and the overall cognitive score [Ravona-Springer et al., 2013]	Abdulwahab et al. (2019) Dincer (2009) Li (2008) Zhang et al. (2008)	↑ $p = .0088$ ↓ for intact protein (not informed) ↑ $p = 7.28\ e^{-12}$ ↑ Ratio 2.0	HP2−2 genotype was associated with increased T2DM risk [Adams et al., 2013]; patients with type 2 diabetes and poor glycaemic control carrying the Hp 1–1 genotype may be at increased risk of cognitive impairment, particularly in the attention/working memory domain [Guerrero-Berroa et al., 2015]
Ig α 1 chain C region (IGHA1)	Hye et al. (2006)	↑$p = .0347$	Not found	Abdulwahab et al. (2019)	↑ $p = .0136$	Not found
Ig μ 1 chain C region (IGHM)	Hye et al. (2006)	↓ $p = .0290$	Not found	Abdulwahab et al. (2019)	↑ $p = .0005$	Not found
Ig κ 1 chain C region (IGKC)	Hye et al. (2006)	↑ $p = .0003$	Not found	Abdulwahab et al. (2019)	↑ $p = .0015$	Not found

(Continues)

TABLE 3 (Continued)

Protein	Alzheimer's disease studies	Evidence of significance	Other studies involving AD	Diabetes mellitus studies	Evidence of significance	Other studies involving diabetes
Inter-alpha trypsin inhibitor heavy chain 1 (ITIH1)	Shen et al. (2017)	↓ Average ratio 0.3	Trans genome-wide significant CpG sites in ITIH1 showed regulation on neprilysin, which have been linked to Alzheimer's pathology [Seeboth et al. (2020)]	Abdulwahab et al. (2019)	↓ $p = .0080$	In vitro study showed that ITIH1 expression was elevated in liver samples from subjects with impaired glucose tolerance and in patients with overt diabetes; neutralization of secreted ITIH1 ameliorated glucose intolerance in obese mice [Kim et al. (2019)]
Inter-alpha trypsin inhibitor heavy chain 2 (ITIH2)	Shen et al. (2017)	↓ Average ratio 0.2	AD-associated SNPs in ITIH2 with $P_{GWAS} < 5E{-}08$ [Nazarian, Yashin, and Kulminski (2020)]	Abdulwahab et al. (2019)	↑ $p = .0307$	In silico analysis with previously published diabetic retinopathy related studies, validated a painel containing the protein-markers APO4, C7, CLU, and ITIH2 to diagnosis [Jin et al. (2016)]
Pancreatic polypeptide (PPY)	Sattlecker et al. (2014) Llano et al. (2013) Hu et al. (2012) Nazeri et al. (2014)	↑ $p = .0009$ ↑ $p < .05$ ↑ OR = 1.085 $p = .0.0239$ (not informed ratio AD x control)	PPY was associated with neocortical amyloid-β burden using protein stepwise regression techniques and support vectors machines [Voyle et al. (2015)]	Jensen et al. (2013)	↑ peak intensity elevated 4%	Pancreatic islets were investigated in young and elderly type 2 Zucker diabetic fatty (ZDF) rats and showed that the percentage of PPY positive cells was unaltered in young but increased in elderly ZDF rats compared to controls [Howarth, Al Kitbi, Hameed, and Adeghate (2011)]

(Continues)

TABLE 3 (Continued)

Protein	Alzheimer's disease studies	Evidence of significance	Other studies involving AD	Diabetes mellitus studies	Evidence of significance	Other studies involving diabetes
Transthyretin (TTR)	Llano et al. (2013) Nazeri et al. (2014)	↓ $p < .05$ $p = .0224$ (not informed ratio AD x control)	Targeted silencing of the endogenous TTR gene accelerated the development of the neuropathologic phenotype in APP23 transgenic murine model of human AD; the APP23 brains showed colocalization of extracellular TTR with Aβ in plaques, and surface plasmon resonance showed evidence of direct protein–protein interaction between TTR and Aβ aggregates [Buxbaum et al. (2008)]	Dincer et al. (2009) Abdulwahab et al. (2019)	↑ (not informed ratio or p value) ↑ $p = .0175$	Immunohistochemistry showed that islets of Langerhans from type−2 diabetic patients had proportionally more transthyretin-reactive islet cells, including beta cells [Westermark and Westermark (2008)]
Zinc alpha−2 glycoprotein (AZGP1)	Shen et al. (2017)	↓ Average ratio 0.4	Using cDNA microarray technology it was observed that AZGP1 were found to be strongly expressed in AD compared to control groups at two fold change and a false discovery rate of 0.05 [Mirza, Kamal, Al-Qahtani, and Karim (2014)]	Abdulwahab et al. (2019)	↑ $p = .0033$	AZGP1 increases the phosphorylation of IRS1 at the Ser307 residue in animal muscle, contributing to insulin resistance; but intravenous administration of AZGP1 to mice decreases fasting blood glucose and improves glucose tolerance; increases urinary glucose excretion and decreases the plasma glucose and insulin levels in oral glucose tolerance tests in mice, as well as promotes the transfer of glucose into skeletal muscle and adipocytes [Wei et al. (2019)]

Note: ↑ upregulated in case × control; ↓ downregulated in case × control; OR, odds ratio; average ratio, abundance AD group, abundance control.

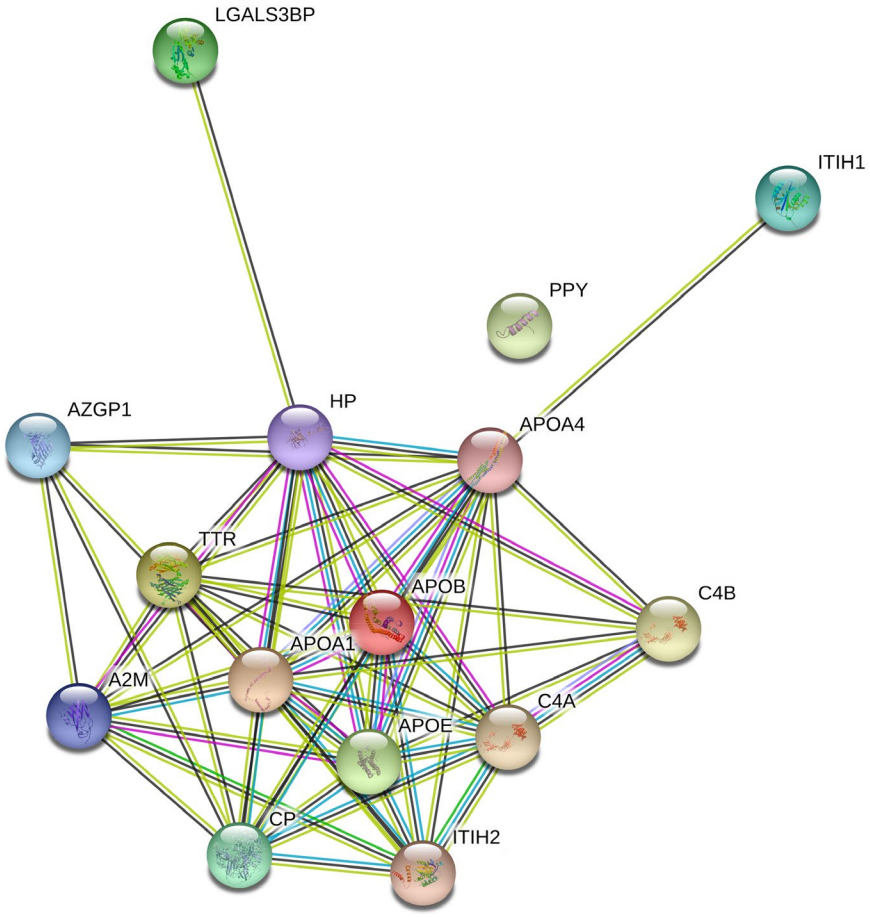

FIGURE 3 Protein–protein interactions. Each node represents a protein and each line refers an interaction. Each circle color indicates the number of protein–protein interactions. There are 56 potential protein–protein interactions. Enrichment *p*-value: $<1.0\ e^{-16}$. Lines: blue – known interaction from curated databases; pink – known interaction experimentally determined; green – textmining; black – co-expression

Mendez, Ricordi, Siotto, & Goldberg, 2019). Both AD and T2DM have shown abnormalities in Cu homeostasis. Indeed, meta-analyses have demonstrated that there is increase in serum Cu levels in both diseases (Qiu, Zhang, Zhu, Wu, & Liang, 2017; Squitti et al., 2014, 2019). It has been suggested that Cu ions appear to modulate Aβ generation, aggregation, and stabilization of the fibrillary form, as well as to promote reactive oxygen species resulting in neuroinflammation processes, aggregation and phosphorylation of tau protein. Accordingly, higher free Cu levels were observed in AD patients in comparison to controls, after adjusting for sex (Rozzini et al., 2018).

The complement system is a part of the innate immune system and plays a key role in the regulation of inflammation. It consists of three distinct pathways of proteolytic cascades, namely the classical, alternative, and lectin pathway. Of particular importance is the activation of complement component C4, which is considered an acute phase protein. A strong relation between C4 levels and adiposity levels, metabolic syndrome (MetS) and diabetes, as well as cardiovascular disease risk, was established in several studies (Copenhaver, Yu, & Hoffman, 2019; Fujita et al., 2013; Nilsson et al., 2014). Complement activation also occurs in the brain of patients with AD and seems to contribute to an important local inflammatory state. Increased expression of C4 has been observed in AD patients when compared to controls in many studies, and the presence of high C4A and C4B copy numbers variation (CNV) in AD patients could explain the possible role for C4 in the risk of developing AD (Zorzetto et al., 2017). However, a recent systematic review and meta-analysis showed that C4 concentrations were not significantly different between AD patients and healthy elderly, and inconsistent results were observed among different studies (Krance et al., 2019), in agreement with the proteomic results (Table 3). Nonetheless, trends in higher C4 levels in CSF from AD patients suggest that C4 should be further investigated in this group (Krance et al. 2019).

Galectin-3-binding protein (LGALS3BP) and its receptor/ligand, galectin-3 (Gal-3), are secreted proteins that can interact with each other to promote cell-to-cell adhesion and are associated with pro-inflammatory signaling cascades (DeRoo et al., 2015). Several studies have demonstrated the relationship between Gal-3 and T2DM. Although Gal-3 is a component of the host defenses and may affect immune/inflammatory cells, justifying the proteomic findings [Abdulwahab et al. (2019)] in diabetes and obesity, Gal-3 may apply some pro-resolutive functions, limiting injury and promoting tissue repair (Menini, Iacobini, Blasetti Fantauzzi, Pesce, & Pugliese, 2016). However, its function is still controversial. Gal-3 has been implicated in chronic complications of diabetes because of its ability to bind the AGEs, which exert pro-inflammatory and pro-oxidant effects. Higher levels of Gal-3 are also involved in the development of obesity and T2DM in parallel with deterioration of glucose homeostasis (Menini et al., 2016). Moreover, blood Gal-3 levels were associated with adverse cardiovascular outcomes in T2DM patients, independent of traditional risk factors (Tan et al., 2019). In addition, Gal-3

binds to the oligosaccharide side chain of insulin receptor in order to prevent its binding to insulin, thus inhibiting insulin-mediated receptor activation with consequent systemic insulin dysfunction (Li et al., 2019). Although the association between Gal-3 and T2DM is already known, the relationship with AD requires further investigations, and reduced expression of LGALS3BP was observed in AD group (Park et al., 2019). Expression of Gal-3 is increased under neuroinflammatory conditions, and neuroinflammation contributes to AD pathogenesis. Its neuronal expression is observed in the cerebral cortex and in diverse other subcortical nuclei in the hypothalamus and brainstem (Boziki et al., 2018). In fact, Wang, Zhang, Lin, Chu, and Yue (2015) found increased Gal-3 serum levels in patients with AD compared to control individuals, but no significant difference between patients with MCI and controls or MCI and AD was observed. Gal-3 seems to represent an important link between AD and T2DM and should be better understood.

Haptoglobin (HP) is an acute-phase protein that scavenges the hemoglobin (Hb)-released into circulation either by hemolysis or by red blood cell turnover, preventing Hb-related oxidative damage (Rodrigues et al., 2019). Song, Kim, Chung, and Cho (2015) observed that mean serum of HP level of AD patients was significantly higher than the controls, as well as they found a significant association between HP levels and the severity of cognitive impairment. Moreover, HP facilitates the formation of the ApoE/ Aβ stable complex, whose effect was more pronounced in the presence of ApoE4 isoform (Spagnuolo et al., 2014). Our previous study showed that Hp levels were higher in T2DM patients as compared to controls and obese T2DM patients had higher Hp levels as compared to obese controls and to non-obese T2DM patients (Rodrigues et al., 2019). Some studies have shown that diabetic patients' HP2 allele carriers have as much as a five times higher susceptibility to cardiovascular diseases compared to patients with the HP1-1 genotype. In addition, HP2-2 genotype also correlates with increased risk for diabetic retinopathy (MacKellar & Vigerust, 2016). Curiously, HP 1-1 genotype was associated with impaired cognitive function and greater cognitive decline than the other Hp genotypes (Beeri et al., 2018). Contradictory results observed in proteomic findings (Table 3) could be associated to different HP isoforms detected in each study.

Ig chain C region proteins are constant regions of immunoglobulin heavy (α-1 and μ) and light (κ) chains produced by B lymphocytes, which have an important role in immune defense, especially in immune response to AGEs that increase and accumulate with persistent high levels of blood glucose in patients with diabetes (de Oliveira et al., 2018). Murri et al., (2013) observed an increased abundance of Ig κ chain C region in visceral adipose tissue from pre-obese diabetic patients compared with pre-obese non-diabetic subjects, probably because of increased circulating IgG concentrations in diabetic patients. Higher levels of this protein were also found in urinary samples from T2DM, with or without diabetic kidney disease, when compared to healthy individuals (Bellei et al., 2008). Although elevated oxidation level of Ig κ chain C has been observed in triple transgenic AD mice when compared to controls (Shen et al., 2016), the involvement of Ig chain C region proteins with AD is unknown. However, one study showed increased IgG uptake and transport through in vitro blood-brain barrier model derived from human induced pluripotent stem cells after the addition of Aβ1 peptide or tumor necrosis factor-α and interleukin-6, suggesting an involvement of immunoglobulins in AD inflammatory process (Mantle & Lee, 2019). Only two proteomic studies identified different rates of IgG expression in AD and T2DM groups [Hye et al. (2006) and Abdulwahab et al. (2019)], with contradictory results, suggesting that further studies should be conducted.

Both inter-alpha-trypsin inhibitor heavy chain 1 (ITIH1) and inter-alpha-trypsin inhibitor heavy chain 2 (ITIH2) are part of a macromolecular complex arrangement of structurally related heavy chain proteins covalently cross-linked to the chondroitin sulfate chain of the proteoglycan bikunin, and are abundant in plasma, associated with inflammation (Toledo, Nilsson, Noborn, Sihlbom, & Larson, 2015). One study showed that ITIH1 is secreted by liver and it is responsible for systemic insulin resistance in animal model. Indeed, liver expression of ITIH1 was positively correlated with routine markers for diabetes in patients with impaired glucose tolerance or diabetes (Kim et al., 2019). On the contrary, lower expression of ITIH2 was observed in diabetic patients with proliferative diabetic retinopathy compared to non-diabetic subjects when evaluated in the vitreous fluid (Garcia-Ramirez et al., 2007), differently of the proteomic results (Table 3). Lower protein levels of ITIH complex were also identified in AD plasma samples when compared to healthy controls (Liao, Yu, Kuo, Lin, & Kuo, 2007), in agreement with Shen et al. (2017) (Table 3). Therefore, the potential role of ITIH proteins in AD or T2DM should be elucidated, since they are considered acute-phase and anti-inflammatory proteins, and both diseases present a low-grade inflammatory evolution.

Pancreatic polypeptide (PPY) is a hormone secreted by peripheral cells on pancreatic Langerhans islets, and its expression was increased in both AD and T2DM groups (Table 3). The roles of this hormone are delayed gastric emptying, pancreatic exocrine function inhibition, including inhibition of insulin secretion and hepatic glucose production. In addition, PPY reduces the amount of food intake. In T2DM subjects, plasma PPY levels are significantly elevated in the post-prandial state compared to non-diabetic subjects (Floyd, Fajans, Pek, & Chance, 1977; Śliwińska-Mossoń, Marek, & Milnerowicz, 2017), corroborating with our observations. Voyle et al. (2015) observed an association between PPY and neocortical amyloid-β burden. Indeed, PPY was also associated with MCI conversion to AD in patients assessed by brain amyloid PET using [^{18}F] Flutemetamol (Westwood et al., 2018). It is important to highlight that misfolding and aggregation pattern of Aβ peptide in plaques in the brain of AD patients are similar to the presence of amyloid deposits in the pancreas of T2DM patients. Therefore, the C-terminus of the PPY presents an amyloidogenic sequence susceptible to folding into beta-pleated sheets, oligomers, and fibrils, which aggregate and induce cellular toxicity and apoptosis (Mietlicki-Baase, 2018). Consequently, PPY could be an important link between these diseases.

Transthyretin (TTR) is a homotetrameric protein synthesized in the liver and choroid plexus, which circulates in the blood and CSF. In CSF, the TTR is the primary carrier of thyroid hormone thyroxine (T4), while in serum TTR is the main transporter of retinol binding protein (RBP). TTR is considered one of the human amyloidogenic proteins associated to pathological conditions (RimáLim et al., 2019). Plasma levels of TTR were independently associated to T2DM, HOMA-IR and triglycerides levels in diabetic patients, and augmented with increasing glucose intolerance severity (Kwanbunjan et al., 2018; Pandey et al., 2015). Indeed, subjects with both obesity and T2DM had the highest levels of TTR when compared to controls or lean T2DM patients (Kwanbunjan et al., 2018; Pandey et al., 2015), in agreement with the proteomic results (Table 3). However, in AD patients the TTR has also been implicated in neuroprotection, since TTR suppresses Aβ aggregation and is involved in brain Aβ efflux and peripheral clearance mediated by its proteolytic function. In addition, TTR levels are reduced both in CSF and blood of AD patients compared with controls (RimáLim et al., 2019; Yang, Joshi, Cho, Johnson, & Murphy, 2013), according to Llano et al. (2013) in a proteomic study (Table 3).

Zinc alpha 2-glycoprotein (AZGP1) is a glycoprotein allocated in the major histocompatibility complex class I family of proteins, which is secreted into many body fluids. AZGP expression was increased in T2DM group in Abdulwahab et al. (2019) in a proteomic study (Table 3). In fact, AZGP1 stimulates lipolysis and is involved in many biological processes, including obesity, as well as the pathogenesis of obesity-related metabolic disorders. An increased retention of insulin by the pancreas, and an improvement in the glucose tolerance, related to AZGP1, was observed in ob/ob mice, an animal model of T2DM and obesity (Wang, Li, Zhang, Zhao, & Liu, 2016). Some studies have suggested that urinary AZGP1 is increased in diabetic patients and that it may be used as a biomarker for the diabetes kidney disease (Jain et al., 2005; Varghese et al., 2007; Wang et al., 2016). However, decrease in circulating AZGP1 levels were observed in newly diagnosed T2DM when compared to controls. In addition, circulating AZGP1 showed positive correlation with HDL-c, and adiponectin, and inverse correlation with BMI, waist-to-hip ratio, body fat percentage, triglycerides, fasting blood glucose, fasting insulin, HbA1c, and homeostasis model assessment of insulin resistance (HOMA-IR) in T2DM patients (Yang, Liu, et al., 2013). Few studies investigated the association between AZGP1 and AD. Evaluation in CSF samples collected in postmortem period showed reduced levels in AZGP1 levels in AD patients when compared to non-AD dementia patients and elderly controls (Roher et al., 2009), in accordance to Shen et (2017) in their proteomic study (Table 3). Further studies are necessary to elucidate the role of AZGP1 in AD and T2DM complications.

It is important to highlight the several interactions identified, which suggest that many proteins contribute to a shared function. Moreover, it is possible to observe many proteins whose genes are correlated in expression (Figure 3). Most of them are related to cholesterol metabolism, including liposoluble vitamins and other fat absorption, which suggest that lipid metabolism is a important pathway involved on AD and T2DM development (Toledo et al., 2017). In addition, inflammation, represented by C4a or C4B proteins, and coagulation cascade showed an important pathway associated with both diseases. In fact, homeostatic mechanism underlies AD characteristics, because postmortem analyses of the brains of AD patients showed small vessels arteriosclerotic disease, with hemorrhagic occurrences and infarcts in more than 50% of the cases (Silva et al., 2019).

In conclusion, we identified a panel of 17 promising biomarkers of AD that were integrated with data from proteomic studies in T2DM, which are alpha-2-macroglobulin, apolipoprotein A1, apolipoprotein A4, apolipoprotein B-100, apolipoprotein E, ceruloplasmin, complement C4, galectin-3–binding protein, haptoglobin, inter-alpha-trypsin inhibitor heavy chain 1, inter-alpha-trypsin inhibitor heavy chain 2, Ig α-1 chain C region, Ig μ chain C region, Ig κ chain C region, pancreatic polypeptide, transthyretin, and zinc alpha 2-glycoprotein. These biomarkers could provide a useful workflow for screening T2DM patients at risk to develop AD. Currently, this biomarkers shortlist should be validated in a large population in order to confirm our hypothesis.

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CONFLICTS OF INTEREST

There is no conflict of interest.

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