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Review

Research Progress of Biomarkers in Diabetes Mellitus combined with Cognitive Impairment

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A B S T R A C T

The prevalence of diabetes mellitus with cognitive impairment is increasing every year, placing a heavy burden on global health care. However, there is still a lack of effective means of early diagnosis of this complication, to the extent that many patients are not effectively recognized at an early stage and subjected to early intervention, leading to the development of severe dementia. In order to change this situation, there is an urgent need for early identification of patients and biomarkers show good potential in this regard. Therefore, this paper provides a review of various biomarkers, such as metabolism-related markers, neurological-related markers, adipokines and inflammatory factors, in an attempt to provide new and valuable strategies for the early clinical diagnosis of cognitive impairment in diabetes mellitus.

Keywords: Diabetes mellitus, Cognitive impairment, Biomarkers

The global pandemic of diabetes mellitus poses a huge threat to global health, with the International Diabetes Federation (IDF) estimating that by 2040, the number of people with diabetes worldwide will reach 642 million, the majority of whom will have type 2 diabetes mellitus (T2DM)[1]. It is well known that people with diabetes suffer from a variety of complications that often attack the kidneys, cardiovascular system, retina and nervous system[2]. It is now widely recognized that there is a strong association between diabetes mellitus and cognitive impairment and that diabetes not only causes cognitive impairment but also accelerates the deterioration of cognitive function in patients. Analysis shows that the combined estimated prevalence of combined mild cognitive impairment (MCI) in T2DM patients is 45% globally, with a prevalence of 46.4% in Asian patients compared to 36.6% in Europe[3]. However, it is still clinically impossible to provide early recognition of diabetic cognitive impairment at an early stage, resulting in patients often having more severe cognitive impairment by the time of detection and missing a good time for intervention. Therefore, there is an urgent need for a biomarker to recognize early cognitive impairment caused by diabetes, so that early intervention and treatment can be provided to improve the prognosis of patients. Studies

have shown that neurodegeneration, abnormal blood glucose regulation, insulin dysregulation and inflammation may all be risk factors for cognitive impairment in combination with diabetes mellitus[4]. Therefore, we believe that certain metabolism-related substances, neurological-related substances and inflammatory factors have the potential to play a role in the early recognition of diabetes mellitus with cognitive impairment. In this paper, we aim to discuss the potential biomarkers associated with diabetes mellitus with cognitive impairment and try to understand the role they play in the pathogenesis of diabetes mellitus with cognitive impairment in order to find effective markers for early recognition.

1. Metabolism-Related Biomarkers

1.1. Hemoglobin A_{1c} (HbA_{1c})

HbA_{1c} is a standard index for monitoring blood sugar control in clinical practice. Studies have shown that a higher HbA_{1c} value is related to a decline of cognitive ability and the higher the HbA_{1c} level, the more significant the cognitive decline was[5]. In a prospective analysis of 5099 participants, Rawlings AM's team found that diabetics do not have an increased risk of mild cognitive impairment (MCI) when blood glucose levels are well controlled (HbA1c<7%), but if blood glucose levels were high (HbA_{1c}≥7%), people with diabetes had a significantly higher risk of developing cognitive impairment than people without diabetes[6]. Therefore, HbA_{1c} has the potential to be a biomarker for the early recognition of cognitive impairment caused by diabetes.

1.2. Amino acids and their metabolic intermediates

Amino acids are one of the most basic substances that make up the human body and are involved in the synthesis and metabolism of many important substances in the body. Meanwhile, amino acids play many important roles in the central nervous system[7]. In a follow-up survey of 427 respondents in the community, K. INOSHITA found that the intake of lysine, phenylalanine, threonine and alanine was beneficial in maintaining cognitive function in older adults[8]. In addition, Ying Zhao analyzed the amino acid spectrum of cerebrospinal fluid of rats and found that the levels of L-alanine, L-lysine, L-threonine and L-serine in the model group of diabetic cognitive impairment were significantly reduced, while the levels of L-glutamine were significantly increased, suggesting that the above amino acids may be potential markers of diabetic cognitive impairment[9]. Lili Song's team found in the urine analysis of mice that the levels of pyroglutamic acid and 5-hydroxy-L-tryptophan in the diabetic cognitive impairment group were significantly lower than those in the normal control group[10]. In another study of T2DM patients aged 50 to 70 years, Lin Sun and colleagues found that elevated glutamate and decreased glutamine were significantly associated with cognitive impairment through metabolomic analysis of the patients[11]. In another study of 2358 subjects, Lieke Bakker et al. found that in patients with type 2 diabetes, the higher the levels of kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and kynurenic acid were less likely to have cognitive dysfunction[12].

Studies have shown that elevated homocysteine (Hcy) levels are associated with cognitive impairment and even Alzheimer's disease and dementia[13]. In addition, there is evidence that hyper homocysteine is a risk factor for T2DM[14]. In a cross-sectional study of 97 T2DM patients younger than 60 years of age, Damanik's team conducted a cross-sectional study of 97 T2DM patients younger than 60 years of age and did not find a significant difference in serum Hcy levels between the mildly cognitively impaired and non-mildly cognitively impaired groups[15]. However, in another study of 285 patients with T2DM, Sai Tian found that plasma total homocysteine (tHcy) levels were significantly higher in the MCI group than in the control group and that higher tHcy levels were associated with poorer cognitive functioning when their cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA)[16]. Together, these studies suggest that amino acids and metabolic intermediates may play an important role in the diagnostic application of diabetic cognitive impairment. However, given the inconsistency of some experimental results, we believe that further research is needed to further explore the role of amino acids and their metabolites in the pathogenesis of cognitive impairment in diabetes.

1.3. Lipids and related substances

Lipids and their associated metabolites may be closely associated with the development of T2DM as well as cognitive dysfunction and a recent study reported that phospholipids may be important biomarkers of cognitive function[17]. A study of 374 diabetic patients found that higher plasma levels of lysophosphatidic acid (LPA) and phospholipids with solubility similar to LPA (PSS-LPA) were associated with lower MoCA scores in T2DM patients with MCI, suggesting that levels of LPA and phospholipids with solubility similar to LPA are negatively associated with cognitive functioning[18]. Another study used an untargeted metabolomics approach based on liquid chromatography-mass spectrometry (LC-MS) and ultimately found that serum phosphatidylethanolamine (PE) up-regulation and phosphatidylcholine (PC) down-regulation may contribute to cognitive impairment in diabetes by affecting lipid metabolic pathways[19].

Free fatty acids (FFAs) stimulate in vitro the assembly of amyloid and tau protein filaments, the two main pathologic lesions of Alzheimer's disease (AD)[20]. Zhu and his team found that plasma FFA concentrations were higher in patients with T2DM combined with MCI than in the non-MCI group and hypothesized that the occurrence of MCI in patients with T2DM may be related to elevated free fatty acids in plasma[21]. However, the role of lipids and their metabolites in early cognitive dysfunction in T2DM patients requires further studies with larger sample sizes.

1.4. Osteocalcin

Osteocalcin is one of the few osteoblast-specific proteins that exists in two forms, carboxylated osteocalcin (cOC) and undercarboxylated osteocalcin (ucOC). Studies have shown that osteocalcin promotes the proliferation of pancreatic beta-cells, influences brain development and function and enhances spatial learning and memory[22,23]. The study showed that ucOC concentrations were significantly lower in cognitively impaired T2DM patients compared to cognitively normal T2DM patients, suggesting that ucOC may be involved in the development of cognitive dysfunction in T2DM patients[24]. Therefore, detection of ucOC levels may be able to identify cognitive impairment in diabetic patients at an early stage.

1.5. Ghrelin

Ghrelin is a 28 amino acid peptide cleaved from the endogenous ligand of the growth hormone prosecretory receptor[25]. Studies have shown that ghrelin leads to higher blood sugar and lower insulin levels[26]. A study found that ghrelin may improve cognitive performance in mice by participating in insulin signaling[27]. In a study of 218 patients with T2DM, researchers found that plasma ghrelin levels were positively correlated with Mini-Mental State Examination (MMSE) scores[28]. These studies suggest that gastric starvation hormone levels may play an important role in the early recognition of diabetic cognitive impairment and that it may be possible to avoid diabetic cognitive impairment by increasing gastric starvation hormone levels in patients.

2. Neuron-Related Biomarkers

2.1. Brain-derived neurotrophic factor (BDNF)

BDNF is a type of nerve growth factor involved in promoting memory and neuronal growth[29]. Meta-analysis showed that serum BDNF levels were significantly lower in AD patients compared to normal controls[30]. BDNF plays an important role in improving systemic glucose homeostasis and increasing insulin sensitivity, so it may contribute to the treatment of T2DM[31]. BDNF levels were found to be negatively correlated with the risk of mild cognitive impairment in patients with T2DM, with the lower the BDNF level, the more likely the patient was to suffer from MCI[29]. In addition, the researchers found that although BDNF levels were significantly lower in patients with T2DM than in healthy controls, there was no significant difference in BDNF levels between patients with amnestic mild cognitive impairment and those without amnestic mild cognitive impairment in patients with T2DM, suggesting that BDNF may not be a biomarker for the diagnosis of cognitive impairment in diabetes mellitus[32]. In addition, another team of researchers instead found that T2DM patients with comorbid MCI had lower levels of BDNF compared to T2DM patients without MCI[33]. Given these results, we believe that further studies are needed to analyze the relationship between BDNF and cognitive impairment in diabetes mellitus.

2.2. Glial fibrillary acidic protein (GFAP)

GFAP is an intermediate filament protein that is an essential component of the astrocyte cytoskeleton[34]. A meta-analysis based on population-based cohort studies shows that blood GFAP levels are negatively correlated with cognitive performance[35]. Another study confirmed that GFAP levels were reduced in the cerebral cortex of diabetic rats[36]. The researchers found that T2DM mice with cognitive impairment had reduced hippocampal cell volume and decreased GFAP levels[37]. This evidence suggests that GFAP may be a biomarker for diabetes mellitus combined with cognitive impairment.

2.3. Beta-site amyloid precursor protein cleaving enzyme 1(BACE1)

BACE1 is required for the generation of all monomeric forms of amyloid-β (Aβ), Therefore, it is considered a key target for AD[38]. High levels of BACE1 lead to decreased insulin signal transduction and glucose uptake[39]. Sai Tian's research on 186 patients with T2DM showed that the plasma BACE1 level in patients with mild cognitive impairment of T2DM was significantly higher than that in normal cognitive group of T2DM and the BACE1 level was negatively correlated with MoCA scores[40]. In a clinical cohort study, Hong Bao found that elevated BACE1 levels in T2DM may contribute to increasing the cognitive impairment risk through both amyloidogenesis[41]. However, further large-scale longitudinal studies are needed to determine the role BACE1 plays in cognitive impairment in people with T2DM.

2.4. Neurofilament light chain (NfL)

NfL is a subunit of neurofilaments (Nfs). In response to CNS axonal damage because of neurodegenerative or vascular injury, the release of NfL sharply increases[42]. Meta-analyses have shown significantly elevated NfL levels in patients with neurodegenerative dementia compared with healthy controls[43]. In a cross-sectional study of 183 people with T2DM, Yinan Zhao found that NFL levels were negatively correlated with Rivermead Behavioral Memory Test (RBMT) scores and that NFL levels helped identify patients with mild cognitive impairment that MMSE scores could not identify[44]. The above study demonstrates the potential of NFL as a biomarker to identify cognitive impairment early in patients with type 2 diabetes.

3. Adipokine-Related Biomarkers

3.1. Resistin

Resistin is a hormone secreted by adipose tissue that resists the action of insulin[45]. Significant correlation between resistin levels and insulin resistance and associated with T2DM in some populations[46]. Studies have shown that high expression of resistin is associated with the development of AD[47]. In a study of Chinese patients with T2DM, Wang and colleagues found that resistin levels were significantly higher in the MCI group than in the non-MCI group and that resistin levels were negatively correlated with cognitive performance[48]. This reveals the potential of resistin as a biomarker of cognitive impairment in diabetes mellitus.

3.2. Nicotinamide phosphoribosyl transferase (Nampt)

Nampt, a key enzyme in the nicotinamide adenine dinucleotide (NAD) repair pathway, has been found to be dysregulated in diabetes expression[49]. Nampt is highly expressed in visceral adipose tissue and is therefore also considered an adipokine, also called visfatin[50]. In pancreatic β-cells, Nampt expression levels regulate glucose-stimulated insulin secretion[51]. In addition, it was found that reduced nampt expression impaired cognitive function in mice[52]. After studying 195 patients with T2DM, Huang and colleagues found that plasma Nampt levels were significantly higher in the MCI group compared to the normal cognition group, suggesting that Nampt may be associated with the development of cognitive impairment in diabetes[53].

3.3. Apelin

Apelin is a peptide with multiple active forms that increase insulin sensitivity[54]. Apelin is mainly produced by adipocytes and is therefore also regarded as an adipokine. Apelin-13 may improve cognitive function by upregulating BDNF through inhibition of glial cell activity and inflammatory factor release[55]. At the same time, apelin can play a neuroprotective role in ischemic stroke, neurodegenerative diseases and other diseases[56]. The above study suggests that epoetin may be involved in the

pathophysiologic processes of both diabetes and cognitive dysfunction. To demonstrate this relationship, a research group studied 235 diabetic patients and showed that the MCI group had lower levels of epoetin than the normal cognitive group, suggesting that epoetin may have a protective effect on cognitive function[57].

3.4. Cholesteryl ester transfer protein (CETP)

CETP is a banana-shaped protein that forms a channel with HDL and LDL or VLDL to mediate the transfer of cholesteryl esters and triglycerides[58]. CETP-mediated cholesteryl ester transfer (CET) plays an essential role in lipoprotein homeostasis and is significantly increased in patients with T2DM[59]. In addition, in a study of 190 Chinese diabetics, Jie Sun found that serum CETP levels were significantly elevated in diabetics with mild cognitive impairment[60]. This provides a possible marker for the early recognition of cognitive impairment caused by diabetes. However, the study was limited to Chinese people and the sample size was small. Further experiments are still needed to investigate the specific role of CETP.

3.5. Lipoprotein lipase (LPL)

LPL promotes the hydrolysis of triglycerides and is regulated by insulin and its activity responds to insulin sensitivity[61]. In addition, studies have shown that mice lacking LPL are susceptible to cognitive deficits[62]. In a study of 170 Chinese patients with T2DM, An and colleagues found that plasma LPL was significantly lower in patients with comorbid cognitive impairment, hypothesizing that low LPL may indicate the onset of early cognitive impairment[63]. The above study suggests the potential of LPL as a biomarker for diabetes mellitus combined with cognitive impairment.

4. Inflammation-related biomarkers

4.1. Interleukin (IL)

Interleukin-1β (IL-1β) is a potent proinflammatory cytokine produced and secreted by a variety of cells that is essential for the host's defense response to infection and injury[64]. IL-1β induces an inflammatory response, leading to impaired insulin secretion and sensitivity in genetically susceptible individuals, ultimately leading to the development of T2DM[65]. In addition, the inflammatory process plays an important role in the pathophysiology of AD. IL-1β is considered to play an important role in the pathogenesis of AD[66]. In a study of 194 subjects conducted by Malgorzata Gorska-Ciebiada's team, they found that serum IL-1β levels were significantly higher in the diabetic cognitive impairment group than in the control group, suggesting that high levels of IL-1β may be a factor in increasing the occurrence of MCI in elderly patients with T2DM[67].

IL-6 has a critical impact on immunomodulatory and nonimmune events in most cell types and tissues outside the immune system[68]. IL-6 levels are independent predictors of T2DM and are thought to be associated with the development of insulin resistance[69]. IL-6 is thought to be harmful to learning and memory and IL-6 levels have been shown to be associated with a higher risk of dementia[70]. In a study of 1066 patients with T2DM, Anniek J. Sluiman and colleagues found that higher IL-6 levels were associated with more pronounced general cognitive decline[71]. However, more research is needed to explore the role of IL in the development of cognitive impairment in diabetes.

4.2. Platelet-lymphocyte ratio (PLR)

The platelet-lymphocyte ratio (PLR), similar to the neutrophil-lymphocyte ratio, is a common marker of subclinical inflammation[72]. PLR was found to be significantly lower in prediabetes and early diabetes, but elevated in later diabetes, which may be related to worsening HbA1c leading to an exacerbation of the underlying chronic low-grade inflammatory state[73,74]. At the same time, persistent inflammation is an important feature of neurodegenerative diseases, so PLR is also thought to assess cognitive dysfunction[75]. Du and colleagues found that PLR levels in patients with T2DM combined with cognitive impairment were higher than those in the diabetes-only group and that higher PLR levels were associated with a higher incidence of cognitive impairment[76]. We believe that further prospective cohort studies and larger sample collections are needed to investigate the role of the PLR in cognitive decline in T2DM patients.

4.3. High sensitivity C-reactive protein (hsCRP)

High sensitivity C-reactive protein (hsCRP) is a known sensitive marker of systemic low-grade inflammation[77]. It was found that elevated hsCRP levels signalled a decline in memory capacity[78]. In a study of 192 T2DM patients, Malgorzata Gorska-Ciebiada's team found that serum hsCRP levels were higher in patients with mild cognitive impairment than in controls[79]. Similarly, in a study of 140 T2DM patients, Rongrong Cai and colleagues also found that plasma hsCRP quality and activity were significantly higher in the MCI group than in the control group and that the MoCA score was negatively correlated with hsCRP quality and activity in MCI patients[80]. The above research shows that hsCRP has potential as a biomarker of cognitive impairment in diabetes to some extent.

4.4. miRNA

MicroRNAs (miRNAs) are short RNA molecules with a size of 19 to 25 nucleotides that regulate the posttranscriptional silencing of target genes. A single miRNA can target hundreds of mRNAs and influence the expression of many genes that are normally involved in functional interaction pathways and miRNAs have been shown to be involved in the pathogenesis of many diseases[81]. With the deepening of miRNA research, an increasing number of experiments have proven that miRNAs play an important role in the occurrence and development of diabetic cognitive impairment. Rui Zhang found that the serum miR-34c was significantly up-regulated in rats with diabetic encephalopathy, suggesting that serum miR-34c levels have the potential to be used as a biomarker for clinical diabetic encephalopathy[82]. In another study of 163 patients with type 2 diabetes, Salama et al. found that plasma miR-132 expression in T2DM patients with MCI was significantly higher than that in those without MCI and cognitively normal healthy individuals[83]. The above studies show the potential of miRNA as a diagnostic marker of diabetic encephalopathy, but further research is needed to find more convincing evidence.

In summary, access to effective biomarkers is essential for early recognition of cognitive impairment in diabetes mellitus. The biomarkers discussed in this review are summarized in **(Table 1)**.

Table1: The biomarkers of cognitive impairment in diabetes discussed in this review.

Biomarker	Research object	Cognitive measure	Association with cognition	Reference
		Proxy interviews, change in cognitive scores on three cognitive tests, MMSE, CDR, FAQ, Z scores from a full battery of 10 neuropsychological tests	Poor glycemic control was associated with worse cognitive outcomes	6
HbA_{1c}	human			
Lysine,			Intake of lysine, phenylalanine, threonine and alanine was important for the maintenance of cognitive function in the elderly	8
phenylalanine,				
threonine,	human	MMSE		
alanine				
L-alanine,	rats	Morris water maze	In the model group of diabetic cognitive impairment, the levels of L-alanine, L-lysine, L-threonine and L-serine were reduced, while the levels of L-glutamine were increased	9
L-lysine,				
L-threonine,				
L-glutamine				
Pyroglutamic acid,	mice	Morris experiments	Decreased pyroglutamic acid and 5-hydroxy-L-tryptophan level were observed in the diabetic cognitive impairment group	10
5-hydroxy-L-tryptophan				
Glu,	human	MoCA,	Glu, Phe, Tyr, Pro and Hcy levels increased with the development of cognitive impairment, while the Gln level decreased.	11
Phe,		MMSE		
Tyr,				
Pro,				
Hcy,				
Gln				
Kynurenine,	human	Verbal Learning Test, the Stroop Color-Word Test, the Letter-Digit Substitution Test, the Concept Shifting Test	The higher the levels of kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and kynurenic acid, the lower the chance of cognitive impairment	12
3-hydroxykynurenine, 3-hydroxyanthranilic acid and kynurenic acid				
Hcy	human	MoCA	No association between serum Hcy and cognitive function	15
tHsy	human	MoCA	High tHcy level was an independent factor for MCI in T2DM patients	16
LPA,	human	MoCA	In type 2 diabetic patients with MCI, there were negative correlations between plasma LPA, PSS-LPA and the MoCA scores.	18
PSS-LPA				
PE,	rats	NORT, the Morris water maze	Up-regulation of serum PE and downregulation of PC may lead to DMMCI	19
PC				
FFA	human	MoCA	FFA levels were independent risk factors for MCI in patients with T2DM	21
ucOC	human	MMSE,	The serum ucOC is positively correlated with RBANS scores in male T2DM patients.	24
		RBANS		
ghrelin	human	MoCA, DST, Word Similarity Test, Trail Making Test, AVLT, VFT, HIS, CDR, activity of daily living scale and selfrating depression scale	ghrelin levels are associated	28
			with MCI, especially with episodic memory dysfunction in T2DM populations.	
BDNF	human	cognitive concern by physician, subject or nurse; impairment in at least 1 of 4 cognitive domains; essentially normal functional activities; and absence of dementia	BDNF levels were inversely correlated with the patient's risk of mild cognitive impairment.	29
BDNF	human	MMSE, CDR, AVLT, CFT, DST, SDMT, TMTA, TMTB, CDT, VFT	the relationship between plasma BDNF and diabetic cognitive dysfunction is still elusive.	32
GFAP	mice	Morris water maze	GFAP was significantly reduced in the hippocampus of KK-Ay mice exhibiting cognitive deficits	37
BACE1	human	MoCA	elevated plasma BACE1 level was a risk factor for MCI in T2DM patients	40
BACE1	human	MoCA,MMSE	The elevated BACE1 levels in T2DM may contribute to increasing the cog-	41
			nitive impairment risk through both amyloidogenesis and insulin resistance.	

Nfl	human	MMSE, RBMT	Plasma NfL levels were correlated with mild cognitive decline	44
Resistin	human	MoCA	Resistin was an independent variable of MCI in all individuals.	48
Nampt	human	MoCA	Higher plasma level of Nampt presages memory dysfunction in MCI in Chinese T2DM patients.	53
Apelin	human	MoCA	Serum apelin level is reduced in T2DM patients with MCI.	57
CETP	human	MoCA	CETP concentration was an independent factor of diabetic MCI	60
LPL	human	MoCA	Decreased plasma level of LPL could probably predict early cognitive deficits	63
IL-1β	human	MoCA	Elderly diabetic patients with MCI, are more likely to have higher levels of IL-1β	67
IL-6	human	LM, Faces subtests of the Wechsler Memory Scale, BVFT, Digit Symbol Test, LNS, Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale.	higher levels of IL-6 may be associated with subsequent cognitive decline in older patients with type 2 diabetes	71
PLR	human	MMSE	higher PLR was associated with cognitive decline in T2DM patients	76
hsCRP	human	MoCA	Higher hsCRP level may be regarded as a state of cognitive impairment in elderly patients with T2DM.	79
miR-34c	rats	Morris water maze test, NORT	Serum miR-34c levels were842 significantly upregulated in patients with diabetic encephalopathy	82
miR-132	human	ACE III test	A significantly over expression of miR-132 was detected among T2DM with MCI compared to those with normal cognition	83

MMSE, mini-mental state examination; CDR, clinical dementia rating; FAQ, functional activities questionnaire; MoCA, Montreal cognitive assessment; NORT, the novel object recognition test; RBANS, repeatable battery for the assessment of neuropsychological Status; DST, digit span test; AVLT, auditory verbal learning test; VFT, verbal fluency test; HIS, Hachinski ischemic score; CFT, Rey-Osterreith complex figure test; SDMT, symbol digit modalities test; TMTA, trail making test-A; TMTB, trail making test-B; CDT, clock drawing test; VFT, verbal fluency test; LM, logical memory; BVFT, Borkowski verbal fluency test; LNS, letter–number sequencing; ACE III, Adenbrooke's cognitive examination III test.

5. Conclusion

Cognitive impairment due to diabetes mellitus is more difficult to recognize in the early stages, but the progression of cognitive dysfunction can seriously affect the quality of life of patients, making early recognition and intervention particularly important. In this paper, we discuss various markers in the field of diabetic cognitive impairment, but we note that these markers have not yet been applied to the clinical field on a large scale, especially that some biomarkers have reached opposite conclusions in different studies and we believe that more and more extensive studies are needed to further reveal the relationship between biomarkers and diabetic cognitive impairment, in order to identify biomarkers with high sensitivity and specificity of biomarkers.

6. Conflicts of Interests

The author declares no conflict of interest.

7. Authors' Contributions

Conceptualization, Xinhuan Zhang; methodology, Ke Zhang and Liping Zheng; resources, Ke Zhang; writing-original draft preparation, Ke Zhang and Liping Zheng; writing-review and editing, Xinhuan Zhang. All authors have read and agreed to the published version of the manuscript.

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