SCIREA Journal of Clinical Medicine
ISSN: 2706-8870
http://www.scirea.org/journal/CM
January 1, 2023
Volume 8, Issue 1, February 2023
https://doi.org/10.54647/cm32970

Neurofilament Light: a biomarker of neurodegeneration correlated with Type 2 diabetes and other related diseases

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Abstract

Type 2 diabetes (T2D) and its related neurodegenerative complications greatly pose a serious health and economic burden. In recent years, neurofilament light (NfL) has been proved to be as a biomarker of neurodegeneration, and the levels of plasma NfL were found to be associated with clinical staging of diabetes mellitus and cognitive decline. In this review, we indicate that the level of NfL in blood may be a valuable clinical tool to distinguish the normal population, pre-diabetes and diabetes patients. In addition, NfL levels of diabetic

patients are closely related to diabetic complications, such as diabetic distal symmetric polyneuropathy, diabetic nephropathy and cardiovascular and cerebrovascular diseases. Furthermore, NfL levels of diabetic patients is also correlated with Alzheimer's disease, Parkinson's disease and COVID-19. Therefore, the level of NfL in blood may be a valuable clinical tool to distinguish the normal population, pre-diabetes and diabetes patients, to identify mild cognitive decline in diabetes patients.

Keywords: type 2 diabetes; neurofilament light; neurodegeneration; biomarker; Alzheimer's disease; Parkinson's disease; COVID-19

1. Introduction

Neurofilament light chain (NfL) is a neuronal cytoplasmic protein that is highly expressed in large calibre myelinated axons [1,2]. NfL can negatively affect the expression of TDP-43 in the central nervous system [3]. Moreover, lacking of NfL protein can result in the changes of the expression of cytoskeletal proteins and other Nf subunits, causing intracellular aggregation in cortical neurons [4]. In various neurological diseases, destruction of nerve fibres in neuronal injury leads to the release of neurotrophic factors into the cerebrospinal fluid (CSF), resulting in an increase in NfL concentrations in the CSF and blood proportional to the degree of axonal injury [5]. As a biomarker of neurodegeneration, NfL has been extensively studied for its potential value in the diagnosis and prediction of disease course in neurological disorders such as multiple sclerosis (MS) [6], Alzheimer's disease (AD) [7], amyotrophic lateral sclerosis (ALS) [8], Parkinson's disease (PD) [9] and traumatic brain injury (TBI) [10] through baseline and/or longitudinal measurements of CSF and blood NfL.

Type 2 diabetes (T2D) is a chronic metabolic disease characterized by insulin resistance and elevated blood glucose levels [11,12]. By 2021, 537 million (10.5%) adults aged 20-79 years have diabetes, resulting in at least US$966 billion in health expenditures (IDF, 10), and the prevalence and economic costs of diabetes are increasing globally. The prevalence and economic costs of diabetes are rising at an alarming rate worldwide, posing a serious health and economic burden [13]. More importantly, once diagnosed, diabetes is almost irreversible and eventually leads to diabetes complications such as diabetic distal symmetric polyneuropathy (DSPN) [14], diabetic nephropathy (DN) [15], cardiovascular and cerebrovascular diseases [16,17]. At the same time, there is a lack of effective treatments to

reverse organ damage [18,19], greatly affecting human health and well-being. Therefore, early diagnosis and monitoring of diabetes and its complications is crucial.

Notably, evidence from epidemiology, cell culture, animal studies and clinical data confirms a strong link between T2D and neurodegeneration as well, with potential mechanisms including advanced glycosylation end products, insulin resistance, impaired neuronal insulin signalling, neuroinflammation, mitochondrial dysfunction and oxidative stress, amyloid deposition and tau protein phosphorylation (Figure 1) [20-25]. The increasing prevalence of neurovascular and neurodegenerative disorders among diabetic patients has resulted in an urgent need to develop biomarkers for their prediction, early detection and course monitoring [26]. Therefore, more and more researchers are gradually focusing on the potential of NfL in the field of T2D. In this paper, we will summarize the studies related to NfL and T2D, and provide a reference for NfL to assist in the early diagnosis and condition monitoring of T2D-related neurodegeneration.

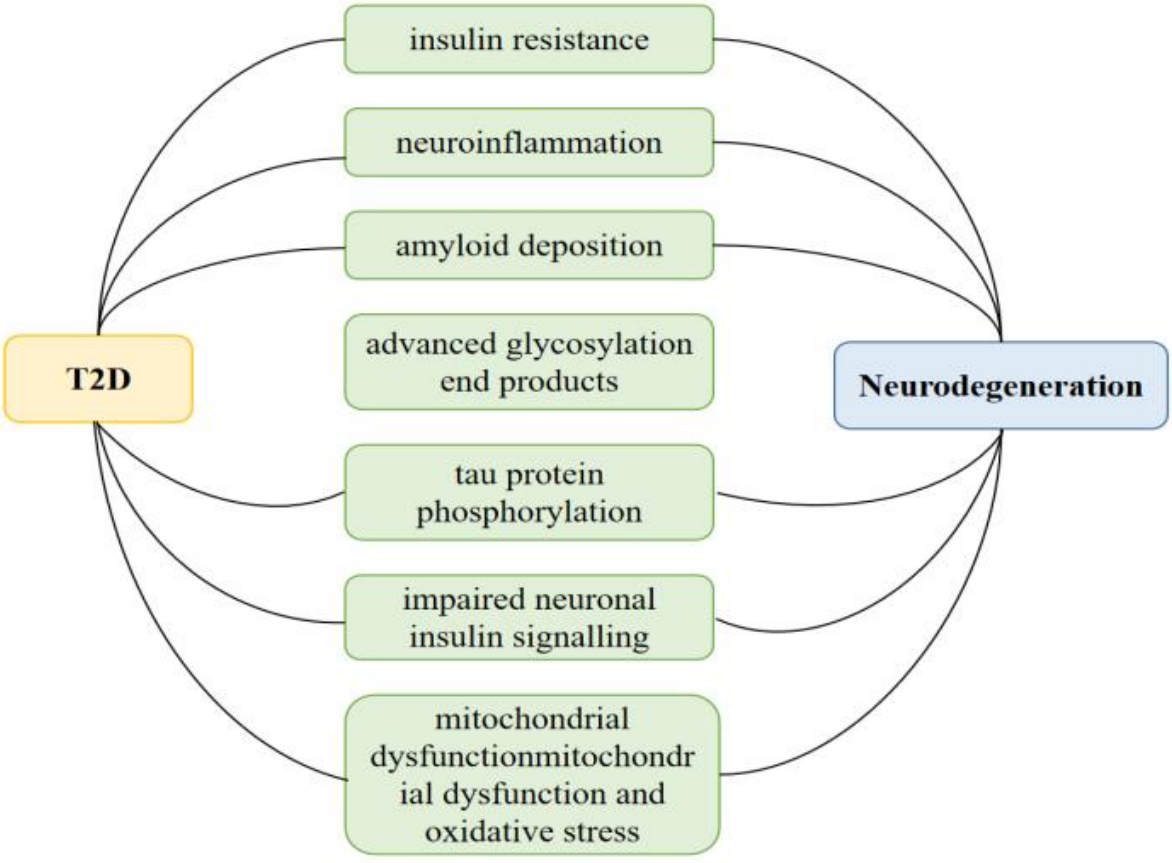

Figure 1. Potential mechanism between T2D and neurodegeneration.

2. Plasma NfL levels are correlated with the blood glucose level

It is now well established that diabetic neuropathy can develop in both pre-diabetic and overtly diabetic states [27], so it is critical to be able to identify and monitor fine fibre damage early and accurately when it is the only pathology.

NfL levels are significantly different among normal people, pre-diabetic people and diabetic people. In a study analysing baseline data from 890 Mexican Americans and 813 non-Hispanic whites, researchers measuring participants' plasma NfL via an ultrasensitive single molecule array (SIMOA) platform found that in an unadjusted model, NfL levels of participants with a diabetes diagnosis (22.25pg/mL, SD=14.08pg/mL) had significantly higher than participants without diabetes (18.01pg/mL, SD=10.69pg/mL), P<.001 [28].

More recently, Thota et al [29] similarly used the SIMOA platform to examine plasma NfL levels in a population and reported for the first time that plasma NfL levels were associated with clinical staging and glycemic control of diabetes mellitus. It appears to increase in the pre-diabetes and diabetes population, and gradually increases with the progress of diabetes. They examined and analysed plasma NfL levels in 30 normal (NG), 48 pre-diabetic and 29 T2D and found that NfL levels were elevated in T2D and pre-diabetic patients, and that NfL levels were significantly higher in the T2D group [12.4(5.21) pg/mL] than in the pre-diabetic group [10.2(4.13) pg/mL] and the NG group [8.37(5.65) pg/mL]. They also suggested that plasma NfL was significantly and positively correlated with fasting glucose, suggesting that glycemic control may be a major modifiable risk factor for neurodegeneration in people at risk for T2D and in newly diagnosed T2D patients.

3. Plasma NfL levels are correlated with neurodegeneration in T2D patients

3.1. Cognitive decline

There is strong and consistent epidemiological evidence that patients with T2D are at increased risk of cognitive impairment. And there is no clear treatment once progression to dementia has occurred [30]. Therefore, it is in bad need to find biomarkers that can simply detect cognitive decline in diabetic patients at an early stage and to intervene early to slow its progression.

In a recent study on plasma NfL levels and cognitive performance in patients with T2D, lower Rivermead Behavioural Memory Test (RBMT), Standardised Spectrum Score (SPS) or Mini

Mental State Examination (MMSE) scores showed that higher plasma NfL levels, i.e. plasma NfL levels were associated with mild cognitive decline [31]. In addition， Ciardullo et al [32] measured 2070 people aged 20-75 years from the general U.S. population (275 with diabetes and 1795 without diabetes), they found that patients with diabetes exhibited higher sNfL levels compared with non-diabetic participants in each age stratum. Moreover, higher sNfL levels were associated with worse performance in all three cognitive function tests (the Registry for Alzheimer's Disease-Word Learning test, the Animal Fluency test and the Digit Symbol Substitution test) in a subset of participants aged 60-75 years.

3.2. AD

AD and T2D are the two most common diseases in the elderly. A meta-analysis of 1746777 participants reported that T2D patients had a 53% higher risk of developing AD [33].

AD has been described as 'Type III diabetes'. Insulin resistance is a major overlapping feature between diabetes and AD, which is closely associated with AD-induced neurodegeneration in the brain [34,35]. An et al [36] found that the abnormality of brain glucose homeostasis is the internal cause of AD. In addition, the regulation of peripheral blood glucose may affect the glucose homeostasis of the central nervous system, and the longitudinal increase of fasting blood glucose level is related to the higher glucose concentration in brain tissue. Another Mendelian randomization analysis showed that higher fasting glucose and lower HOMA-β-cell function indicating pancreatic β-cell dysfunction, were causally associated with a substantial increase in risk of AD [37]. At the same time, the hypertension and diabetes of chronic diabetes may accelerate and promote the onset of neurodegeneration, leading to its accelerated progression to dementia [38]. Besides, many studies have shown that diabetes drugs (such as metformin, sulfonylureas, and pioglitazone etc.) not only play a role in blood glycemic control, but also can impact on neuroprotection, neurogenesis, neuroinflammation, synaptic plasticity, and proteins aggregationthrough different mechanisms and linking pathways, in order to reduce the risk of suffering from AD [39-44]. Moreover, early and effective control of hyperglycemia has a positive impact on reducing the risk of AD and delaying the progress of AD, and neurodegeneration plays an important role in this process.

It has been found that AD biomarkers are also related to diabetes. For example, diabetes is associated with higher Aβ40 (P<.001), Aβ42 (P<.001), total tau (P<.001), and NfL (P<.001) levels [45]. NfL, as a great potential biomarker, is widely concerned by researchers. A number of studies have shown that blood NfL levels are elevated in patients with AD and

predict future cognitive decline [46-51]. And plasma NfL is associated with PET findings in brain regions typically affected by AD [52]. At the same time, within-person analysis of serum NfL dynamics further revealed that the rate of change of serum NfL could discriminate mutation carriers from non-mutation carriers almost a decade earlier than cross-sectional absolute NfL levels. And serum NfL rate of change peaked in participants converting from the presymptomatic to the symptomatic stage and was associated with cortical thinning assessed by magnetic resonance imaging [53]. Thus, NfL is an effective biomarker for predicting disease progression and cranial neurodegeneration in the early presymptomatic stages of AD. Moreover, it can assistthe clinical diagnosis of AD, and show particular potential for translation into clinical practice. As the pathophysiological mechanisms of diabetes and AD are closely linked, the hypothesis that blood NfL levels can be used to monitor changes in cognitive function and thus predict the onset of AD in a population with diabetes warrants further investigation.

3.3. PD

At present, it has been confirmed that plasma NfL levels correlated with disease severity and progression in terms of both motor and cognitive functions in PD. And it is a useful prognostic biomarker for PD [54,55].

Recently, there has been new findings about diabetes in PD patients. For example, Uyar et al [56] used the SIMOA method to determine serum NfL concentrations in 195 PD patients with normal glycosylated haemoglobin (HbA1c). They found that serum NfL levels were higher in PD patients with combined diabetes, and higher HbA1c levels were associated with increased NfL in a model unadjusted for age and BMI. After adjusting for age, BMI, hypertension, hypercholesterolaemia and history of stroke, diabetes remained significantly associated with higher serum NfL levels in patients with PD. Vijiaratnam et al [57] subsequently confirmed the finding of significantly higher serum NfL levels in patients with PD-DM in 280 patients with PD (29 with prevalent T2D). And regression analysis indicated that NfL levels in diabetic patients were significantly correlated with their disease status (correlation coefficient: 0.82, 95% confidence interval: 0.45-1, $p<0.0001$). Obviously, it is not difficult to find that diabetes has a certain impact on NfL levels in patients with PD.

Table 1 showed that the level of blood NfL is closely related to the blood glucose level, and it could reflect the neurodegeneration in diabetes patients.

Table 1. NfL levels are correlated with the blood glucose level and neurodegeneration.

Authors	Reference	sample	Population	NfL levels
O'Bryant et al.	[28]	n=1705	Without diabetes \ Diabetes	Diabetes ＞ Without diabetes
Thota et al.	[29]	n=107	Normal glycaemia \ Pre-diabetes \ T2D	①T2D ＞ Pre-diabetes ＞ Normal glycaemia; ②Positive correlation with fasting glucose
Marutani et al.	[31]	n=183	T2D	Mild cognitive decline ↑
Ciardullo et al.	[32]	n=2070	Diabetes \ Non-diabetic participants	①Diabetes ＞ Non-diabetic participants; ②Cognitive decline ↑
Uyar et al.	[56]	n=195	PD	①PD patients with diabetes ↑; ②Associated with higher HbA1c levels
Vijiaratnam et al.	[57]	n=280	PD	①PD patients with diabetes ↑; ②Significantly correlated with the disease status

4. NfL levels are correlated with diabetes complications

4.1. DSPN

DSPN is a common and well-represented complication of diabetes associated with increased mortality, neuropathic pain, foot ulcers and lower limb amputations [58] and there is evidence that DSPN, particularly the painful small fibre neuropathy subtype, may be present in 10-30% of subjects with impaired glucose tolerance, also known as pre-diabetes [59]. Therefore, accurate identification and intervention in the early stages of neuropathy is extremely important for the treatment and care of diabetic neuropathy.

In an analysis of baseline, 12-month and 24-month data from 92 participants with T2D and 30 control participants, it was found that NfL levels in peripheral blood were significantly higher in patients with diabetic neuropathy ($P<0.05$) and that increased NfL was associated with a nociceptive hypersensitivity phenotype after follow-up ($P<0.05$) [60]. Additionally, Kender et al [61] conducted detailed clinical assessments on sixty-four patients with T2D and 27 healthy controls, and calculated the nerve's fractional anisotropy (FA, a surrogate marker for microstructure of peripheral nerves, is a sensitive parameter for structural and functional nerve damage in patients with DPN), they found that increased levels of NfL were associated with loss of sciatic nerve FA ($r=-0.4$; $p<0.001$). This is the first study showing that non-invasive assessments of microstructural nerve integrity and microvascular markers are associated with nerve fiber damage in diabetic neuropathy. Furthermore, in a prospective

clinical study of 45 pre-diabetic patients and 30 normal subjects, mRNA levels of neuron-specific enolase (NSE) and NfL in blood were measured by real-time polymerase chain reaction and NfL mRNA levels were found to be significantly higher in pre-diabetic patients with peripheral neuropathy than in those without peripheral neuropathy ($p=0.038$). Also according to correlation analysis, NfL mRNA levels were positively correlated with scores on the Douleur Neuropathique 4 questionnaire in pre-diabetic patients ($r=0.302$, $p=0.044$). This is the first study to suggest blood NfL mRNA as a surrogate marker for early predictio n of pre-diabetic peripheral neuropathy [62]. More recently, Maalmi et al [63] measured serum NfL levels in 423 adults with onset diabetes within one year, 66 of whom had DSPN, and higher serum levels of NfL were associated with the development of DSPN after adjusting for age, sex, waist circumference, height, HbA1c, and duration of diabetes (RR(95%CI)1.92(1.50,2.45) ($p<0.0001$)).

Therefore, NfL levels may be useful in detecting the identification of the occurrence of DSPN in diabetic patients and are promising biomarkers in the management of DSPN.

4.2. DN

DN is a clinical syndrome characterized by persistent proteinuria and progressive decline in renal function, it is the main cause of end-stage renal disease [64]. DN complicates the course of many diabetic patients [65] and requires timely diagnosis and intervention at an early stage of renal function decline. In clinical practice, most commonly used markers of renal disease and progression are serum creatinine, estimated glomerular filtration rate and proteinuria or albuminuria. Unfortunately, they are all insensitive [66].

At present, it has been found that in normal elderly individuals, age ($\beta=0.394$, $p<0.001$), renal function ($\beta=0.376$, $p<0.001$), blood volume ($\beta=-0.198$, $p=0.008$) and high density lipoprotein (HDL) ($\beta=0.149$, $p=0.013$) were associated with sNfL levels [67]. At the same time, the study pointed out that a preferable relation was observed between NfL concentration and glomerular filtration rate (eGFR) (Spearman's rho:−0.492; $p<0.0001$). When patients were separated into normal eGFR (≥60mL/min/1.73m2) or decreased kidney function (eGFR<60mL/min/1.73m2), the median NfL concentration was 1.5-fold higher in subjects with altered kidney function (18.5ng/mL and 28.4ng/mL, respectively; $p<0.0001$) [68]. Notably, in a study further exploring the relationship between blood NfL levels and renal function in diabetic patients, researchers measured and analysed blood NfL in 43 healthy subjects aged 60 years or older and 188 diabetic patients and found a significant positive correlation between blood NfL

levels and blood creatinine levels in each group (r=0.50, 0.56), suggesting that in older adults who are healthy or have T2D, there was a moderate correlation between blood NfL levels and renal function independent of age, sex and BMI; in other words, blood NfL levels may partially respond to the effects of renal function, especially in the elderly [69].

Therefore, changes in blood NfL levels undoubtedly provide a novel perspective for the detection of diabetic renal function. In the following clinical practice, we can try to monitor the changes of renal function in diabetes population by measuring the level of blood NfL, in order to reduce the incidence of DN.

4.3. Cardiovascular and cerebrovascular diseases

4.3.1. LVH

Left ventricular hypertrophy (LVH) is highly prevalent in patients with T2D [70,71], and independently associated with cognitive impairment, dementia and cardiovascular (CV) events [72-74]. Recently, Patel et al [75] investigate the relationship between LVH, NfL levels and brain atrophy in people with T2D. They completed a detailed assessment of 137 T2D participants and found that plasma NfL was correlated positively with age, HbA1c, and LV mass and negatively with cortical thickness. And they found that median plasma NfL levels were significantly higher in LVH participants (21(14, 28) vs.15(11, 22) pg/mL) and LVH was an independent predictor of NfL levels (coefficient 0.19, p=0.04) by comparing participants with and without LVH in the T2D population. This indicates that in addition to HbA1c, LVH also affects NfL levels in T2D patients.

4.3.2. AF

Previous studies have shown that serum NfL was elevated in patients with AF compared with matched controls without AF. Ongoing AF rhythm was associated with even higher levels of serum NfL than in patients with a diagnosis of AF but currently not in AF rhythm [76]. Recently, in a cross-sectional analysis of the Swiss Atrial Fibrillation (Swiss-AF) cohort study, a history of diabetes was found to result in a 26.8% increase in serum NfL levels, similar to a 10-year increase in age [77]. This suggests that we should pay attention to the influence of diabetes on NfL level in the following study of patients with atrial fibrillation.

4.3.3. Stroke

It has been shown that serum NfL levels are significantly elevated in patients with acute cerebral small vessel disease stroke and remain elevated for at least 3 months after stroke

[78,79]. And interestingly, a recent study found that in patients with diabetes, serum NfL levels strongly predicted stroke events. Researchers investigated the use of single molecule array technology (Quanterix) to measure NfL levels in baseline samples, and after adjusting for age, race, blood pressure, weight and Framingham stroke risk score, stroke subjects had higher baseline NfL levels than controls, while incorporating NfL levels into prediction scores, by taking the score's c-statistic from 0.71 [95% CI: 0.66, 0.77] to 0.78, significantly improving the ability of the Framingham risk score to discriminate between strokes [80]. Thus, blood NfL levels undoubtedly play an important role in predicting the occurrence of stroke events in diabetic patients.

In a word, these clinical studies indicate that the level of NfL not only increased to varying degrees in diabetes complications, such as DSPN, DN, LVH, AF and stroke, but also had a certain correlation with the clinical classification and predicted incidence of complications (Table 2).

Table 2. NfL levels correlated with diabetes complications.

	Authors	**Reference**	**sample**	**Population**	**NfL levels**
DSPN	Morgenstern et al.	[60]	n=122	T2D	①T2D with DPN↑; ②Associated with the development of a hyperalgesic phenotype
	Kender et al.	[61]	n=91	T2D	Associated with loss of sciatic nerve FA
	Celikbilek et al.	[62]	n=75	Pre-diabetes	（NfL mRNA levels） Pre-diabetic patients with DPN ＞ Without DPN
	Maalmi et al.	[63]	n=423	T2D	Associated with the development of DSPN
DN	Akamine et al.	[69]	n=231	T2D	Significant positive correlation with blood creatinine level
Cardiovascular and cerebrovascular diseases	Patel et al.	[75]	n=137	T2D	①T2D with LVH ＞ Without LVH; ②Positive correlation with HbA1c
	Polymeris et al.	[77]	n=1379	AF	Related to the history of diabetes
	Korley et al.	[80]	n=363	Stroke	①Stroke subjects ＞ Controls; ②Significantly improving the ability of the

5. NfL levels are correlated with diabetes patients with COVID-19

In the context of the global human health of the new coronary epidemic, the presence of diabetes and diabetes complications, such as cardiovascular disease and nephropathy, is widely considered as a risk factor for the serious outcomes of COVID-19, among those with poor glycemic control [81]. In other words, T2D may contribute to amplifying the severity of COVID-19, while the liability to COVID-19 may increase the risk for T2D [82]. Meanwhile, the risk of long-term neurological consequences is beginning to be of concern. Recent studies have shown that in patients with COVID-19, the level of blood NfL increases and is related to the severity of the disease [83-85]. A study comparing NfL levels in 89 COVID-19 positive (COVID-pos), 11 COVID negative (COVID-neg) and healthy controls (n=8), found that NfL levels of COVID-pos patients with diabetes were 102% higher than those without diabetes [86]. Therefore, the role of diabetes in the blood NfL level of COVID-19 patients cannot be ignored, and it needs to be focused in the next research.

6. Conclusions and future directions

Therefore, it is reasonable to assume that blood NfL levels could be used as a potential biomarker to identify and monitor the emergence and progression of early neurodegeneration in diabetes. In addition, NfL levels were worth further studying in clinical practice to prevent and manage complications of diabetes. However, studies on blood NfL in relation to diabetes are still in their early stages, because of small sample sizes and no extensive clinical studies to validate the sensitivity and specificity of blood NfL. At the same time, the NfL level which is a single biomarker, cannot accurately identify diabetes-related neuropathy. Therefore, multiple biomarkers need to be combined for multiple analyses in order to achieve accurate screening, diagnosis and monitoring of diabetes and complications.

In future research and exploration, there is a need for a wide range of researchers not only to collect further large numbers of samples and expand the scope of studies to validate the current findings, but also to actively explore the correlation between blood NfL levels and

existing established clinical diagnostic criteria, thus further promoting NfL in the clinic as an aid to early diagnosis and condition monitoring of T2D-related neurodegeneration.

Author Contributions: Originally drafted, revised and edited the manuscript, Liya Tian; Conceptualized, supervised, drafted and revised the manuscript, Yao Liu; Supervised, reviewed and edited the manuscript, Weihua Liu; Reviewed and edited the manuscript, Wenjing Jiang and Nan Fu. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Shandong Province Chinese Medicine Science and Technology Development Program Project 2017-252.

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