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ORIGINAL ARTICLE

Hyperglycemia-Driven Alterations in Amyloid β Metabolism and Neprilysin Expression: A Biochemical Link to Neurocomplexity of Diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a metabolic disorder associated with neurological abnormalities, particularly in patients with prolonged disease duration. Given the similarities between diabetes and Alzheimer's disease, amyloidogenic mechanisms may contribute to the pathogenesis of hyperglycemia; however, the precise roles of amyloid-related proteins and amyloid-β (Aβ) metabolism in diabetes-induced neural injury remain unclear. This study aimed to evaluate the involvement of Aβ-42, soluble amyloid precursor protein-α (sAPPα), β-secretase (BACE1), and neprilysin (NEP) in the pathogenesis of diabetes. For this purpose, the fasting blood samples from were prepared from patients with T2DM and age- and sex-matched healthy controls were analyzed for the levels of Aβ-42, sAPPα, BACE1, and NEP using enzyme-linked immunosorbent assay. Patients with T2DM showed remarkably higher FBS, HbA1c, insulin, and HOMA-IR values compared with controls. Serum level of Aβ-42 and BACE1 were significantly raised in T2DM group, whereas sAPPα levels were markedly downregulated. Blood concentration of NEP was increased in the T2DM and exhibited a positive correlation with HOMA-IR. According to the results, hyperglycemia promotes amyloidogenic APP processing and Aβ-42 accumulation, whereas the elevated NEP level may represent a compensatory response to increased Aβ production. These findings highlight a potential molecular link between T2DM and amyloid-associated neurodegeneration.

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1- INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder characterized by hyperglycemia resulting from a combination of insulin resistance in peripheral tissues (muscle, fat, liver) and a relative deficiency of insulin secretion from pancreatic β-cells [1]. The incidence of this disease is increasing in all of the word due to inactive lifestyle and high fact diet [1]. Over time, chronic hyperglycemia and lipid toxicity cause β-cell impairment and the pancreas cannot sustain increased insulin output, leading to relative insulin deficiency and finally amyloid deposition in pancreatic islets and oxidative stress further damage β-cells and reduce insulin secretion in diabetic patients [2]. In addition to insulin impairment, hyperglycemia raises plasma osmolarity and causes cellular dehydration also [1]. While excess glucose induces non-enzymatic glycation of macromolecules, especially proteins which change their structure, function and also half-life [3]. By considering all the factors mentioned, almost all tissues of the body are involved in symptoms of diabetes especially in long-standing conditions [1, 2]. In T2DM, chronic hyperglycemia induces some structural and functional damages to both the

central and peripheral nervous systems due to high sensitivity and low regeneration rate of neural cells, this condition is broadly called Diabetic Neuropathy (DN) [4].

DN is a common and serious complication of diabetes mellitus, resulting from chronic hyperglycemia and metabolic disturbances that damage peripheral nerves [4]. The underlying mechanism is multifactorial, involving metabolic, vascular, and oxidative stress pathways. Certainly, one of the important mechanisms is upregulation of polyol pathway that causes increased sorbitol leads to osmotic stress and neural cell injuries [5]. Other damages are due to non-enzymatic glycation of proteins and lipids that causes advanced glycation end-products (AGE) deposition in nervous tissues [6]. AGEs bind to their receptor (RAGE) on neurons, Schwann cells, and endothelial cells and trigger inflammatory cascades, oxidative stress, and microvascular damages, leading to axonal degeneration [6]. Although β-amyloid is best known for its role in Alzheimer's disease (AD), recent evidence shows that similar amyloidogenic processes occur in peripheral nerves and contribute to neurological complexities in diabetes [7]. Chronic hyperglycemia in T2DM increases oxidative stress and inflammation, which could alter the processing of amyloid precursor protein (APP). Normally, APP is cleaved by α-secretase in a non-amyloidogenic pathway but in neuropathy disorders, oxidative and metabolic stress increases β-amyloid (Aβ) peptides formation possibly trough activation of β- and γ-secretases enzymes or other pathways that need to further investigation [8]. Recent studies confirmed that diabetes is a remarkable risk factor for incidence and developing of AD and there is a close relationship between hyperglycemia and dementia, both of them cause neurodegeneration [9]. Because insulin receptors are highly expressed in brain regions applicable for cognition and memory, such as the cortex and hippocampus, and insulin has been shown to influence memory; Aβ oligomers make insulin resistance in hippocampal neurons and cause a type of brain diabetes as a result of Aβ fibrillation; and upregulation of Aβ and hyperglycemia induce neurovascular damages and impair Aβ clearance pathways [10]. Therefore, Aβ metabolism (production and degrading) plays crucial role in diabetes complexity and could be considered as a potential candidate in DN pathology. Because of Aβ peptides can accumulate in peripheral nerves, dorsal root ganglia, and Schwann cells and lead them to a premature apoptosis [7] which has been observed in DN. Therefore, this study aimed to investigate the possible role of Aβ metabolism in DN. For this purpose, the concentration of sAPPα and Aβ-42 was measured in T2DM patients and compared with healthy individuals as control in the first step. Neprilysin (NEP) enzyme has been reported to be the dominant peptidase regulating the steady-state level of the primarily pathogenic Aβ species, Aβ-42 [11]. β-secretase (BACE 1) is also believed to be the rate limiting enzyme for Aβ production [12]. By considering the crucial role of these enzymes in the regulation of Aβ's circular content, BACE 1 and NEP enzymes were evaluated in blood serum of T2DM patients and compared with control group to elucidate the possible dysregulation of Aβ metabolism in diabetes. Understanding the role of Aβ in the pathogenesis of T2DM and related neurological complexities may provide new therapeutic targets for preventing or slowing neuronal damage in diabetic patients.

2- MATERIALS AND METHODS

2.1. Experimental design and sample preparation

This study aimed to evaluate the Aβ-42 peptide and sAPPα, NEP and BACE 1 proteins in blood serum of the T2DM patients in comparison with the healthy control were not prescribe to suffer from T2DM. All of diabetic patients were referred to the Imam Reza hospital (Tabriz, Iran) for treatment between 1 July and 30 December (2023). We used 50 patients with T2DM and 50 healthy participants as control. All participants were screened through clinical history and laboratory tests to confirm eligibility and to exclude any underlying metabolic or neurological disorders that could interfere with the study outcomes. The study was approved by the Ethics Committee of the Health Center, and all participants provided informed consent in accordance with the Declaration of Helsinki. The HbA1c more than 6.5 % was used as the diagnosis criteria for T2DM and samples with HbA1c more that 7 % was considered as poorly controlled T2DM. The cut-off value for fasting blood sugar (FBS) among diabetic patients was set at 200 mg/L. Patients with liver deficiency, kidney disorder, thyroid disorder, acute coronary syndromes, AD, different cancers, patients taking vitamin supplements and patients with family history of dementia were excluded from the study. The control group consisted of age- and sex-matched healthy individuals who had not been diagnosed with diabetes or prediabetes and did not suffer from cardiovascular disease, thyroid disorders, AD, or other neurological conditions. The two experimental groups were comparable in terms of gender and age, with no significant differences observed. In this study, 5 mL of blood was collected from each patient and centrifuged at 10,000 rpm for 5 minutes to obtain serum, which was then stored at −20 °C until analysis. Sociodemographic, clinical, and laboratory data were retrieved from patients' medical records and systematically recorded on a data collection sheet. Anthropometric measurements, including body weight and height, were obtained using standard procedures and body mass index (BMI) is not significantly deferent between two groups. Table 1 presents the demographic and clinical characteristics of the patients and control participants. Compared with the control group, the T2DM group exhibited significantly

higher levels of body weight ($p = 0.047$), fasting blood sugar (FBS; $p = 0.012$), HbA1c ($p = 0.0001$), and insulin ($p = 0.0001$). Although HDL levels were lower in the T2DM group than in controls, this difference was not statistically significant ($p = 0.198$).

Table (1): Demographic and clinical characteristics of the patients and control participants

Parameter	Control	T2DM Patients	P-value
Age (Years)	59.13±8.34	63.52±10.08	0.097
Weight (kg)	79.35±9.35	83.63±15.29	0.047*
BMI (kg/cm^2)	28.98±4.37	30.01±5.43	0.357
FBS (mg/l)	95.87±7.14	245.96±45. 9	0.012*
HbA1C (%)	3.98±0.60	7.89±3.10	0.0001*
Insulin (µU/ml)	7.24±1.32	25.68±8.24	0.0001*
Cholesterol (mg/dl)	173.47±12.36	201.89±85.39	0.216
Triglyceride (mg/dl)	151.98±15.24	173.61±71.45	0.897
HDL (mg/dl)	38.68±6.17	37.34±7.25	0.198

2.2. Insulin measurement and HOMA-IR calculation

Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [13]. Fasting blood samples were collected after an overnight fast of at least 8 hours, and serum fasting glucose and insulin concentrations were measured. Serum insulin concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit from Elabscience (E-EL-H2665), following the manufacturer's instructions. All samples were analyzed in duplicate to ensure accuracy. HOMA-IR was calculated according to the following formula for each participant:

HOMA-IR = [Fasting insulin (µU/mL) × Fasting glucose (mg/dL)] / 405.

2.3. Evaluating of Aβ peptide and proteins in blood serum

The levels of the following peptide and proteins were determined by ELISA Kit. Human ELISA kits were used for estimating of Aβ-42 in serum samples (Abcam, ab289832), sAPPα (MyBioSource, MBS7269331), NEP (Elabscience, E-EL-H0801) and BACE1 (MyBioSource, MBS2882274) according to the manufacture guideline in each case. All of the reagents and solution were placed on bench 30 min before test.

2.4. Statistical analysis

Statistical analyses were performed using analysis of variance (ANOVA) to assess differences among the T2DM and control groups. For comparisons involving two experimental groups, the Student's *t*-test was applied. All statistical procedures were carried out using GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD). A *p*-value of less than 0.05 was considered statistically significant.

3- RESULTS AND DISCUSSION

High blood glucose level over time can injure nerves throughout the body and cause neurological complications, but it most often affects the nerves in the legs and feet that known as DN [4]. DN is a type of nerve damages that occurs in people with diabetes. The exact mechanism by which hyperglycemia damages neural cells and leads them to the apoptosis is not fully understood yet. Amyloid fibrillation has been shown to play an important role in peripheral neuropathy among patients with various diseases, including rare familial or acquired amyloid polyneuropathies and chronic inflammatory disorders [7]. Increasing evidence suggests that Aβ, a peptide with strong potential to promote amyloid fibril formation and deposition, may contribute to neuronal damage through mechanisms involving oxidative stress, inflammation, and protein aggregation [7, 8]. Therefore, Aβ could be considered a potential contributing factor to the development of neurological abnormalities in T2DM patients. Accordingly, this study aimed to investigate the potential involvement of Aβ, sAPPα, and their metabolizing enzymes (NEP and BACE 1) in the pathogenesis of T2DM.

3.1 Insulin Resistance is remarkably higher in patients with T2DM

HOMA-IR was calculated using FBS and fasting insulin concentrations in both the T2DM and control groups. This index was used to compare insulin resistance between diabetic patients and healthy controls [13]. According to the results, the mean HOMA-IR value was 1.4 ± 0.5 in control participants and 4.3 ± 1.1 in diabetic patients. Statistical analysis revealed a significant increase in HOMA-IR value in the T2DM group compared with the control group ($P < 0.0001$, ****), indicating a markedly greater degree of insulin resistance among diabetic individuals (Figure 1).

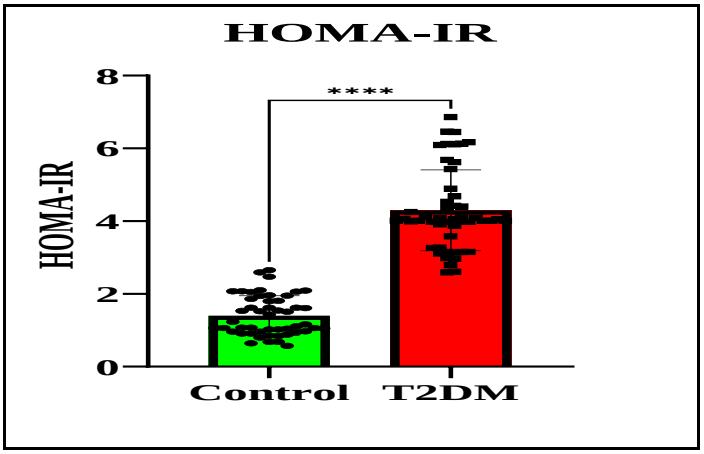

Figure (1): Increased HOMA-IR value of diabetic patients showed insulin resistance in hyperglycemia condition. Data was expressed as mean ±SD and significant differences were showed by star symbol (P<0.0001, **)**

3.2 T2DM induces significant changes in circular concentration of Aβ and sAPPα

Figure 2A shows the concentration of Aβ-42 peptide in the blood serum of individuals from the T2DM and healthy control groups. The mean concentration of Aβ-42 was 9.72 ± 2.98 pg/mL in healthy controls and 13.50 ± 2.73 pg/mL in patients with T2DM. Statistical analysis confirmed that hyperglycemia was associated with a significant increase in Aβ-42 levels in the T2DM group compared with controls ($p < 0.0001$, ****).

The precursor of Aβ-42, soluble type of amyloid precursor protein (sAPPα), was also assessed in this study and is presented in Figure 2B. According to the results, the mean serum concentration of sAPPα in diabetic patients was 4.06 ± 0.78 ng/mL, which was significantly lower than that observed in non-diabetic controls (5.11 ± 0.84 ng/mL). Statistical analysis confirmed that hyperglycemia was associated with a significant reduction in circulating sAPPα levels among diabetic participants ($p < 0.0001$, ****).

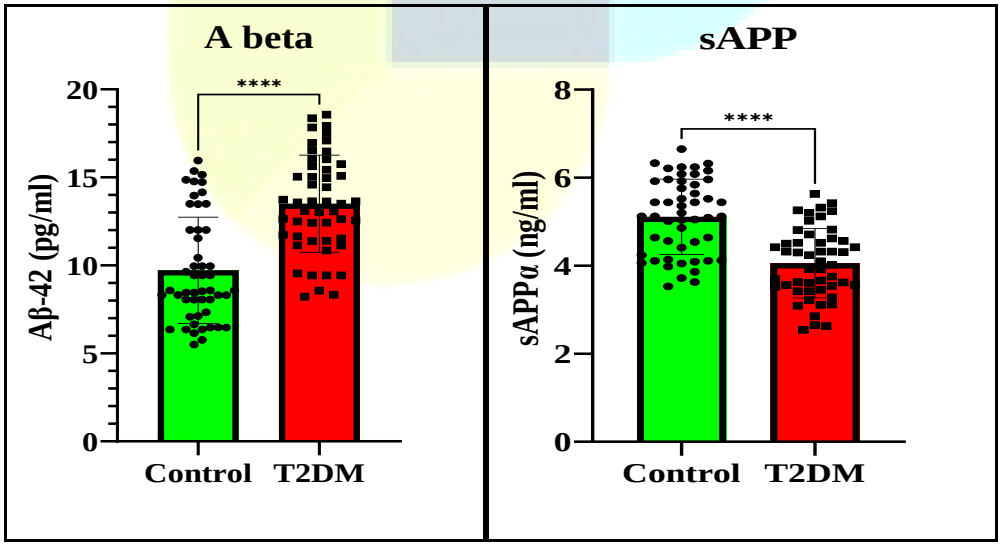

Figure (2): Circulating concentration of Aβ and sAPP in experimental groups. (A) Aβ increased as results of hyperglycemia in T2DM (B) sAPPα peptide decreased in diabetic patients. Data was expressed as mean ±SD and significant differences were showed by star symbol (P<0.0001, **)**

3.3. Hyperglycemia induces remarkable alterations in the concentration of BACE 1 and NEP

The steady-state concentration of Aβ-42 can be influenced by β-secretase (BACE1), which converts APP into Aβ, and by NEP, an important enzyme responsible for Aβ degradation [11, 12]. Therefore, both enzymes can affect Aβ-42 levels and contribute to its associated pathological processes. According to Figure 3A, the concentration of BACE1 in the blood serum of healthy controls was 8.94 ± 3.16 pg/mL, whereas in

diabetic patients it was significantly higher at 15.96 ± 5.12 pg/mL. Statistical analysis confirmed that hyperglycemia condition in T2DM was associated with a significant increase in BACE1 levels ($p < 0.0001$, ****).

Figure 3B shows the concentration of NEP in the blood serum of the two experimental groups. The mean circulating concentration of NEP was 181.39 ± 23.36 ng/mL in healthy controls, whereas it was significantly higher (232.36 ± 24.44 ng/mL) in diabetic patients. Statistical analysis confirmed a significant increase in NEP level in the T2DM group compared with the control group ($p < 0.0001$, ****).

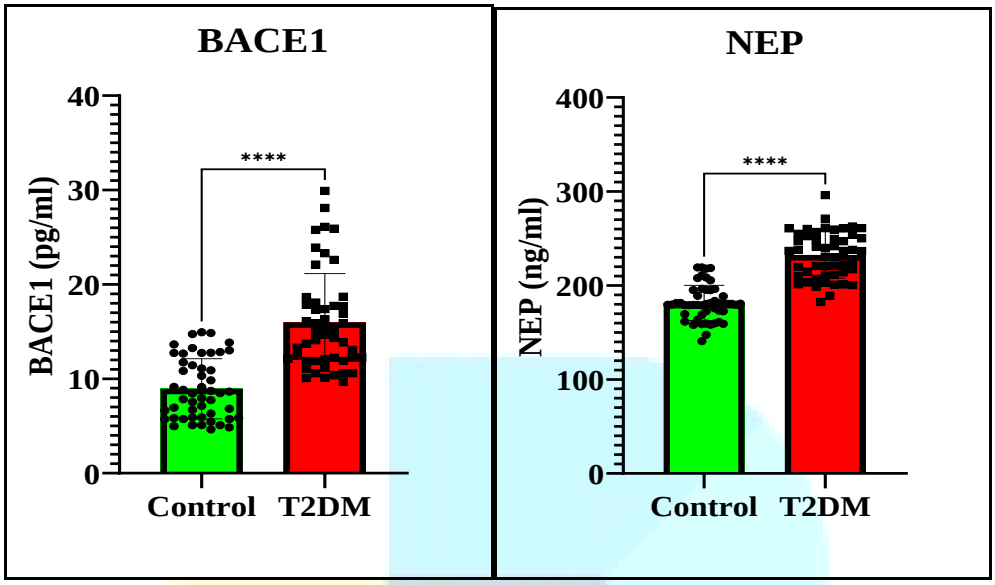

Figure (3): Concentration of BACE 1 and NEP in blood samples of participants. (A) BACE 1 increased significantly in hyperglycemia condition. (B) NEP enzyme level increased in diabetic patients. Data was expressed as mean ±SD and significant differences were showed by star symbol (P<0.0001, **)**

3.4. Correlation between HOMA-IR and NEP content

A detailed analysis of the results confirmed that the increase in serum NEP concentration was accompanied with increased insulin resistance. As shown in Figure 4, a positive correlation was observed between HOMA-IR and serum concentrations of NEP, with a calculated R^2 value of 0.71. This linear association implies that as insulin resistance (HOMA-IR) increases, circulating NEP levels tend to rise correspondingly in both healthy and diabetic participants. In contrast, our analysis did not reveal any significant correlation between HOMA-IR and circulating levels of BACE1, Aβ-42, or sAPPα (data not shown).

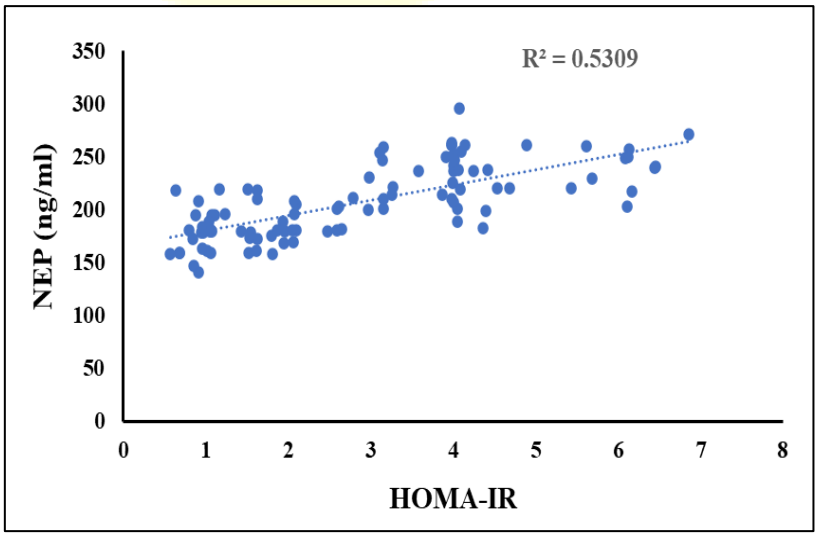

Figure (4): Positive correlation between blood concentration of NEP enzyme and HOMA-IR in diabetic patients and healthy controls.

T2DM is a complex metabolic disorder that is recognized by hyperglycemia in body fluids and can trigger neurological complexities, especially in sustained conditions [1, 6]. In diabetic patients, a cascade of neurodegenerative events, including oxidative stress, mitochondrial dysfunction, and inflammation in peripheral and central nervous systems are promoted by chronic hyperglycemia, insulin resistance, and vascular dysfunction contribute [6]. These pathological conditions can interrupt neuronal integrity, impair axonal transport, and induce apoptosis in neural cells, totally lead to DN and cognitive decline [5]. A growing body of evidences suggests a robust bidirectional relationship between T2DM and AD [10]. Previous studies reported that patients with diabetes are at a remarkably higher risk of AD and other forms of dementia incidence [10]. The mentioned association possibly is due to overlapping molecular mechanisms, including insulin resistance, long lasting hyperglycemia, oxidative and mitochondrial stress, and inflammation in nervous system. Insulin plays crucial role in neurogenesis, neuronal development, synaptic remodeling, and cognitive processes such as learning and memory in central nervous system [9]. Defective insulin signaling could impair neuronal function and energy metabolism in T2DM, as well as facilitating amyloidogenic processing and tau hyperphosphorylation—hallmarks of AD pathogenesis [10]. Therefore, dysregulation of Aβ metabolism is one of the key molecular links between diabetes and AD which increases the Aβ-42/Aβ-40 ratio in both diseases.

According to our knowledge, Aβ-40 and Aβ-42 are the main proteolytic fragments derived from the successive hydrolysis of APP by BACE1 and γ-secretase [14]. Among these, Aβ-42 is more aggregation-prone due to its high hydrophobicity, making it the primary species involved in amyloid fibril formation and neurotoxicity [14]. Under physiological conditions, Aβ peptides are efficiently cleared by several hydrolyzing and transport systems. NEP, insulin-degrading enzyme (IDE), and endothelin-converting enzyme (ECE) have a central role in Aβ degradation in the extracellular and intracellular spaces [15]. However, the balance between Aβ production and degradation is interrupted in pathological conditions like AD, oxidative stress, and aging [16]. According to our previous results, enhanced BACE1 activity and reduced efficiency of NEP and IDE lead to increased accumulation of Aβ, which could promote amyloid fibrillation, inflammation, and neuronal damage in AD [15].

According to our results, in T2DM patients, the circulating level of Aβ-42 is raised, while sAPPα concentrations are downregulated, displaying a pattern similar to that of AD patients. The increased concentration of Aβ-42 in blood serum could be interpreted as its enhanced accumulation in neural cells; its strong tendency to aggregate could promote amyloid deposition and following neuronal damage. Previously reported, that peripheral nerve cell degeneration is one of the major pathological features of DN that could be observed in about 15% of diabetic patients [4, 5]. Such degeneration is related to chronic hyperglycemia, oxidative stress, and impaired neurotrophic support at first; however, our results suggest that amyloid fibrillation may also contribute to this process by worsening neuronal dysfunction and inducing apoptotic events. Because, according to our data, the BACE1 enzyme was also upregulated under hyperglycemic conditions, which is in agreement with the observed upregulation in circulating Aβ-42 levels. The simultaneous upregulation of BACE1 and downregulation of sAPPα observed in diabetic patients suggests a metabolic shift from the non-amyloidogenic to the amyloidogenic pathway of APP processing. Under physiological conditions, APP is primarily cleaved by α-secretase to produce soluble sAPPα, a fragment known for its neuroprotective and trophic properties [12]. In contrast, hyperglycemia stimulates BACE1 activity, promoting cleavage of APP through the amyloidogenic route and leading to increased Aβ production. Consequently, reduced sAPPα levels may reflect a suppression of neuroprotective signaling alongside enhanced amyloid formation [17]. This dual effect—loss of sAPP's protective role and accumulation of Aβ-42—may contribute to neural dysfunction and the heightened vulnerability to neuropathy observed in diabetic patients.

According to our results, the hyperglycemic condition causes an upregulation of circular NEP concentration in comparison with healthy control participants, despite its well-known anti-amyloidogenic features. The elevated circulating levels of NEP in diabetic patients appear to represent a compensatory response aimed at degrading the increased Aβ and preventing its fibrillation. This is consistent with the role of NEP as one of the principal enzymes responsible for Aβ catabolism and clearance [15]. A deep analysis of our data confirmed that the upregulation in serum NEP concentration was accompanied by increased insulin resistance. As shown in Figure 4, a strong positive correlation was observed between HOMA-IR values and circulating NEP levels ($R^2 = 0.71$), indicating that higher degrees of insulin resistance were generally associated with increased NEP concentrations in both healthy individuals and diabetic patients. The observed positive association suggests that metabolic dysregulation in T2DM may directly influence NEP expression [18] or may represent a compensatory response to increased Aβ production under hyperglycemic conditions. However, chronic hyperglycemia and oxidative stress can impair NEP function despite its elevated levels, leading to reduced Aβ clearance and promoting amyloid accumulation. This mechanism may cause initiation or developing of DN in T2DM patients by influencing amyloid-related neurotoxicity and inflammation in peripheral nerve cells [19].

Understanding this relationship could provide valuable insight into how metabolic dysregulation in diabetes contributes to impaired Aβ clearance and the development of neuropathic complications. The absence of a

significant correlation between HOMA-IR and the serum levels of BACE1, Aβ-42, and sAPPα suggests that the regulation of these amyloid-related proteins may not be directly driven by insulin resistance alone [20]. It is possible that chronic hyperglycemia-related factors such as oxidative stress, inflammation, and metabolic dysregulation affect their dysregulation in T2DM. Therefore, while insulin resistance appears to change NEP levels, the upstream amyloidogenic processes involving BACE1 and APP may be controlled by tissue-specific mechanisms independent of peripheral metabolic status, which need further investigation.

4- CONCLUSION

The present study provides novel insight into the potential involvement of amyloidogenic mechanisms in the pathogenesis of T2DM. Our results revealed that hyperglycemia in patients with T2DM was accompanied by a significant increase in circulating Aβ-42 and BACE1 levels, alongside a remarkable decrease in sAPPα concentration. These modifications suggest a metabolic shift toward the amyloidogenic hydrolysis of APP under hyperglycemia conditions, similar to mechanisms observed in AD. In contrast, NEP was significantly upregulated in diabetic patients as a key Aβ-hydrolysing enzyme, while we found a strong positive correlation with insulin resistance, indicating a possible compensatory response to increased Aβ content. According to the evidence, NEP is an anti-amyloidogenic enzyme, but chronic hyperglycemia conditions, non-enzymatic glycations, and oxidative stress could change its catalytic ability and limit its protective functions. Understanding these molecular links between diabetes and amyloid pathology could open new insights for therapeutic strategies aimed at preventing or improving DN through modulation of APP processing and Aβ degradation pathways.

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