Association between Inflammatory Markers and Alzheimer's Disease among Elderly Patients with Type 2 Diabetes

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ABSTRACT

Background: Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are prevalent conditions impacting the geriatric demographic. The interplay of inflammation and dysregulated glucose metabolism in T2DM serves as an additional risk factor for the development of AD.

Objective: To explore the correlation between inflammatory biomarkers and AD in geriatric patients diagnosed with T2DM.

Material and methods: The investigation was conducted on a cohort of 80 participants, stratified into three groups: 30 individuals diagnosed with T2DM, 20 suffering from both T2DM and AD, and 30 healthy controls. Each subject underwent evaluation process that included a detailed review of their medical history, a comprehensive clinical examination, and a cognitive function assessment. Laboratory analyses encompassed the quantification of hs-CRP, serum IL-6, creatinine, postprandial blood glucose (PPS), fasting blood glucose (FBS), HbA1c, and a full lipid profile.

Results: Patients with T2DM and concurrent AD demonstrated significantly elevated hs-CRP levels in comparison with those without AD ($p<0.001$). Additionally, serum IL-6 concentrations were notably higher in T2DM with AD (mean 22.5 ± 21.5) and T2DM alone (mean 15.5 ± 11.6) in comparison with the control group (mean 6.2 ± 3.2). Subjects with both T2DM and AD also exhibited increased FBS, PPS, and HbA1c in comparison with those with T2DM without AD.

Conclusion: Inflammatory biomarkers were elevated in T2DM patients and correlated with an increased risk of AD within this group.

Keywords: Alzheimer disease, inflammation, type2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus when inadequately managed leads to a range of microvascular and macrovascular complications. Although the pathways leading to diabetic complications are well-documented, the impact of diabetes on neurological functions, especially concerning cognitive deterioration, remains poorly understood [1].

Impaired glucose metabolism, the brain is unable to make or even store glucose, it must rely on glucose from the peripheral circulation to continue carrying out vital metabolic processes. A substantial correlation exists between T2DM, poor glucose metabolism, and AD. The dysregulation in insulin signaling and glucose homeostasis observed in T2DM may additionally act as an indicative risk marker for the initiation of AD [2].

AD represents the predominant form of significant neurocognitive disorders and dementia in the elderly, comprising 60-80% of such diagnoses. Clinically, AD manifests through a gradual onset of memory deterioration accompanied by a progressive decline in cognitive functions, culminating in premature mortality several years following its initial diagnosis [3].

Neuroinflammation is characterized as the intrinsic inflammatory response of the nervous system, mediated through an array of reactive oxygen species, cytokines, chemokines, and additional molecular agents [4]. Chronic inflammation is implicated in the onset of T2DM and AD [5, 6].

The objective of this study was to investigate the correlation between inflammatory biomarkers (hs-CRP and IL-6) and Alzheimer's disease within the elderly population diagnosed with type 2 diabetes.

SUBJECTS AND METHODS

The study encompassed 80 aged subjects (65-years-old and above) categorized into:

- Group 1 (Diabetic without AD): Include 30 diabetic patients type 2 without AD.
- Group 2 (Diabetic with AD): Include 20 diabetic patients type 2 with AD (Mini-Mental State Examination scores within the range of 12 to 26).
- Group 3 (Control): Include 30 normal subjects.

Participants were recruited from the Departments of Internal Medicine and Neurology at the Faculty of Medicine, University of Alexandria. The principal diagnostic protocols applied for the assessment of AD comprised the stipulations delineated by the National Institute on Aging and the Alzheimer's Association (NIA-AA), in concert with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [7, 8].

Inclusion criteria: Type 2 DM elderly patients, age (65-year-old and above**)**.

Exclusion criteria: Type 1 DM patients with acute diabetic complications, acute or chronic liver or renal failure, active treatment of cancer or history of cancer within the last 3 years. Patients with neurological diseases (seizure disorder, stroke, Parkinson's disease, head injury with loss of consciousness within the past

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year). Patients with psychiatric disorders (schizophrenia, bipolar or unipolar depression)

All subjects underwent detailed history taking including demographics and disease characteristics, in addition to complete physical examination with special emphasis on neurological examination and cognitive assessment.

Cognitive evaluation was conducted employing the following:

- General Practitioner Assessment of Cognition (GPCOG) [9].
- Folstein Mini-Mental Status Examination (MMSE) [10].
- Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) [11].
- Mini-Cognitive Assessment Instrument (Mini-Cog) [12].

And laboratory investigations included:

Complete blood picture, fasting plasma glucose, post prandial blood glucose, Glycated hemoglobin (HbA1C), creatinine, ALT , total cholesterol, HDL, LDL, triglycerides and hs-CRP. IL-6 concentrations were quantified utilizing a sandwich enzyme-linked immunosorbent assay (ELISA) methodology.

Ethical approval: The research was meticulously executed in strict adherence to the ethical principles articulated by the Declaration of Helsinki, and it was approved from the institutional review board of Alexandria university. Informed consent was diligently secured from all participants involved in the study. For individuals who were incapacitated and unable to provide consent autonomously, requisite authorization was obtained from their legally designated relatives or caregivers.

Statistical analysis

The process of data acquisition and analysis was meticulously conducted using IBM SPSS software, version 20.0 (Armonk, New York: IBM Corporation). Descriptive statistical evaluations for quantitative variables included calculating the range (from minimum to maximum), mean, standard deviation, median, and interquartile range (IQR). To assess the distribution of quantitative variables across different groups, the Analysis of Variance (ANOVA) test was implemented. Post hoc pairwise comparisons were subsequently performed using the Tukey test. A P values < 0.05 was considered to denote statistical significance.

RESULTS

Statistical analysis revealed no significant differences among the groups concerning age (p=0.713) and gender (p=0.825). Detailed demographics and clinical profiles of the participants are presented in table 1.

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

Parameters	Diabetic patients without AD (n=30)	Diabetic patients with AD (n=20)
Age (Year)	69.1±7.50	70.4±5.34
Male	12	9
Female	18	11
BMI	29.5+2.1	31+3.2
Disease duration (Year)	17.5±2.4 [a]	19.7±3.5[a,b]
Medications	• Metformin 60% • Short acting sulfonyl urea 20% • DPP4 inhibitors 3% • Insulin 17%	• DPP4 inhibitors 5% • Insulin 23% • Metformin 56% • Short acting sulfonyl urea 16%

Data presented as Mean ± SD a: Significantly different from control group by ANOVA, b: Significantly different from diabetic patients without AD by ANOVA.

In terms of inflammatory markers, hs-CRP levels were markedly elevated in diabetic patients with AD compared to the other groups (p<0.001), as illustrated in table 2 and figure 1. Additionally, the mean IL-6 concentration was found to be higher in patients with AD (22.5 ± 21.5) than in those with T2DM without AD (15.2 ± 11.6). Table 2 and figure 2.

Table (2): Comparison between the three studied groups according to hs-CRP and IL6

	Group 1 (n = 30)	Group 2 (n = 20)	Group 3 (n = 30)	Test of sig	p
Hs-CRP (mg/dl) Mean ± SD.	2.47[b] ± 0.49	3.13[a] ± 0.60	1.25[c] ± 0.27	F= 123.583*	<0.001*
Sig. bet. groups.	P_1<0.001*, p_2<0.001*, p_3<0.001*				
IL6 (pg/ml) Mean ± SD.	15.2 ± 1.6	22.5 ± 2.5	6.2 ± 1.2	H= 18.603	<0.001*
Sig. bet. groups.	p_1=0.280, p_2=0.001*, p_3<0.001*				

SD: Standard deviation, **F**: **F for One-way ANOVA test**, pairwise comparison bet. each 2 groups were done using **Post Hoc Test (Tukey),** H: H for **Kruskal Wallis test,** pairwise comparison bet. each 2 groups were done using **Post Hoc Test (Dunn's for multiple comparisons test).**

The p-value (p) represents the comparison across all studied groups. The p1 value indicates the comparison between Group 1 and Group 2, while p2 denotes the comparison between Group 1 and Group 3. The p3 value reflects the comparison between Group 2 and Group 3. An asterisk (*) denotes statistical significance at $p \leq 0.05$. Means or medians that share **common letters** are not significantly different, while those with **different letters** indicate significant differences.

Laboratory investigations of the studied groups showed that diabetic patients with AD have higher FBS, PPS and HbA1C levels than diabetic patients without AD table 3.

Table (3): Laboratory investigations among the three groups

Parameters	Diabetic patients without AD (n=30)	Diabetic patients with AD (n=20)	Control (n=30)
FBS (mg/dl)	210.5±10.8 [a]	223.5±42.3 [a]	**98.9**±7.9
PPS (mg/dl)	280.2±12.2 [a]	294.3±36.8[a,b]	148.7±8.6
HBA1C (%)	7.55±0.35 [a]	8.10±0.31[a,b]	5.58±0.34
Cholesterol(mg/dl)	233.6±16.5[a]	251.7±9.1 [a]	178.8±12.0
HDL-C(mg/dl)	42.2±3.4 [a]	41.2±6.4 [a]	58.1±5.5
LDL-C(mg/dl)	164.3±17.9[a]	175.1±11.5 [a]	101.6±14.1
Triglycerides(mg/dl)	135.3±12.6[a]	176.4±13.9[a,b]	95.6±12.9

Data presented as Mean ± SD a: Significantly different from control group by ANOVA, b: Significantly different from diabetic patients without AD by ANOVA

In the behavioral assessment of the groups under study, it was observed that the ADAS-Cog scores were significantly elevated in the diabetic patients with AD group when compared to both diabetic patients without AD and the control group. Conversely, individuals with T2DM concomitant with AD demonstrated markedly diminished scores on the Mini-Mental State Examination (MMSE). Analogously, the General Practitioner Assessment of Cognition (GPCOG) and Mini-Cog assessments revealed substantially lower scores in this subset of patients relative to the other groups table 4.

Table (4): Cognitive assessment among the three groups

Parameters	Diabetic patients without AD (n=30)	Diabetic patients with AD (n=20)	Control (n=30)
GPCOG	8.3±0.57	2.6±0.62[a,b]	8.4±0.46
Mini-Cog	4.4±0.44	1.7±0.40[a,b]	4.5±0.30
ADAS-Cog	10.5±3.6	31.7±2.0[a,b]	6.3±2.4
MMSE	27.3±0.75	19.3±1.26[a,b]	28.2±1.1

Data presented as Mean ± SD a: Significantly different from control group by ANOVA, b: Significantly different from diabetic patients without AD by ANOVA, c: Significantly different from diabetic patients with AD by ANOVA.

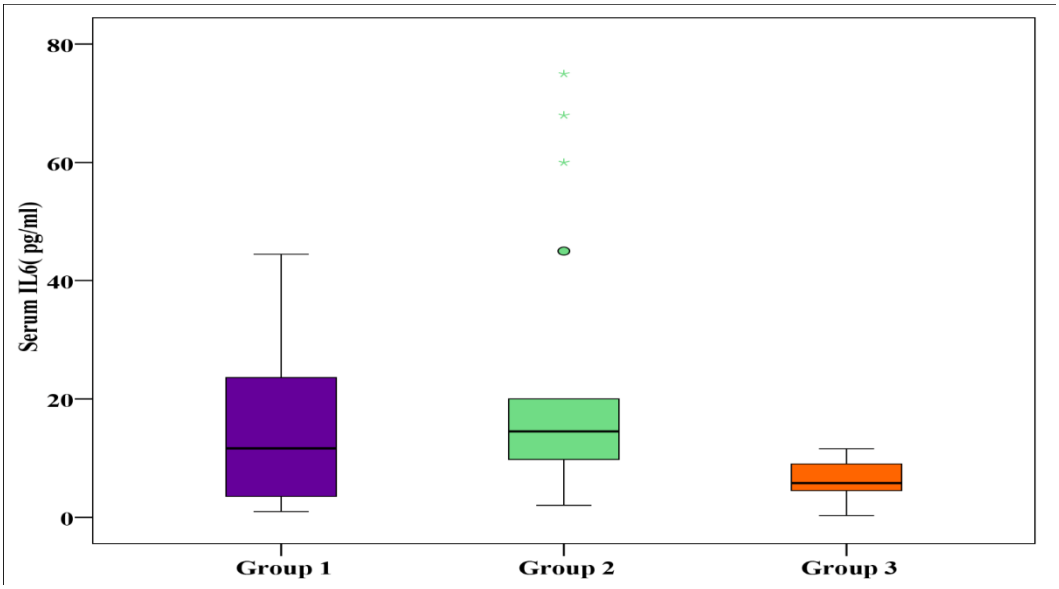

Figure (1): Comparison between the three studied groups according to hs-CRP.

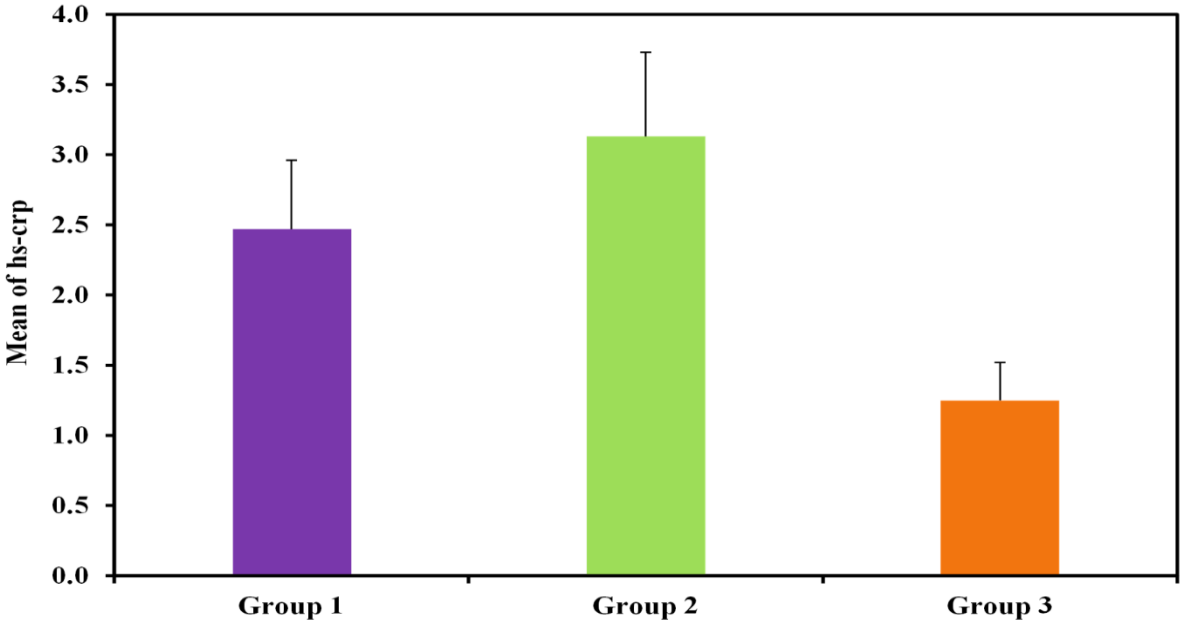

Figure (2): Comparison between the three studied groups according to IL6.

DISCUSSION

As Egypt's elderly population continues to expand rapidly, the incidence of new and existing cases of Alzheimer's disease (AD) is also expected to rise. So, looking for and controlling risk factors of AD will be of great concern to decrease the number of new cases, In 2013, nearly four million of the Egyptian population were above the age of 65 with an expected increase of this age group to 13.3% by 2050, consequences of dementia will also increase. [13].

The interplay of inflammation and dysregulated glucose metabolism in T2DM serves as an additional risk factor for the development of AD. A multitude of studies have rigorously substantiated a profound correlation between T2DM and the incidence of AD [14]. Many epidemiological studies probing the association between inflammatory biomarkers and AD risk in individuals with T2DM have elucidated a connection between elevated concentrations of hs-CRP or IL-6 and an augmented risk of AD onset [15].

In the current study, it was observed that fasting and postprandial blood glucose levels were elevated in diabetic patients with AD compared to both the control group and diabetic patients without AD. This finding suggests that glucose dysregulation is a significant risk factor for AD and implies a shared pathogenic mechanism between AD and type 2 diabetes. These results align with the findings of **Baker *et al.*** which also established a correlation between glucose dysregulation in diabetes and a heightened incidence of AD [16].

Hs-CRP levels were markedly elevated in diabetic patients with AD compared to both control subjects and diabetic patients without AD, implying a connection between chronic inflammation and both T2DM and AD. This relationship was corroborated by a longitudinal study conducted by **Yaffe *et al.*** which

identified association between elevated hs-CRP levels and the onset of cognitive decline [17]. In contrast, the study by **Schram *et al.*** yielded different results, indicating a minimal to no significant association between hs-CRP levels and the incidence of Alzheimer's disease [18].

Additionally, we found that IL-6 was elevated in diabetic individuals with AD compared to both control and diabetic patients without AD. This result is in line with a study by **Schuitemaker *et al.*** that found patients with cognitive impairment had significantly higher serum IL-6 levels. These results introduce the possibility that inflammatory mechanisms could be active in the early phases of AD, with different inflammatory markers becoming relevant at various stages of cognitive deterioration [19]. Furthermore, the research by **Wyss-Coray** highlighted an association between interleukin 6 and AD [20].

CONCLUSIONS

Inflammatory markers were higher among diabetic patients with AD, and this supports the hypothesis that inflammation and T2DM can act as a risk factor in AD development.

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