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Alternations in Blood Serum Levels of Aβ (1-40) and Superoxide Dismutase in Type 2 Diabetes and Alzheimer's Disease Patients in Saudi Population: an Observational Study

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Abstract: The prevalence of Alzheimer's disease (AD) in the Middle East including Saudi Arabia is increasing rapidly. The results of recent epidemiological investigation have suggested possible associations and some common pathophysiological mechanisms between Type 2 Diabetes (T2DM) and AD like amyloid beta (Aβ) formation and oxidative stress with antioxidant enzymes. To gain insights on this relation, an observational study was initiated. We recruited and interviewed 300 research participants (age ≥ 65 years) from King Abdulaziz Hospital outpatient clinics and Mental Health Hospital in Jeddah, Saudi Arabia in a period from July 2018 to January 2019: 100 control, 100 T2DM and 100 AD subjects. We assessed the association between glycated hemoglobin (HbA1c%) and Mini Mental State Examination (MMSE) with Aβ (1-40) and antioxidant enzyme superoxide dismutase (SOD) for all groups. No Significant differences between groups were observed for age and body mass index (BMI) ($p < 0.0001$). AD patients have significant decrease in MMSE among other groups. The highest level of HbA1c%, Aβ (1-40) and SOD was found in T2DM group. Negative relation was found between HbA1c% score and Aβ (1-40) and SOD. MMSE score was negatively related with HbA1c% while positively correlated with Aβ (1-40) and SOD. These results suggest that T2DM associated with higher Aβ (1-40) and antioxidants power while AD associated with lower Aβ (1-40) and antioxidant power. Serum Aβ (1-40) seems the most promising biomarker for AD diagnosis. More investigations to clarify this association are warranted.
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1. Introduction

Dementia, including AD, is one of the most global public health problem especially in Middle East. The World Health Organization dementia report expect 125% increase in patients by 2050 in the Middle East and North Africa (Abyad, 2015). The estimated number of patients with AD in Saudi Arabia is more than 50 thousand and most of them are women (Basheikh, 2014). AD is a gradual neurodegenerative disease identified by the progressive decline of memory, cognitive functions and changes in behavior and personality. The results of recent epidemiological and basic science investigation have suggested possible associations and some common pathophysiological mechanisms between T2DM and AD like Aβ formation and oxidative stress with antioxidant enzymes (Kandimalla et al, 2017).

Aβ collection in the brain is the hallmark of AD (Nagai et al, 2016). Aβ plaques include many proteins, but in particular Aβ in its (1-40) and (1-42) amino acid form (Reale et al, 2014). Aβ elicits a cascade of events that leads to neuronal dysfunction, neurodegeneration and finally to clinical dementia (Craft et al, 2012). Deposition of Aβ in brain and pancreatic islet cells explains a pathogenic similarity between AD and T2DM. On the other hand, researchers have found that under high glucose conditions, Aβ degradation and elimination from the brain will reduce (Nagai et al, 2016). Recently, a study examined 11 subjects and found the density of Aβ (1-40) did seem to be associated with the duration of diabetes, a finding that was cleared as being supportive of an association between AD and T2DM (Janson et al, 2004).

There is a obvious relationship between Aβ (1–40) and oxidative stress. It is known that Aβ can cause increased production of reactive oxygen species and also damage mitochondria, which can lead to further over production (Kandimalla et al, 2017). Both AD and T2DM are prototypical models of oxidative stress induced disease processes (Butterfield et al, 2014). Schmidt et al, 1998 found that high levels of plasma reactive oxygen species have been shown to correlate with a subsequent cognitive decline in healthy subjects

suggesting their potential in expecting deterioration of cognitive functions.

SOD is important antioxidant enzymes which do a role in oxidant defense of body and often as the first line of defense against oxidative stress by catalyses the conversion of superoxide radical into ordinary molecular oxygen or hydrogen peroxide (Zarei et al, 2016). The activity of SOD in serum was reduced in T2DM and AD patients compared to controls and was negatively correlated to the lipid peroxidation markers (Flekac et al, 2008). With the accumulative evidence for oxidative stress as an important factor in T2DM and AD, several trials have been concluded treating or preventing the disease using antioxidants (Persson et al, 2014).

Our present study is the first to determine the serum levels of Aβ (1-40) and SOD in elderly subjects and examine the associations of these parameters with MMSE and HbA1c in T2DM and AD in Saudi population.

2. Materials and Methods

An observational, descriptive study was conducted among selected 300 elders (168 women) who attended outpatient clinics at King Abdulaziz Hospital and Mental health hospital in Jeddah during the period from July 2018 till January 2019. The targeted sample of this study was all patients aged 65 and over without cognitive disabilities. The sample was divided into 3 groups. The control group comprised of (100) healthy individuals (75% females) were selected from the staff of the hospitals and attendances. They had no history of T2DM or AD. These subjects had previously undergone complete neurological examinations and were judged to be in good health based on their clinical history. The T2DM group comprised of (100) patients suffering from T2DM (50% females) with a target HbA1c of < 7%. The AD group comprised of (100) patients suffering from AD (67% females). Diagnosis of probable AD was according to standard clinical procedures and followed the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria.

Cognitive performance and alterations were evaluated according to Arabic version of MMSE and the Global Deterioration Scale. Also a Neurological specialist showed the cases and had judge if this patients had AD or not.

All subjects included in the study did not present major comorbidity such as cancer. All subjects were Saudis and reported that their body weight had been stable for at least 3 months before the study.

Demographic data, including age, sex, and duration of diabetes, were recorded. All subjects were evaluated by BMI; weight in kilograms divided by the square of height in meters. The mean of these measurements was used for this study.

Participants were screened using the Arabic version of Folstein MMSE, which is a brief 30-point questionnaire test that is used to screen for cognitive impairment. In a time span of about 10 min, various functions for cognitive functions which reflects orientation, memory, attention, ability to follow verbal and written commands, writing, and copying are tested. The total score of the exam ranges from 0–30 points. Subjects showing scores of 25-30 out of 30 are considered normal (no cognitive impairment), 21-24 as mild cognitive impairment, 10-20 as moderate cognitive impairment and <10 as severe impairment.

About 5 ml of the blood was drawn from subjects between 10 AM and 2 PM after 10–12 h overnight fasting for all groups. The blood samples were allowed to clot for 10 minutes at room temperature, and then centrifuged at (at 2000*g* at a temperature of 4 °C for 20 minutes). The separated serum was drawn, divided into aliquots and stored in a deep freezing (-40°C) until time of use.

All biochemical measurements were performed in a Biochemistry Lab at King Abduulaziz University Hospital. HbA1c% were taken from the subjects files'. Spectrophotometric assays were performed in duplicate using a Lambda EZ 210 spectrometer (Perkin-Elmer, Foster City, CA, USA). Serum Aβ (1-40) assay (ng/L) was performed using quantitative human immunoassay ELISA kit (Cat # E1230Hu, BT LAB, Shanghi, China). Measurements of SOD activity (U/L) was done using quantitative human immunoassay ELISA kit (Cat # E0918Hu, BT LAB, Shanghi, China). Detection limit of the assay was 0.25 ng/L for Aβ (1-40) and 1.52 U/L for SOD. The percentage coefficients of variation for all parameters ranged from 10% (inter-assay) and 8% (intra-assay).

Our study protocol was approved by Researches unit in Directorate of Health Affairs in Jeddah (document number 00914/A00580). The researchers were worked on this study had a certificate from The National Institutes of Health, Office of Extramural Research certifies (document number 2664385). Written informed consent was obtained from all subjects or their legal caregivers.

A Statistical Package for the Social Sciences (SPSS) software for Windows (version 13.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis of data. After normalizing the distribution of data by log transformation, z-Test: two-Sample for means was used for comparing the means of quantitative variables in two groups. Data are expressed as means ± standard deviation. The strength of association between pairs of variables was assessed using Pearson's correlation coefficient. The level of *P*

≤ 0.01 was considered significant and highly" significant at $P \leq 0.005$.

3. Results

In the present study, the female percentage was 64% and the mean of T2DM duration was 14±8.48 in T2DM group. There were no significant differences in age and BMI among 3 studied groups.

HbA1c% levels were significantly higher in T2DM than in control and AD groups. No significant difference was found in HbA1c% levels between control group and AD group. MMSE levels were significantly lower in AD comparing with control and T2DM groups. No significant difference was assessed in MMSE levels between control and T2DM groups. Aβ (1-40) levels was significantly higher in T2DM group comparing with control and AD groups. Aβ (1-40) levels were significantly higher in control group comparing with the AD group. SOD levels were significantly higher in T2DM group comparing with the control and AD groups. SOD levels were significantly higher in control group comparing with AD group (Table. 1).

Table 1 Anthropometric and biochemical parameters in 3 studied groups.

Parameter	Control Group	T2DM Group	AD Group	P-Value (P< 0.001)
No.	100	100	100	-
Female [n (%)]	75	50	67	-
Age (yr)	72 ± 8.49	72 ± 4.52	75 ± 7.79	-
BMI (kg/m2)	27.6 ± 6.07	27.67 ± 2.65	27.9 ± 3.28	-
Diabetes Duration (yr)	-	14 ± 8.48	-	-
HbA1c %	5.57 ± 0.79	7.83 ± 1.27	5.86 ± 0.74	a, c
MMSE	29 ± 0.8	26 ± 1.93	14 ± 4.63	b, c
Aβ (1-40) (pg/ml)	246.5 ± 34.35	426.1 ± 84.41	127.3 ± 17.23	a,b,c
SOD (U/L)	291.2 ± 54.77	582.9 ± 108.47	87.02 ± 27.38	a,b,c

P value "highly" significant at < 0.001, a – comparing: control group– T2DM group, b – comparing: control group – AD group, c – comparing: T2DM group – AD group.

For correlation with HbA1c%; there was a significant negative correlation between HbA1c% and MMSE level in 3 studied groups. A significant inverse correlation between HbA1c% and Aβ (1-40) in control group and AD group, no such correlation in T2DM group. HbA1c% score was found to be significant negatively correlated with SOD in T2DM group while no correlation in control and AD group (Table 2).

For correlation with Aβ (1-40); a significant correlation between MMSE and Aβ (1-40) in AD group while no correlation in control and T2DM groups. There was a significant positive relation between MMSE and SOD level in the T2DM and AD groups and no relation in control group (Table 3).

Table 2 The Correlations of HbA1c% with MMSE, Aβ (1-40) and SOD in 3 studied groups.

Parameter	Control group	T2DM group	AD group
MMSE	-0.461*	-0.343*	-0.711**
Aβ (1-40)	-0.393*	-0.033	-0.684**
SOD	-0.110	-0.375*	-0.176

*P significant at 0.01, ** P is highly significant at 0.005

Table 3. The Correlations of MMSE with HbA1c%, Aβ (1-40) and SOD in 3 studied groups.

Parameter	Control group	T2D group	AD group
HbA1c	-0.461*	-0.343*	-0.711**
Aβ (1-40)	0.148	0.004	0.698**
SOD	0.015	0.389*	0.764**

*P significant at 0.01, ** P is highly significant at 0.005

4. Discussion

The prevalence of AD in the Middle East including Saudi Arabia is increasing rapidly. Many studies support an association between T2DM and AD. This study is the first to examine the associations of Aβ (1-40) and SOD with MMSE and HbA1c% in T2DM and AD in Saudi population.

In our results, HbA1c% levels were significantly higher in T2DM than in control and AD groups. No significant difference in HbA1c% levels between

control group and AD group. These results are in agreement with the previously studies by Harten *et al.* 2007 and Ragy and Kamal 2017. Also epidemiological investigation in a Pakistani population identified that the average HbA1c% level in T2DM participants was 2.2 times higher as compared to AD and control subjects (Noreen et al, 2018). In contrast of our study, a case-control study by Razay et al, 2005 that found a higher HbA1c% levels in AD group comparing with control group. This differences in results between studies it may be due to life style or diet habits that effect on HbA1c% levels in serum.

MMSE is one of the most widely used screening tests for AD. Our findings was suggested that MMSE levels were significantly lower in AD comparing with control and T2DM groups. No significant difference in MMSE levels between control group and T2DM group. These results agreed with studies by Ragy and Kamal 2017, Razay *et al.* 2007 and Hazari *et al.* 2010.

For correlation, in this study, HbA1c% were negatively correlated with MMSE level in 3 studied groups. These findings are supported by the findings of Munshi *et al.* 2006. On the other hand, Huang et al, 2017 reported in nondemented elderly patients (age ≥ 80 years) with T2DM that there is no significant correlation between HbA1c% levels and cognitive function. Differences in results in studies may because of advanced age, education level, duration of T2DM, hypertension and other vascular risks.

Studies to date suggest that T2DM increase risk for AD possibly through their effects on Aβ (1-40) metabolism. Localised progressive amyloidosis is seen in both AD and T2DM. In our study, Aβ (1-40) levels was significantly higher in T2DM group comparing with the control and AD groups. Aβ (1-40) levels were significantly higher in control group comparing with the AD group. A significant inverse correlation between HbA1c and Aβ (1-40) in control group and AD group, no correlation such in T2DM group. A high significant correlation between MMSE and Aβ (1-40) in AD group while no correlation in control and T2DM groups. Many previous studies had results as our studies such as Liu et al, 2008 that found Aβ (1–40) levels significantly increased in temporal cortex and hippocampus of the T2DM rats. The reason for high level of Aβ (1–40) in T2DM group because Aβ (1–40) accumulation is found in pancreatic islets, misfolding of insoluble proteins leads to an interaction with cell membrane and a loss of normal cell function and ultimately cell mass. This can be considered to be a low grade inflammatory reaction associated with the elevation of circulating pro-inflammatory cytokines and acute phase proteins including serum Aβ (1–40). Also BALTAZAR study by Hanon et al, 2018 suggested that plasma levels of Aβ (1–40) reduced in AD group dementia and higher plasma levels of Aβ (1–40) associated with HbA1c% in AD. The decrease of plasma Aβ level during the AD process could be explained by Aβ clearance decrease from the brain CSF to the peripheral fluid (blood) because of alteration of blood brain barrier permeability. In contrast of our results, studies by Mehta et al, 2000 and Reale et al, 2014 found that mean plasma Aβ (1-40) levels were higher in the AD group and levels of Aβ (1-40) and showed no association with MMSE. A matched case-control study by Peters et al, 2017found that median Aβ (1-40) concentrations were significantly lower in those with T2DM comparing with control.

Numerous epidemiological studies confirm the contribution of oxidative stress to the pathogenesis of T2DM and AD. Our findings were suggested that SOD levels were significantly higher in T2DM group comparing with the control and AD groups. SOD levels were significantly higher in control group comparing with AD group. HbA1c% score was found to be significant negatively correlated with SOD in T2DM group while no correlation in control and AD group. High level of SOD in T2DM group due to increase of free radicals in T2DM may increase antioxidant enzyme activities. In addition, high blood glucose can combine with the protein enzymes so that in patients with T2DM extracellular SOD is highly glycosylated comparing to healthy subjects. Our findings are supported by the many findings of Kimaru *et al.* 2003, Ahmed *et al*. 2006 and Padurariu *et al.* 2010. In contrast of our investigations, many studies by Colak et al, 2015, Briggs et al, 2013 and Madi et al, 2016 suggested that serum SOD activity was significantly decreased in T1DM and T2DM subjects compared to the control subjects. Our present study showed that there was a high significant positive correlation between MMSE and SOD level in T2DM and AD groups and no correlation in control group in consistent with the study of Ansari and Scheff, 2010. The opposite of our findings found by Sun et al, 2019 Chinese study suggested that higher serum SOD activity was negatively associated with MMSE levels and elevated risk of cognitive decline among older adults. Many of the conflicting findings between various studies may be due to methodological differences between studies, including variations in sample size, correction for increased mortality in T2DM and AD subjects and also increase of free radicals in T2DM may increase antioxidant enzyme activities.

5. Conclusions

The demographic changes and social and economic developments in Saudi Arabia have to create new realities in an unprecedented growth of the elderly population. So more elderly population that

means more AD and T2DM patients. As this study is the first to examine the associations of serum levels Aβ (1-40) and SOD with MMSE and HbA1c% in T2DM and AD in Saudi elderly population. In conclusion for our study, blood serum levels of Aβ (1-40) and SOD decreased in patients with AD while increased in T2DM patients in Saudi population. So T2DM associated with higher Aβ (1-40) and antioxidants power while AD associated with lower Aβ (1-40) and antioxidant power. Serum Aβ (1-40) seems the most promising biomarker for AD diagnosis. Antioxidants such as SOD could be use for treating or preventing AD. More investigations to clarify the association of T2DM with AD are warranted. These investigations may help to increase our understanding of AD and open a new door to the development of therapeutics.

There are some limitations to our study should be considered; the small sample size, we did not evaluate the effects of exercise and diabetic medications on MMSE and HbA1c%. Our subjects in our study were Saudi elderly, so these results may not be generalized to other populations of different nationalities or ages.

Despite limitations, the chief strength of the present study: is the first to determine the serum levels of Aβ (1-40) and SOD in elderly subjects and examine the associations of these parameters with MMSE and HbA1c in T2DM and AD in Saudi population.

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