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RESEARCH ARTICLE

EFFECT OF SERUM LIPIDS AND LIPOPROTEINS ON COGNITIVE IMPAIRMENT IN DEMENTIA PATIENTS OF WESTERN INDIAN REGION

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ABSTRACT

Background: Despite much research,there are currently no established blood-based biomarkers for dementia.The aim of the present study was to assess the circulatory biochemical parameters and their association with cognitive markers in serum of patients with Dementia and Mild Cognitive Impairment (MCI) and compare with elderly age-matched controls.

Materials & Methods: The study population consisted of patients with Dementia (Group A, n = 32), Mild Cognitive Impairment (Group B, n = 28), and elderly age-matched Controls (Group C, n = 30). All the participants were subjected to psychological assessment, anthropometric measurements and serum biochemical estimations like blood sugar, lipid profile, lipoproteins, and thyroid profile.

Results: We observed significantly reduced levels of Total Cholesterol, High Density Lipoprotein-Cholesterol, Apolipoprotein B and total T4 in serum of Dementia patients compared to elderly age-matched controls ($p < 0.05$). While decreased Apolipoprotein A1 levels were found in serum of Dementia and MCI patients compared to elderly age-matched controls ($p < 0.01$). Finally, a positive correlation of Apolipoprotein A1 and total T4 levels with markers of cognitive impairment was observed in Dementia and MCI patients.

Conclusion: Our findings suggest the importance of serum lipids, lipoproteins and thyroid hormones in cognitive impairment in patients with Dementia and MCI.

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INTRODUCTION

Dementia, including Alzheimer's disease, remains one of the biggest global public health challenges facing today's geriatric population. An estimated 47.5 million people are currently living with dementia and 60% of this disease burden falls on low and middle-income countries, which have the least capacity to cope. As population ageing continues to accelerate, the number of dementia cases is expected to nearly double every 20 years (WHO Dementia Fact sheet 2015). But presently there is no comprehensive and affordable plan for coping with the tidal wave of dementia. Given this epidemic scale, and with no known cure, it's crucial that we look at what we can do to reduce the risk or delay the onset of developing the disease. Detecting dementia at the earliest possible stage is vital to enable trials for disease modifying agents, as considerable efforts are being invested in the identification of biomarkers for this purpose. The current focus is to explore modifiable risk factors which can be used for prevention and treatment at economical rates. In human system, lipids are considered as the basic structural component of neuronal (nerve) cell membranes, and constitute the major dry weight of brain. It is the most cholesterol-rich organ, containing 30% of the body's total cholesterol and plays a crucial role in the development and maintenance of neuronal plasticity and function. Dyslipidemia is considered as one of the risk factor in development of dementia (Wanamaker *et al.,* 2015; Reitz, 2013; 2012). A history of vascular disease including heart disease and cerebrovascular disease has a negative impact on cognition in old age (Laukka, Fratiglioni, Backman, 2010). High serum total cholesterol at midlife is a risk factor for Alzheimer's disease (AD) and other dementia types in later life (Kivipelto *et al.,* 2001; Whitmer, Sidney *et al.,* 2005). Clinical and epidemiological studies support a strong relationship between AD and cardiovascular disease (CVD) risk factors such as high density lipoprotein (HDL) levels, low density

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lipoprotein (LDL) levels and the presence of atherosclerosis and hypertension (Martins, Hone *et al.,* 2006). Interesting findings from genetic research, animal models and in vitro studies strongly suggest an important role for brain cholesterol metabolism and transport in AD neuropathology. Findings on the association between cholesterol level and dementia are inconsistent. Studies have shown that similar to body weight and blood pressure, cholesterol levels may decline more rapidly from midlife to late-life in those who go on to develop dementia, particularly AD (Martin Prince *et al.,* 2014). Research in this line of action may yet help to identify novel therapeutic targets.

Apolipoproteins (Apo) are a group of proteins related to cholesterol and lipid metabolism and recent findings indicate that apolipoproteins might also be involved in neurodegenerative processes (Takechi, Galloway *et al.,* 2010; Lewis, Cao *et al.,* 2010). Apolipoprotein A1 (ApoA1) is one of the Aβ-binding proteins and the major component of high-density lipoprotein (HDL). Several antiatherogenic functions have been attributed to apoA1 including reverse cholesterol transport and protection against thrombosis and oxidation (Scanu, Edelstein, 2008; Camont, Chapman, Kontush, 2011; McGrowder, Riley *et al.,* 2011). In particular, apolipoprotein A1 (apoA1)and B (apoB) have not been studied for their role in cognitive changes despite their role in lipid metabolism and associations with CVD risk. ApoB seems to form the primary protein component of atherogenic lipoprotein particles (e.g. LDL) while apoA1 forms the primary anti-atherogenic lipoprotein particles (HDL) (Scanu AM, Edelstein C. 2008). ApoB acts as a receptor ligand for LDL receptors while apoA1 promotes the effusion of cholesterol from tissues (Walldius G, Jungner, 2007). ApoB, apoA1, and their ratio (apoB /apoA1) may be more reliable predictors of cardiovascular events and coronary heart disease mortality compared to routine lipid measurements (Sierra-Johnson, Fisher *et al.,* 2009; Thompson, Danesh, 2006).

Normal thyroid function appears to be an important factor in retaining optimal cognition in human aging (Loosen P.T., 1992). Thyroid function has been measured in serum in the form of thyroid-stimulating hormone (TSH) or thyroid hormones (total or free thyroxine (T4), total or free triiodothyronine (T3), or T3 resin uptake). Overall, many studies suggest that there may be a continuum describing the impact of thyroid function on cognition in which cognitive dysfunction results from either chronically increased or decreased concentrations of thyroid hormones. Low thyroid function at any age causes cognition to deteriorate because hypothyroidism prevents the brain from adequately sustaining the energy (glucose)-consuming processes needed for neurotransmission, memory, and other higher brain functions. Low brain uptake of glucose is commonly associated with deteriorating cognition and Alzheimer's disease and can be present decades before clinical evidence of Alzheimer's disease occurs (Freemantle, Vandal, Tremblay-Mercier *et al.,* 2006; Reiman, Chen, Alexander *et al.,* 2004). Clearly, the results from various studies are disparate and conflicting as to which indicator of thyroid function is the most relevant marker of specific cognitive function, and which domain of cognitive functioning is primarily affected by thyroid hormonal variations.

However, the overall findings suggest that, although thyroid hormones may have an impact on a variety of cognitive functions, only a link to certain memory functions has been so far highlighted. Hence, the present study was undertaken to assess biochemical and cognitive markers in patients with Dementia and Mild Cognitive Impairment (MCI) and compare them with age-matched healthy controls. The objectives of the study were i) to assess theeffect of serum biochemical parameters such as lipid profile, lipoproteins, thyroid profile (T3, T4 & TSH), SGOT, SGPT, etc. in patients withDementia and MCI and ii) To study their relationship with markers of cognitive impairment such as Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination (ACE).

METHODS

Ethics Statement

The procedures of this study were approved by the Scientific Advisory Committee and the Institutional Ethics Committee. The study was carried out in accordance with the "Ethical Guidelines for Biomedical Research on Human Participants, 2006" by the Indian Council of Medical Research and the Declaration of Helsinki, 2008, and written informed consent was obtained from all participants involved in this study.

Subjects and samples

In this prospective study, total of 90 study participants aged >50yrs were enrolled. The study population was divided into three groups; viz., patients suffering from AD and Vascular Dementia as well as patients with Vascular Cognitive impairment (VCI) not amounting to Dementia (Group A, n=32), patients with MCI (Group B, n=28) and elderly age-matched controls (Group C, n=30). The diagnosis of Dementia and MCI cases was made according to the standard Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) diagnostic criterion. Dementia and MCI cases were referred from two hospitals located in Mumbai; Sir H. N. Reliance Foundation Hospital &Research Centre, Mumbai, India and T. N. Medical College & B.Y.L. Nair Hospital, Mumbai, India. Elderly age matched controls were healthy individuals from the nearby vicinity of Sir H.N. Reliance Foundation Hospital & Research Centre falling in the same age category.At the time of recruitment, all the participants were subjected to a baseline clinical and neurological examination.

Psychological assessment

Cognitive assessment of participants enrolled for this study was conducted by a Clinical Psychologist. All the participants underwent a comprehensive geriatric assessment, including history, medication history, physical and neurological examination. They were put through questions for assessment of the MMSE and ACE. In MMSE, functions such as registration, attention, calculation, recall, language (Comprehension, reading, writing and naming), ability to follow simple commands and orientation were examined. However, in ACE along with MMSE other additional questions for remote memory, verbal fluency, naming, language and visuospatial were assessed to test various

specific domains of cognition. For MMSE, Scores 27 or above are considered normal. However, scores below 24 indicates impairment in cognition. Similarly, in ACE, Scores 90 or above are considered normal and scores below 90 indicates cognitive impairment.

Clinical and biochemical evaluations

Anthropometric measurements such as height and weight of each study participant, were calculated. BMI was calculated as weight / (height) 2 and expressed in kilograms per square meter. Two readings of blood pressure (systolic and diastolic) were recorded using mercury sphygmomanometer as recommended by the American Society of Hypertension, and the average was used for analysis. Six milliliters of blood was collected via venipuncture after overnight fasting, and transferred into Ethylenediaminetetraaceticacid (EDTA), Sodium chloride and plain serum vacutainers. Blood samples from the plain bulb were centrifuged at 3000rpm at room temperature for 10minutes. Supernatant serum was collected into sterile polypropylene tubes and immediately used for biochemistry analysis. Serum sample was used for estimation of blood glucose levels, lipid profile, Serum glutamic oxaloacetic transaminase (SGOT) Serum glutamic pyruvic transaminase (SGPT) and Thyroid profile (T3, T4 and TSH), while blood samples from EDTA bulb and sodium chloride bulb were used for complete blood count (CBC) and erythrocyte sedimentation rate (ESR) analysis respectively. Postprandial blood sugar was measured at 2 h post lunch also. All the measurements except ESR measurement which was done immediately after blood collection, were done within 2 h of collection.

All the above mentioned biochemical estimations were performed using a clinical chemistry auto analyzer (Thermo Scientific, Waltham, USA).

Blood sugar was analyzed by the glucose oxidase method (Spin react, Spain), SGOT and SGPT by International Federation of Clinical Chemistry (IFCC) method (Erba Mannheim Gmbh, Germany), cholesterol by the oxidase/peroxidase (CHOD–POD) method (Agappe Diagnostics, India), triglycerides by the enzymatic GPO–POD method (Innoline, Merck India), and high-density lipoprotein by enzyme selective protection method (Agappe Diagnostics, India). T3, T4 and TSH estimations were done by Enzyme-linked fluorescence assay (ELFA) method using MiniVidas Version B 03/2003 instrument (Biomerieux, France). In haematology, ESR and CBC were performed using VES-MATIC 20 and Sysmex 2000I haematology analyser respectively.

Statistical analysis

Statistical evaluation of the results was performed using the statistical software SPSS, version 21.0 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to confirm assumptions of normal distributions. Comparison between groups was done using either one-way analysis of variance-ANOVA- (if normally distributed) or Kruskal-Wallis test (if not normally distributed) with post-hoc tests. Correlation between two numerical variables was assessed using Spearman's rho correlation coefficient. Student's t-test was used to compare the patient group with the control group. Baseline differences were analysed using Mann–Whitney U-test and independent samples t-tests (continuous data).A p-value < 0.05 was accepted as statistically significant.

Table 1. Anthropometric characteristics across three study groups (mean ± SD)

Parameter	Dementia (n=32)	MCI (n=28)	Controls (n=30)	Overall P value (post hoc P value after Bonferroni's correction)
Age in yrs	68.5 ± 6.9	65.4 ± 8.4	66.8 ± 7.7	0.305
Weight in kg	59.01 ± 12.8	63.5 ± 10.3	59.8 ± 14.1	0.375
Height in inches	5.2 ± 0.4	5.3 ± 0.3	5.2 ± 0.3	0.857
BMI inKg/m^2	10.76 ± 2.06	10.95 ± 1.89	10.15 ± 2.27	0.776
Diastolic blood pressure in mmHg	78.8 ± 5.65	78.8 ± 10.2	82.7 ± 6.48	0.09
Systolic blood pressure in mmHg	123.93± 15.1	129.6 ± 25.8	126.2 ± 15.4	0.830

Table 2. Biochemical parameters across the three study groups (mean ± SD)

Parameter	Dementia (n=32)	MCI (n=28)	Controls (n=30)	Overall P value (post hoc P valueafter Bonferroni's correction)
Glucose profile				
Fasting blood sugar(mg/dl)	111.4 ± 38.7	110.5 ± 46.2	95.9 ± 21.86	0.18
Post-prandial bloodsugar (mg/dl)	152.4 ± 76.7	157.8 ± 84.4	121.6 ± 45.1	0.13
Lipid profile				
Total cholesterol (TC)(mg/dl)	178.4 ± 26.5	178.9 ± 34.8	210.0 ± 63.3	0.01 (0.03^a; 0.02^c)
High-density lipoprotein(HDL) (mg/dl)	49.1 ± 11.7	51.0 ± 14.4	73.0 ± 55.5	0.01^a
Low-density lipoprotein(LDL) (mg/dl)	108.4 ± 29.7	97.0 ± 31.7	108.1 ± 26.3	0.26
Very low-densitylipoprotein (VLDL)(mg/dl)	24.9 ± 2.8	29.7 ± 8.6	20.9 ± 7.47	0.12
Triglycerides (mg/dl)	124.7 ± 79.2	148.5 ± 93.6	104.79 ± 37.3	0.14
Apolipoprotein A1(g/L)	1.24 ± 0.1	1.29 ± 0.1	1.43 ± 0.2	0.000 (0.000^a; 0.003^b)
Apolipoprotein B (g/L)	1.05 ± 0.1	1.15 ± 0.18	1.15 ± 0.16	0.024 (0.04^a)
Apolipoprotein B/AI ratio	0.84 ± 0.05	0.88 ± 0.16	0.81 ± 0.19	0.21
Thyroid profile				
Total T3 (ng/dL)	92.6 ± 18.8	96.1 ± 28.5	97.6 ± 18.0	0.65
Total T4 (µg/dL)	4.29 ± 2.5	6.23 ± 2.5	6.83 ± 1.4	0.000^a
Thyroid stimulatingHormone (TSH) (µIU/mL)	3.56 ± 1.3	2.74 ± 1.7	3.15 ± 1.14	0.35
Liver function tests				
Serum glutamic oxaloacetic transaminase (SGOT) (U/L)	19.4 ± 8.1	20.2 ± 6.8	22.3 ± 7.8	0.31
Serum glutamic pyruvic transaminase (SGPT) (U/L)	17.1 ± 9.2	17.4 ± 6.9	20.1 ± 9.6	0.35

a: Dementia Vs Controls; b: MCI Vs Controls; c: Dementia Vs MCI

RESULTS

Demographics

As shown from Table 1, all the groups were comparable with respect to the demographic details and anthropometric measurements.

Biochemical estimations

Table 2 shows that Total Cholesterol and HDL concentrations were significantly lower in patients with Dementia compared to MCI and elderly age-matched controls (all $p < 0.05$). We observed a significant decrease in serum ApoA1 levels in Dementia and MCI patients compared to elderly age-matched controls ($p < 0.01$). Similarly serum ApoB levels were found to be decreased significantly only in patients with Dementia compared to elderly age-matched controls($p < 0.05$).In thyroid profile, significant decrease in Total T4 serum levels was observed in patients with Dementia compared to elderly age-matched controls ($p < 0.001$).

Markers of cognitive impairment

Fig 1 shows significantly lower MMSE score in patients with dementia and MCI group when compared to age-matched controls. ACE score was found to be significantly lower in dementia group as compared to age-matched controls. Also significant difference was observed between MMSE and ACE score of dementia and MCI group ($P < 0.001$).

Correlation analysis

From Table 3, our study demonstrated a positive correlation of ApoA1 and total T4 levels with markers of cognitive impairment (i.e. MMSE and ACE) ($p< 0.05$). Similarly, HDL showed moderately positive correlation with ApoA1 ($p< 0.01$) and negative correlation with total T4 in Dementia and MCI patients ($p< 0.05$).

DISCUSSION

Worldwide, the biggest global public health challenge facing our generationis the increasing number of people living with dementia. Looking at this epidemic with no possibility for cure, it's crucial to look at what we can do to reduce the risk or delay the onset of developing the disease. Although non-modifiable risk factors (age, gender and genetic factors) are very important in diagnosis of the disease, the current focus on modifiable risk factors is justified by their potential to be targeted for prevention. Our findings suggest that the impact of lipids and lipoproteins on cognitive behavior have shown a marked effect in elderly individuals. Moreover, the results emphasize the importance of serum lipids (HDL & ApoA1)and total T4 levels in cognitive impairment in patients with Dementia and MCI. We observed significantly reduced levels of total cholesterol, HDL-C and total T4 in Dementia patients compared to elderly age matched controls. Serum ApoB levels were found to be decreased significantly only in Dementia patients compared to elderly age-matched controls ($p<0.05$). However, only one parameter i.e. ApoA1, was found to be decreased in Dementia and MCI patients compared to elderly age-matched controls ($p < 0.01$).

Table 3. Relationship between Biochemical parameters and markers of cognitive impairment in Dementia and MCI patients

Parameter1	Parameter 2	Spearman's correlation coefficient
MMSE	Apolipoprotein A1	0.35*
	Total T4 (µg/dL)	0.35*
ACE	Apolipoprotein A1	0.34*
	Total T4 (µg/dL)	0.35*
High Density Lipoprotein (mg/dl)	Apolipoprotein A1	0.41**
	Total T4 (µg/dL)	-0.32*

*: $p< 0.05$; **: $p<0.001$

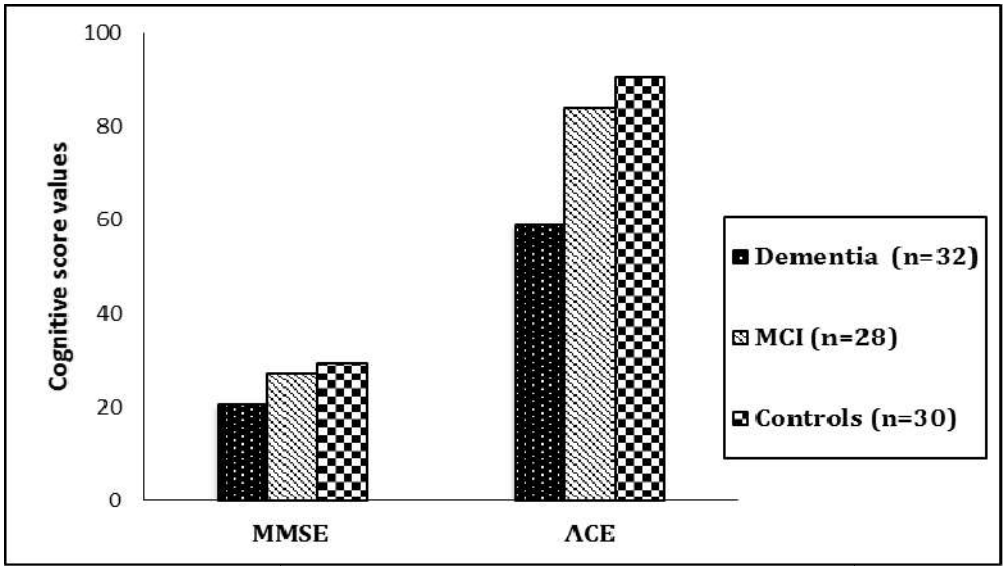

Figure 1. Comparison of markers of cognitive impairment by MMSE (0-30) and ACE (0-100) scores

Finally, the importance of lipid and lipoprotein levels in cognitive decline was extended from a positive correlation of ApoA1 and total T4 levels with markers of cognitive impairment (MMSE and ACE) and moderately significant negative correlation between HDL-C and total T4 levels. Several cardiovascular risk factors are also risk factors for dementia, including hypertension, high LDL cholesterol, low HDL cholesterol and especially diabetes (Stampfer, 2006). In our study, we observed reduced levels of serum total cholesterol and HDL-C in Dementia patients compared to MCI and elderly age matched controls. These results are in concordance with results of Merched *et al.* (2000) and Mielke *et al.* (2005) Similarly, a new French study by Raffaitin *et al*. have found that elderly individuals with metabolic syndrome were 20% more likely to show cognitive decline on a memory test (MMSE) over a two or four year interval. Specifically, higher triglycerides and low HDL cholesterol were linked to poorer memory scores (Raffaitin *et al.,* 2011).

Our study showed that serum levels of ApoA1 were significantly decreased in patients with Dementia and MCI when compared to elderly age-matched controls. Also a moderate positive correlation was observed between ApoA1 levels and markers of cognitive impairment (MMSE and ACE). These findings suggests possibility that reduced ApoA1 levels may play role in impairment of cognitive skills in elderly individuals. Various previous animal model studies have demonstrated that there is an association of ApoA1 declines with AD and AD animal modelsas well as mild cognitive impairment (Liu, Hu, Chang *et al.,* 2006; Lefterov, Fitz NF, Cronican *et al.,* 2010; Song, Poljak, Smythe *et al.,* 2009). A triple transgenic mouse model (over expressing mutant forms of APP, PS1 and ApoA1) showed that over expression of ApoA1 prevented the development of age-related learning and memory deficits despite continued Aβ deposition and hence increased ApoA1 benefits cognitive performance in an AD mouse model (Lewis *et al.,* 2010).Similarly in our study, serum ApoB levels were found to be decreased significantly only in patients with Dementia compared to elderly age-matched controls.

These results are in discordance with findings of the previous studies which have found significantly higher levels of ApoB in the serum of AD subjects (Caramelli, Nitrini, Maranhao, Lourenco, Damasceno *et al.,* 1999; Zhang, Barker, Pinchev, Marshall, Rasamoelisolo *et al.,* 2004). Also, Bereczki *et al.,* showed that overexpression of human ApoB in the serum of transgenic mice caused the formation of amyloid plaques and extensive neuronal death (Bereczki, Bernat, Csont, Ferdinandy, Scheich *et al.,* 2008). This study highlights the presence of positive association between ApoA1 and markers of cognitive impairment and hence ApoA1 has potential to serve as an early marker of cognitive impairment in elderly individuals. Adequate thyroid function is essential for normal development and retention of cognitive function throughout life. Several clinical and epidemiological studies have supported a link between thyroid hormones and Alzheimer's pathophysiology (Dugbartey, 1998; Latasa, Belandia, and Pascual, 1998; Luo *et al.,* 2002; Van der Cammen, Raso, de Jage, and van Harskamp, 2003; Ganguli *et al.,* 1996). In our study, we found significantly reduced levels of total T4 in Dementia patients compared to elderly age matched controls. The observations of our study corroborated with the results of the Women's Health and Aging Study, which reported cognitive decline in women with low levels of total thyroxine (T4) over a three year period (Volpato *et al.,* 2002). However, our results did not match with the findings of the Leiden-85 study, which showed noassociation of levels of thyroid stimulating hormone (TSH) and free thyroxine (FT4) (Gussekloo *et al.,* 2004) with cognitive impairment. Also a positive correlation of total T4 levels with markers of cognitive impairment (MMSE and ACE) and negative correlation with HDL concentrations in Dementia and MCI patients ($p < 0.05$) was observed. Therefore, the observations of present study point to the possibility of role of thyroid dysfunction in cognitive impairment in elderly individuals. Further analysis of our data according to gender did not show any association between thyroid hormones and cognitive impairment.

However, several limitation of this study must also be considered. First, the relatively small sample size in this study has limited the significance of statistical inference of the available data. The study could benefit from a larger sample size. Second, the study had not been able to exclude all possible confounding factors that may affect the participant's cognitive functioning, such as social activities, alcohol intake, smoking habit, mental activities, and many other factors that may have had influenced participant's cognitive function. To validate the clinical utility of the current study results, an independent study is required of a greater size, which should include large, longitudinal, population-based cohorts to test the accuracy of this panel of biomarkers. Such a study would be able to address potential confounding factors of the data reported in this study including site-specific effects and representativeness of the cohorts. In conclusion, the findings of the present study reveals that reduced serum levels of lipids (Total cholesterol and HDL-C), lipoproteins (apolipoprotein A1) and thyroid dysfunction (Total T4) may aid in early diagnosis of cognitive impairment in elderly individuals. Therefore, keeping a regular check on these biomarker levels from the age of 45 will be helpful in reducing the risk or delaying the onset of developing dementia.

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