Asian Journal of Clinical Nutrition

ISSN 1992-1470

science alert

ANSInet
an open access publisher
http://ansinet.com

OPEN ACCESS Asian Journal of Clinical Nutrition

ISSN 1992-1470
DOI: 10.3923/ajcn.2017.17.23

Research Article
High Sensitivity C-reactive Protein may be used as a Marker for Cognitive Impairment in Obese Egyptian Middle Age Females

Yusr M.I. Kazem, Salwa M. El Shebini, Maha I.A. Moaty, Suzanne Fouad, Nihad H. Ahmed and Salwa T. Tapozada

Department of Nutrition and Food Science, National Research Centre, Cairo, Egypt

Abstract

Background: Peripheral inflammatory markers are elevated in obese patients. Controlling inflammation and reducing inflammatory markers by diet and losing weight may help to slow down the cognitive dysfunction accompanying the aging process. **Objective:** We examined whether high sensitivity C-reactive protein hs.CRP level in midlife is correlated to cognition and subsequent cognitive functions improvement with diet modification and weight loss. **Methodology:** Ninety one obese volunteer women participated in this study which lasted for 8 weeks. The patients were to follow balanced low caloric diet (900-1000 cal day^{-1}) with 8 servings of fresh vegetables and fruits. The patients mean age was 48.23±5.32 years and had a mean Body Mass Index (BMI) of 36.75±2.89 kg m^{-2}. Evaluations were made at base line and 8 weeks later. This included: Quantitative determination of hs.CRP, cognitive and mental evaluation (MMSE), clinical examination and anthropometric measurements. Fasting blood glucose (FBG), serum lipid profile and C-peptide were assessed and insulin resistance was calculated. **Results:** After intervention, improvement in cognitive functions were recorded with decrease in hs.CRP serum levels. Significant inverse correlation was found between cognitive functions and hs.CRP levels, insulin resistance, waist circumference and BMI. **Conclusion:** Serum hs.CRP level may be used as a marker for cognitive functions impairment in obese middle age females and could serve as a base for intervention.

Key words: hs.CRP, inflammation, obesity, cognitive functions, insulin resistance, diet, midlife, women

Received: August 25, 2016 Accepted: November 03, 2016 Published: December 15, 2016

Citation: Yusr M.I. Kazem, Salwa M. El Shebini, Maha I.A. Moaty, Suzanne Fouad, Nihad H. Ahmed and Salwa T. Tapozada, 2017. High sensitivity C-reactive protein may be used as a marker for cognitive impairment in obese Egyptian middle age females. Asian J. Clin. Nutr., 9: 17-23.

Corresponding Author: Yusr M.I. Kazem, Department of Nutrition and Food Science, National Research Centre, Cairo, Egypt

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Several studies have proved that obesity is an important risk factor for cognitive impairment. Dementia and obesity frequently coexist; they share many common pathways such as inflammation, oxidative stress and insulin resistance[1-3].

Inflammation is a common factor between obesity and impaired cognitive functions. Systemic inflammation has been demonstrated in both obesity and dementia suggesting a possible interaction between them[4,5].

Adipose tissue is considered as an active endocrine organ, it produces bioactive mediators (adipokines) that affects lipid and glucose-metabolism. The CRP elevations are correlated with obesity in general and abdominal obesity in particular[6,7].

As an important source for proinflammatory cytokines such as interleukin-6, the main stimulator of the production of C-reactive protein in the liver, adipose tissue plays a major role in regulating inflammation, coagulation and fibrinolysis[8].

C-reactive protein (CRP) is an acute phase reactant, it is produced by the liver in response to inflammation within the body. Chronic low-grade state of inflammation and CRP levels are often elevated in obese men and women[9,10].

Systemic inflammatory markers, such as CRP have been reported to be elevated when cognitive performance scores are low[11]. In general CRP levels are higher in females, possibly mediated by estrogen as most studies have found. It is a possibility that higher CRP levels in women is a reflection to sex-related differences in the inflammatory response to obesity[12].

In patients with cognitive impairment, inflammatory markers, including acute-phase inflammatory reactants and proinflammatory cytokines have been found in the cerebrospinal fluid CSF and β-amyloid plaques. Inflammation is a feature of dementia; amyloid deposition stimulates neuroinflammatory processes with neurotoxic effects that increase neuronal damage. Some studies reported elevations in circulating levels of inflammatory markers before clinical onset of dementia. Some studies reported that elevation of CRP predicts dementia[13,14].

In addition, obesity is accompanied by insulin resistance, lipid profile dysfunction, namely elevated triglycerides and reduced High Density Lipoprotein (HDL) which may also be of interest to search their relation with CRP levels. In several studies females showed higher levels of HDL, with inverse associations between HDL and CRP[15,16].

In obesity, the increased production of acute-phase proteins and cytokines CRP, interleukin-6 and tumor necrosis factor-α), may enhance the development of behavioral symptoms, including cognitive decline, sleep disorders and depressive symptoms. Inflammation is suggested to contribute to cognitive decline and dementia. Many studies reported the ability of cytokines to affect cerebral functions and trigger the development of behavioral alterations[17-20].

The aim of this study is to study the relation between serum hs.CRP level and cognitive functions among a group of obese middle age Egyptian females and studying the effect of following a sliming balanced low caloric diet rich in fresh fruits and vegetables on these variables, raising the issue of whether hs.CRP as an inflammatory marker may be used as a marker of cognitive decline among obese women in their midlife.

MATERIALS AND METHODS

Subjects: Ninety one obese women participated as volunteers in this study which lasted for 8 weeks. The patient were to follow a balanced low caloric diet (900-1000 cal day^{-1}, with 8 servings of fresh vegetables and fruits). The patients mean age (48.23±5.32 years) and had a mean BMI of (36.75±2.89 kg m^{-2}). Measurements were taken at base line and 8 weeks later.

Exclusion criteria: Out of 140 volunteer, 91 obese women were included in this study. Exclusion criteria were as follows: Inflammatory or other chronic diseases as hypertension, diabetes mellitus, cardiovascular or cerebrovascular diseases, liver or endocrine disease. Chronic use of medication, smoking and infection occurring at the time of the examination were additional exclusion criteria.

The study was approved by the institutional ethics committee and all participants had given their informed consent.

Methods: All women were subjected to thorough clinical examination. Relevant anthropometric measurements (body weight, height and minimal waist circumference and body mass index) and blood pressure were reported.

Dietary recalls: Collecting detailed data about nutritional habits and intake through 24 h recall diet history was done. Analysis of food items was done using World Food Dietary Assessment System, (WFDAS), 1995, USA, University of California.

Cognitive and mental evaluation: Mini Mental State Examination (MMSE) was performed for evaluation of mental and cognitive status. The MMSE is the most commonly used test for complaints of memory problems.

It is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document an individual's response to treatment. Administration of the test takes between 5-10 min and examines functions including registration, attention and calculation, recall, language, commands and orientation[21].

Blood collection and laboratory investigations: Six milliliters venous blood was withdrawn from all subjects, after 12 h fasting. The blood was collected on plain tubes and was allowed to clot and the sera were separated for measurements of glucose and lipid profile. Fasting Blood Glucose (FBG) and lipid profile [total cholesterol, triglycerides (TG) and High Density Lipoprotein (HDL)] were assessed in fresh sera by Olympus AU400 clinical chemistry auto analyzer.

The remaining sera were stored at -70°C in aliquot until used for further analysis. Fasting C-peptide level was measured by ELISA method[22] using Monobind Inc. Lake forest, CA 92630, USA.

According to Li *et al.*[23], insulin resistance was expressed by modified homeostasis model assessment-insulin resistance (M.HOMA-IR), where:

$$\text{M.HOMA-IR} = \frac{1.5+\text{FBG (mg dL}^{-1}) \times \text{fasting C-peptide (ng mL}^{-1})}{2{,}800}$$

High-sensitivity C-reactive (hs.CRP) protein was estimated by ELISA kit supplied by DRG® International Inc. (EIA-3954), USA[24].

Statistics: Descriptive results for continuous variables are expressed as Mean±SD. Differences dependent samples t-test and correlations were explored with Pearson's. The reported p-values are two tailed. Significance was defined at the 5% level >0.05. Analysis was performed using SPSS version 10 (SPSS Inc. Chicago, IL).

RESULTS

All our patients were healthy females with mean age (48.23±5.32 years).

Table 1 showed that significant improvement is seen in cognitive functions, accompanied by reduction in BMI, hs.CRP levels, MWC and triglycerides level. Also, insulin resistance and fasting blood glucose were significantly reduced, while HDL levels were increased.

Table 2 showed the total caloric intake and the percent of calories delivered from protein, fat and total carbohydrate (CHO) ingested by the obese patients, before and after intervention. Total caloric intake of the habitual diet was higher than the total calories of the ingested regimen. The percent of calories delivered from fat in the habitual diet was higher compared to that delivered from the regimen, while the opposite values were observed as regard protein and total CHO percent.

Table 3 showed that at base line significant inverse correlation was found between cognitive functions and hs.CRP levels, insulin resistance, MWC and BMI and direct correlation with HDL level, while no significant correlation with triglycerides level.

Significant direct correlation was found between hs.CRP level and BMI, MWC and insulin resistance and significant inverse correlation with HDL level. No significant correlation was found with triglycerides.

Table 4 showed that after following the interventional diet for 8 weeks significant inverse correlation was found between cognitive functions and hs.CRP levels, insulin resistance, MWC and BMI and direct correlation with HDL level, while no significant correlation with triglycerides level.

Significant direct correlation was found between hs.CRP level and BMI, MWC and insulin resistance and significant

Table 1: Data represented as Mean±SD of the obese patients at base line and after intervention

	Mean±SD (No. = 91)		
Variables	Base line	After intervention	p-value
BMI (kg m^{-2})	36.75±2.89	35.55±2.58)	<0.01
MWC (cm)	98.50±8.23	88.11±9.15	<0.001
Triglycerides (mg dL^{-1})	99.58±12.14	83.16±13.11	<0.001
HDL-C (mg dL^{-1})	43.80±4.12	50.64±3.81	<0.001
Fasting blood sugar (mg dL^{-1})	96.79±11.46	86.00±12.31	<0.001
M.HOMA-IR	1.61±0.11	1.55±0.10	<0.01
hs.CRP (mg L^{-1})	7.31±1.72	5.56±1.52	<0.01
MMSE	27.31 = 2.1	29.10 = 2.4	<0.01

p-value is significant in all included variables, BMI: Body mass index, MWC: Minimal waist circumference, HDL-C: High density lipoprotein-cholesterol, M. HOMA-IR: Modified homeostatic model assessment of insulin resistance, hs.CRP: High sensitivity C-reactive protein, MMSE: Mini mental state examination

Table 2: Percent of calories delivered from protein, fat and total carbohydrate (CHO) campared to total calories, before and after intervention

	Habitual diet		Hypo-caloric regimen	
Nutrient	Mean±SD	Total calories (%)	Mean±SD	Total calories (%)
Energy (kcal)	2717.53±235.01		902.65±23.10	
Fat (g)	123.57±37.08	40.92	27.61±11.02	27.53
Protein (g)	91.23±27.30	13.43	52.64±10.23	23.33
Total CHO (g)	310.12±60.96	45.65	110.90±14.35	49.14

Table 3: Pearson correlation between different variables at base line

Variables	MMSE	hs.CRP (mg L^{-1})	M.HOMA-IR	MWC (cm)	BMI (kg m^{-2})	Triglycerides (mg dL^{-1})	HDL (mg dL^{-1})
MMSE	--	-0.688**	-0.703**	-530**	-0.521**	NS	0.372*
hs.CRP (mg L^{-1})	-0.688**	--	0.589**	0.421*	0.367*	NS	-0.321*
M.HOMA-IR	-0.703**	0.589**	--	0.483**	0.369*	NS	-0.345*
MWC (cm)	-0.530**	0.421*	0.483**	--	0.788**	NS	-0.388*
BMI (kg m^{-2})	-0.521**	367*	0.369*	0.788**	--	NS	-0.341*
Triglycerides (mg dL^{-1})	NS	NS	NS	NS	NS	--	-0.332*
HDL (mg dL^{-1})	0.372*	-0.321*	-0.345*	-0.388*	-0.341*	-0.332*	--

Numbers presented are the value of r = correlation coefficient, BMI: Body mass index, MWC: Minimal waist circumference, HDL-C: High density lipoprotein-cholesterol, M.HOMA-IR: Modified homeostatic model assessment of insulin resistance, hs.CRP: High sensitivity C-reactive protein, MMSE: Mini mental state examination

Table 4: Pearson correlation between different variables after intervention

Variables	MMSE	hs.CRP (mg L^{-1})	M.HOMA-IR	MWC (cm)	BMI (kg m^{-2})	Triglycerides (mg dL^{-1})	HDL (mg dL^{-1})
MMSE	--	-0.718**	-0.764**	-549**	-0.561**	NS	0.380*
hs.CRP (mg L^{-1})	-0.718**	--	0.591**	0.430*	0.381*	NS	-0.332*
M.HOMA-IR	-0.764**	0.601**	--	0.502**	0.419*	NS	-0.361*
MWC (cm)	-0.549**	0.430*	0.502**	--	0.811**	NS	-0.398*
BMI (kg m^{-2})	-0.561**	0.381*	0.419*	0.811**	.--	NS	-0.346*
Triglycerides (mg dL^{-1})	NS	NS	NS	NS	NS	--	0.344*
HDL (mg dL^{-1})	0.380*	-0.332*	-0.361*	-0.398*	-0.346*	-0.344*	--

BMI: Body mass index, MWC: Minimal waist circumference, HDL-C: High density lipoprotein-cholesterol, M.HOMA-IR: Modified homeostatic model assessment of insulin resistance, hs.CRP: High sensitivity C-reactive protein, MMSE: Mini mental state examination, Numbers presented are the value of r = correlation coefficient, *Correlation is significant at the 0.05 level, **Correlation is significant at the 0.001 level

inverse correlation with HDL level. No significant correlation was found with triglycerides.

It is important to mention that previous studies compared high-sensitivity C-reactive protein (hs-CRP) and CRP. A significant correlation was noted between hs.CRP and CRP levels ($r = 0.98$, $p<0.001$). The slope was near one. The CRP standard estimation is a reasonable alternative to the hs-CRP[25]. But the reason we used hs.CRP is that CRP is a biomarker of any acute inflammation. Accordingly plasma CRP concentrations increase rapidly and dramatically as a reaction to any tissue inflammation or trauma. High-sensitivity CRP (hs.CRP) is more specific than standard CRP when measuring normal baseline concentrations and enables to measure chronic inflammation, this was reported by Mayo clinic medical laboratories.

The reference range for C-reactive protein and high-sensitivity C-reactive protein are as follows:

- CRP: 0-10 mg dL^{-1}
- hs.CRP: <3 mg L^{-1}

DISCUSSION

The principle result of our study suggested that the inflammatory marker hs.CRP is correlated with cognitive functions in obese women, a significant inverse correlation was found between the values of Mini Mental State Examination (MMSE) for cognition evaluation and levels of hs.CRP both before and after intervention. It has been reported in some studies that obesity is accompanied by low-grade systemic inflammation in women and men. Previous studies support our results[16,26].

The link between systemic inflammation and dementia was suggested after discovery of increased inflammatory processes in localized areas of post-mortem brain specimens of patients suffering from Alzheimer's disease (AD). Later, research has found significant association between dementia and markers of systemic inflammation[27,28].

In addition, in humans, systemic inflammation has been observed to increase with age in relevance to cognitive ageing and this is called 'Inflammaging'. This age-related finding includes a decrease in adaptive immune mechanisms and up-regulation of the innate immune system. In addition to low-grade chronic inflammatory response. This finding has been supported by studies on cognitively normal community-dwelling populations, which evaluate the effect of systemic inflammation on cognitive function. High levels of CRP have been repeatedly associated with poor cognitive performance in older cohorts. Other studies have suggested a reverse attitude, that it is the cognitive functions that predicts the degree of inflammation, meaning that cognitive impairment in childhood or early adulthood predicts increased systemic inflammation later in life. Inflammation is likely to play a role mediated by its effect on cerebral small-vessel pathology which has a direct impact on cognitive functions later in life[29-31].

A study reported that brains of patients with cognitive impairment show activated inflammatory factors, microglia

and high circulating inflammatory markers. In the Honolulu Aging Study CRP was measured 25 years prior to the assessment of cognitive impairment. Patients with higher levels of CRP had greater risk of dementia. Obesity, infection, trauma, ischemia or accumulation of lipids can trigger inflammatory responses and elevation in inflammatory markers levels in addition to dementia-related processes. In our case obesity is the trigger of inflammatory status. Meta-analysis of studies searching the relation between CRP and cognition concluded that higher levels of CRP were predictive of cognitive decline. Another study found that higher initial CRP levels in elderly women can predict poorer memory years later[20,32,33].

Inflammatory markers may influence cognitive functions through their prothrombotic effects; they may be involved in atherothrombotic vascular complications and are linked to minor brain infarction[34].

In addition, some studies suggests that CRP may promote atherothrombosis and attenuate nitric oxide formation which decreases angiogenesis. This has important consequences on frontal lobes in particular because they have poor collateral circulation than the rest of the brain. Accordingly they have more susceptibility to microvascular disease resulting in vascular dementia[35,36].

Also in our study, following the low caloric diet rich in fresh fruits and vegetables resulted in significant decrease in the inflammatory marker hs-CR, this was correlated and accompanied with weight loss and reduced waist size, lower BMI, less insulin resistance and increased HDL. No correlation was found between triglycerides and hs.CRP. It is important to mention that this diet was selected to be rich in anti-inflammatory and antioxidants elements and rich in fibers to help reduce inflammatory status and aid weight loss[6].

Several studies supporting our results. Previous studies found positive associations between CRP and waist circumference. A weak but statistically significant negative association was detected between CRP and HDL, but no significant correlation was found between CRP and triglycerides[7,10].

It is known that obesity is associated with a low grade inflammatory status[37]. It is expected to detect an elevation in CRP, as an inflammatory marker in our patients since they are obese subjects. In addition, obesity is accompanied by insulin resistance[38]. Both the elevated CRP level and the increased insulin resistance can explain the cognitive impairment correlation detected in our study.

Our study included only females. Most studies have found that CRP levels are generally higher in females, possibly mediated by estrogen. However, higher CRP levels in women is a result of sex-related differences in the inflammatory response to obesity between women and men[39].

It is known that, in general, HDL levels are higher among females, higher HDL levels may be neuroprotective as reported previously. It is also known that CRP levels are higher in females and among overweight obese individuals. In most studies significant associations between CRP and cognition were only found among obese females not males[40,41].

CONCLUSION AND RECOMMENDATIONS

Among obese women, significant correlation was detected between the high sensitivity C-reactive protein hs.CRP levels and cognitive functions before and after the intervention. Following a balanced low caloric diet high in fresh vegetables and fruits and rich in anti-inflammatory and anti-oxidants elements resulted in significant weight loss and improvement in the cognitive functions coupled with significant reduction in hs.CRP levels. It is proposed that hs.CRP serum level can be used as a marker for cognitive functions in obese middle age females.

We recommend further research to examine the role of weight loss and diet rich in anti-inflammatory elements in controlling inflammatory status and its complication including cognitive functions impairment.

REFERENCES

1. Cournot, M., J.C. Marquie, D. Ansiau, C. Martinaud, H. Fonds, J. Ferrieres and J.B. Ruidavets, 2006. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology, 67: 1208-1214.
2. Gunstad, J., R.H. Paul, R.A. Cohen, D.F. Tate, M.B. Spitznagel and E. Gordon, 2007. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Comprehen. Psychiatry, 48: 57-61.
3. Sweat, V., V. Starr, H. Bruehl, A. Arentoft, A. Tirsi, E. Javier and A. Convit, 2008. C-reactive protein is linked to lower cognitive performance in overweight and obese women. Inflammation, 31: 198-207.
4. Lasselin, J. and L. Capuron, 2014. Chronic low-grade inflammation in metabolic disorders: relevance for behavioral symptoms. Neuroimmunomodulation, 21: 95-101.
5. Warnberg, J., S. Gomez-Martinez, J. Romeo, L.E. Diaz and A. Marcos, 2009. Nutrition, inflammation and cognitive function. Ann. NY. Acad. Sci., 1153: 164-175.
6. El Shebini, S.M., M.I.A. Moaty, N.H. Ahmed, M.S. Mohamed, Y.M.I. Kazem, S.T. Tapozada and L.M. Hanna, 2015. Association of nuts and whole grains intake, inflammation and the metabolic syndrome. Res. J. Med. Med. Sci., 8: 55-63.

7. Rexrode, K.M., A. Pradhan, J.E. Manson, J.E. Buring and P.M. Ridker, 2003. Relationship of total and abdominal adiposity with CRP and IL-6 in women. Ann. Epidemiol., 13: 674-682.
8. Galic, S., J.S. Oakhill and G.R. Steinberg, 2010. Adipose tissue as an endocrine organ. Mol. Cell. Endocrinol., 316: 129-139.
9. Wasir, J.S., A. Misra, N.K. Vikram, R.M. Pandey and K. Luthra, 2007. C-reactive protein, obesity and insulin resistance in postmenopausal women in urban slums of North India. Diabetes Metabol. Syndrome: Clin. Res. Rev., 1: 83-89.
10. Lee, W.Y., J.S. Park, S.Y. Noh, E.J. Rhee and K.C. Sung *et al*., 2004. C-reactive protein concentrations are related to insulin resistance and metabolic syndrome as defined by the ATP III report. Int. J. Cardiol., 97: 101-106.
11. Noble, J.M., J.J. Manly, N. Schupf, M.X. Tang, R. Mayeux and J.A. Luchsinger, 2010. Association of C-reactive protein with cognitive impairment. Arch. Neurol., 67: 87-92.
12. Thorand, B., J. Baumert, A. Doring, C. Herder and H. Kolb *et al*., 2006. Sex differences in the relation of body composition to markers of inflammation. Atherosclerosis, 184: 216-224.
13. Sundelof, J., L. Kilander, J. Helmersson, A. Larsson and E. Ronnemaa *et al*., 2009. Systemic inflammation and the risk of Alzheimer's disease and dementia: A prospective population-based study. J. Alzheimer's Dis., 18: 79-87.
14. Komulainen, P., T.A. Lakka, M. Kivipelto, M. Hassinen and I.M. Penttila *et al*., 2007. Serum high sensitivity C-reactive protein and cognitive function in elderly women. Age Ageing, 36: 443-448.
15. Chen, J.M., G.H. Cui, G.X. Jiang, R.F. Xu and H.D. Tang *et al*., 2014. Cognitive impairment among elderly individuals in Shanghai suburb, China: Association of c-reactive protein and its interactions with other relevant factors. Am. J. Alzheimer's Dis. Other Dementias, 29: 712-717.
16. Weuve, J., P.M. Ridker, N.R. Cook, J.E. Buring and F. Grodstein, 2006. High-sensitivity C-reactive protein and cognitive function in older women. Epidemiology, 17: 183-189.
17. Kuo, H.K., C.J. Yen, C.H. Chang, C.K. Kuo, J.H. Chen and F. Sorond, 2005. Relation of C-reactive protein to stroke, cognitive disorders and depression in the general population: Systematic review and meta-analysis. Lancet Neurol., 4: 371-380.
18. Motta, M., R. Imbesi, M. Di Rosa, F. Stivala and L. Malaguarnera, 2007. Altered plasma cytokine levels in Alzheimer's disease: Correlation with the disease progression. Immunol. Lett., 114: 46-51.
19. Schram, M.T., S.M. Euser, A.J.M. de Craen, J.C. Witteman and M. Frolich *et al*., 2007. Systemic markers of inflammation and cognitive decline in old age. J. Am. Geriatr. Soc., 55: 708-716.
20. Trollor, J.N., E. Smith, E. Agars, S.A. Kuan and B.T. Baune *et al*., 2012. The association between systemic inflammation and cognitive performance in the elderly: The Sydney memory and ageing study. AGE, 34: 1295-1308.
21. Folstein, M.F., S.E. Folstein and P.R. Mc Hugh, 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res., 12: 189-198.
22. Ashley, J.P. and B.M. Frier, 1981. Circulating C-peptide: Measurement and clinical application. Ann. Clin. Biochem., 18: 125-130.
23. Li, X., Z.G. Zhou, H.Y. Qi, X.Y. Chen and G. Huang, 2004. [Replacement of insulin by fasting C-peptide in modified homeostasis model assessment to evaluate insulin resistance and islet beta cell function]. J. Cent. South Univ. Med. Sci., 29: 419-423, (In Chinese).
24. Roberts, W.L., R. Sedrick, L. Moulton, A. Spencer and N. Rifai, 2000. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Clin. Chem., 46: 461-468.
25. Helal, I., L. Zerelli, M. Krid, F. ElYounsi and H.B. Maiz *et al*., 2012. Comparison of C-reactive protein and high-sensitivity C-reactive protein levels in patients on hemodialysis. Saudi J. Kidney Dis. Transplant., 23: 477-483.
26. Lee, H., I.S. Lee and R. Choue, 2013. Obesity, inflammation and diet. Pediatr. Gastroenterol. Hepatol. Nutr., 16: 143-152.
27. Satizabal, C.L., Y.C. Zhu, B. Mazoyer, C. Dufouil and C. Tzourio, 2012. Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-dijon study. Neurology, 78: 720-727.
28. Schmidt, R., H. Schmidt, J.D. Curb, K. Masaki, L.R. White and L.J. Launer, 2002. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia aging study. Ann. Neurol., 52: 168-174.
29. Giunta, B., F. Fernandez, W.V. Nikolic, D. Obregon, E. Rrapo, T. Town and J. Tan, 2008. Inflammaging as a prodrome to Alzheimer's disease. J. Neuroinflammation, Vol. 5. 10.1186/1742-2094-5-51.
30. Singh-Manoux, A., A. Dugravot, E. Brunner, M. Kumari, M. Shipley, A. Elbaz and M. Kivimaki, 2014. Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife. Neurology, 83: 486-493.
31. Van Dijk, E.J., N.D. Prins, S.E. Vermeer, H.A. Vrooman, A. Hofman, P.J. Koudstaal and M.M.B. Breteler, 2005. C-reactive protein and cerebral small-vessel disease: The Rotterdam scan study. Circulation, 112: 900-905.
32. Choi, A.J.S. and S.W. Ryter, 2014. Inflammasomes: Molecular regulation and implications for metabolic and cognitive diseases. Mol. Cells, 37: 441-448.
33. Tan, Z.S., A.S. Beiser, R.S. Vasan, R. Roubenoff and C. A. Dinarello *et al*., 2007. Inflammatory markers and the risk of Alzheimer disease: The framingham study. Neurology, 68: 1902-1908.
34. Hoshi, T., K. Kitagawa, H. Yamagami, S. Furukado, H. Hougaku and M. Hori, 2005. Relations of serum high-sensitivity C-reactive protein and interleukin-6 levels with silent brain infarction. Stroke, 36: 768-772.

35. Paganelli, R., A. Di Iorio, L. Patricelli, F. Ripani and E. Sparvieri *et al*., 2002. Proinflammatory cytokines in sera of elderly patients with dementia: Levels in vascular injury are higher than those of mild-moderate Alzheimer's disease patients. Exp. Gerontol., 37: 257-263.
36. Verma, S., C.H. Wang, S.H. Li, A.S. Dumont and P.W. Fedak *et al*., 2002. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation, 106: 913-919.
37. Marchesi, V.T., 2011. Alzheimer's dementia begins as a disease of small blood vessels, damaged by oxidative-induced inflammation and dysregulated amyloid metabolism: Implications for early detection and therapy. FASEB J., 25: 5-13.
38. Kazem, Y.M.I., M.I.A. Moaty, N.H.A. El-Arabi and S.M. El Shebini, 2011. The relation between insulin resistance and cognitive functions among a group of healthy obese Egyptian females. Int. J. Acad. Res., 3: 575-579.
39. Gorelick, P.B., 2010. Role of inflammation in cognitive impairment: Results of observational epidemiological studies and clinical trials. Ann. N. Y. Acad. Sci., 1207: 155-162.
40. Petelin, A., M. Bizjak, M. Cernelic-Bizjak, M. Jurdana, T. Jakus and Z. Jenko-Praznikar, 2014. Low-grade inflammation in overweight and obese adults is affected by weight loss program. J. Endocrinol. Invest., 37: 745-755.
41. Phillips, A.C., G.D. Batty, J.J.C.S.V. van Zanten, L.H. Mortensen, I.J. Deary, C.M. Calvin and D. Carroll, 2011. Cognitive ability in early adulthood is associated with systemic inflammation in middle age: The Vietnam experience study. Brain Behav. Immunity, 25: 298-301.