ORIGINAL ARTICLE

Arch AHS

Archives of Allied Health Sciences 2021; 33(2): 19-27.

Cognitive function and arterial stiffness in overweight and obese diabetes compared with non-obese diabetes individuals

Nantinee Nualnim[1*], Tititip Ariyasoponwong[1], Kanokporn Pakdeesang[1]

[1] Faculty of Physical Therapy, Mahidol University, Nakhon Pathom, Thailand.

KEYWORDS
Obesity;
Type 2 diabetes;
Arterial stiffness;
Cognitive function.

ABSTRACT

Arterial stiffness is commonly observed in type 2 diabetes (T2DM) patients and may explain the cognitive dysfunction. Obesity is associated with T2DM; however, the additive effects of overweight and obesity on cognitive function and arterial stiffness have not been investigated. The aim of this study was to determine whether the concomitance of obesity and T2DM cause a further impairment of arterial stiffness and cognitive function. Arterial stiffness and cognitive function were measured in sedentary healthy subjects, T2DM with normal body mass index and T2DM with obesity patients. Carotid- femoral pulse wave velocity (cfPWV) and brachial ankle PWV (baPWV), measures of central arterial stiffness, were higher (p-value < 0.05) in diabetes with obesity and diabetic patients than in sedentary controls. There was no difference in central and peripheral arterial stiffness between normal weight and obese T2DM groups. The Montreal Cognitive Assessment (MOCA) score was higher (p-value < 0.05) in diabetes with obesity than in diabetic patients and sedentary controls. In conclusion, diabetes with obesity showed the cognitive function higher than diabetic patient with normal weight. The level of arterial stiffness was not related to cognitive function in diabetic with obesity patients.

* **Corresponding author:** Nantinee Nualnim, PhD. Faculty of Physical Therapy, Mahidol University, 999 Phuttamonthon 4 RD., Salaya, Phuttamonthon, Nakhon Pathom, 73170, Thailand. E-mail: nantinee.nua@mahidol.edu
Received: 27 January 2021/ Revised: 4 April 2021/ Accepted: 30 April 2021

Introduction

Type 2 diabetes mellitus (T2DM) is one of the cardiovascular disease risks. Because of the high prevalence, diabetes is certain to be the most challenging health problem worldwide in the 21st century. The strong evidence revealed the epidemiological association between T2DM and obesity. Obesity amplifies the risk of cardiovascular disease (CVD) in T2DM because of poorer glycemic control, blood pressure, and lipid profiles[1].

In light of high numbers of elderly population, the burden of cognitive dysfunction becomes increasingly for health care resources. Cardiovascular risk factors are important predictors of cognitive decline and dementia. Cognitive dysfunction is an important complication of T2DM. Compared to the general population, people with diabetes have a 1.5 fold greater risk of cognitive decline and a 1.6 fold greater risk of future dementia[2]. Obesity is also associated with a cognitive dysfunction[3]. Moreover, many studies indicate obesity during midlife increases the risk of dementias such as Alzheimer's disease later in life[4,5]. The possible mechanisms that obesity might be impacting cognitive function are early changes in neuro-chemical composition related to neuro-inflammation[6]. Previous studies reported that higher plasma levels of interleukin (IL)-12 and 6 are linked to reduced speed in processing information and a faster rate of cognitive decline[7,8].

Although evidence suggests the relationship between obesity and T2DM, an additive effect of obesity on type 2 diabetes on cognitive impairment has not been investigated. This is critical because obesity is a modifiable risk factor for DM. As an initial step to address the association between a number of cardiovascular risk factors and cognitive function, we performed a cross-sectional study involving middle-aged lean diabetes, diabetes with obesity and healthy sedentary individuals.

The mechanisms underpinning diabetes and obesity with cognitive impairment have been the subject of debate, but may include vascular degenerative process. It has been reported that individuals with either diabetes[9,10] or obesity[11,12] have an increase in stiffness of central elastic arteries. Although the associations between diabetes and arterial stiffness, and obesity and arterial stiffness have been explored in previous studies, the degree to which obesity mediates the association between diabetes and arterial stiffness has not been determined.

Moreover, evidence showed that central elastic arterial stiffness is associated with brain aging and cognitive decline[13,14]. Indeed, obese diabetes patients may be prone to have higher level of central arterial stiffness than lean diabetes; it is plausible to speculate that arterial stiffness mediated an association between cognitive function and number of cardiovascular disease risk factors.

To the best of our knowledge, the contribution of arterial stiffness to the mechanisms of cognitive impairment observed in obese type 2 DM patients has not been published. Thus, the overall goal of this study was to investigate whether arterial stiffness and cognitive function in diabetes with obesity are different from those with normal body mass index (BMI) diabetes and age-matched healthy participants.

Materials and methods

Subjects

We studied 22 sedentary healthy, 20 diabetes with normal BMI and 18 diabetes with obese subjects (age range 40-65 years). All of the diabetes subjects were diagnosed of type 2 diabetes according to the American Diabetes Association Guidelines[15], or current treatment with glucose lowering drugs. Diabetes with obesity had BMI ≥ 25 kg/m^2. Exclusion criteria include smoking, documented coronary and cerebrovascular disease, chronic kidney disease, current insulin therapy, non-cardiovascular medications interfering with vascular function including hormonal therapy, steroidal and non-steroidal anti-inflammatory drugs and resting systolic blood pressure greater than 160 mmHg and/or resting diastolic blood pressure greater than 110 mmHg. Control subjects were healthy, non-smoking, non-obese, and free of overt cardiovascular disease or diabetes assessed by screening health

questionnaire, blood pressure measurement and blood chemistry. All subjects gave written informed consent for their participation in the study which was approved by the Mahidol University Ethics Committee.

Before they were tested, subjects had abstained from food, alcohol, and caffeine for at least 4 hours (overnight 12-hour fast for metabolic risk factors). Premenopausal women were tested during the early follicular phase of the menstrual cycle. Each participant rested supine for 15 min in a quiet dimly lit, temperature-controlled laboratory room (24 ± 2 °C).

Anthropometric measurements

Body weight was determined on two occasions using an electronic scale, with the subject wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Diabetic participants who have a value higher of 25 kg/m^2 would be considered overweight and obesity. Waist circumference was measured as following: the upper border of the iliac crests will be located, and the tape would be wrapped around above this point, ensuring that it was adjusted without compressing the skin.

Pulse wave velocity (PWV) measurement

Heart rate (HR), blood pressure (BP), and pulse wave velocity (PWV) were measured by the automatic vascular screening device (VP-1000; Colin Corp. CO., Ltd, Komaki, Japan). Subjects were instructed to rest quietly for 10 minutes in the supine position. Applanation tonometry was used to detect pressure waveforms. Heart rate, bilateral brachial and ankle blood pressures, carotid and femoral pulse waves were measured. Central and peripheral PWV were automatically calculated as the ratio of the surfaced distance between the two recording sites and wave transit time[16]. Ankle brachial index (ABI) was calculated by the ratio of the ankle systolic pressure and brachial systolic pressure. The measurement was repeated three times at 2 min intervals. Average HR, BP, PWV and ABI were calculated and used for data analyses.

Cognitive testing

Mild cognitive impairment (MCI) was assessed using the Montreal Cognitive Assessment (MOCA) which is a paper-and-pencil format test. Scores range from 0 to 30. An initial validation study concluded that score below 25 is likely to indicate MCI. Previous study reported that the sensitivity and specificity of MOCA were 67% and 93% respectively in the T2DM with mean age of 59.9 ± 7.1 years[17].

Blood chemistry

Blood samples were obtained from an antecubital vein after an overnight fast at local diabetes outpatient clinic. Metabolic risk factors for cardiovascular disease including glucose, cholesterol, and triglycerides were analyzed from plasma samples.

Statistical analyses

Diabetic, diabetic with obesity patients and age-matched sedentary controls were compared using one-way ANOVA. Pearson correlation coefficients were used to examine the association between arterial stiffness, cognitive function and cardiovascular risk factors. A significance level of p-value < 0.05 was used to determine statistical significance.

Results

As presented in Table 1, there were no group differences in age and height. BMI and waist circumference were higher *(p*-value < 0.05*)* in diabetes with obesity group than in sedentary controls and diabetic patients. Sedentary control had significantly lower fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol and triglyceride concentrations than diabetes with obesity. Total cholesterol concentrations were significant higher in diabetic patients than in sedentary controls.

There was no significant difference among groups in heart rate at rest. Brachial systolic blood pressure, mean blood pressure, diastolic blood pressure and pulse pressure were higher *(p*-value < 0.05*)* in diabetes with obesity and diabetic patients than in sedentary controls.

Table 1 Selected subject characteristics

Variable	Sedentary (n = 22)	Diabetes (n = 20)	Diabetes with obesity (n = 18)
Men / women	2 / 20	3 / 17	4 / 14
Age (years)	54 ± 7	57 ± 7	54 ± 6
Height (cm)	157 ± 6	154 ± 8	160 ± 7
Body mass (kg)	53.6 ± 6.6	56.4 ± 7.2	77.2 ± 14.5 * ϒ
Body mass index (kg/m^2)	21.7 ± 2.4	23.3 ± 1.5	29.7 ± 4.3 * ϒ
Waist circumference (cm)	74 ± 5	79 ± 6	96 ± 8 * ϒ
Plasma glucose (mg/dl)	89 ± 12	131 ± 29*	136 ± 30 * ϒ
Total cholesterol (mg/dl)	193 ± 29	214 ± 32	243 ± 25 *
Low-density lipoprotein cholesterol (mg/dl)	132 ± 48	145 ± 30	152 ± 35 *
High-density lipoprotein cholesterol (mg/dl)	47 ± 5	44 ± 8	45 ± 8
Triglyceride (mg/dl)	155 ± 72	147 ± 56	167 ± 67 * ϒ
Heart rate (beats/min)	60 ± 2	60 ± 3	68 ± 2
Systolic blood pressure (mmHg)	118 ± 9	136 ± 11*	135 ± 11*
Mean blood pressure (mmHg)	92 ± 10	104 ± 6*	107 ± 14*
Diastolic blood pressure (mmHg)	71 ± 11	81 ± 6*	87 ± 9*
Pulse pressure (mmHg)	45 ± 8	56 ± 10*	57 ± 12*

Note: Values are means ± SD. * *p*-value < 0.05 versus sedentary, ϒ *p*-value < 0.05 versus diabetes.

Central artery stiffness measured by carotid-femoral pulse wave velocity and brachial-ankle pulse wave velocity was higher (*p*-value < 0.05) in diabetes with obesity and diabetic patients than in sedentary controls (Table 2). Carotid-femoral pulse wave velocity and brachial-ankle pulse wave velocity of diabetes with obesity tended to be higher than in diabetic patients but this did not achieve statistical significance (*p*-value = 0.08 and *p*-value = 0.07 respectively).

Unlike measurements of central artery stiffness, measurements of peripheral artery stiffness, femoral-ankle pulse wave velocity, were not different among 3 groups. Ankle brachial index, screening variable for peripheral arterial disease, was higher (*p*-value < 0.05) in diabetes with obesity than in diabetic patients and sedentary controls.

Table 2 Pulse wave velocity (PWV) and ankle brachial index (ABI)

Variable	Sedentary (n = 22)	Diabetes (n = 20)	Diabetes with obesity (n = 18)
Carotid-femoral PWV (cm/sec)	825 ± 124	1012 ± 90*	1083 ± 105*
Brachial-ankle PWV (cm/sec)	1329 ± 112	1692 ± 77*	1760 ± 109*
Femoral-ankle PWV (cm/sec)	1083 ± 137	1157 ± 171	1162 ± 105
Ankle-brachial index	1.08 ± 0.07	1.13 ± 0.08	1.18 ± 0.06*

Note: Values are means ± SD. *p-value < *0.05* versus sedentary. PWV, pulse wave velocity. Cognitive function measured by Montreal Cognitive Assessment (MOCA) score was higher (p-value < *0.05*) in diabetes with obesity than in diabetic patients and sedentary controls (Figure 1).

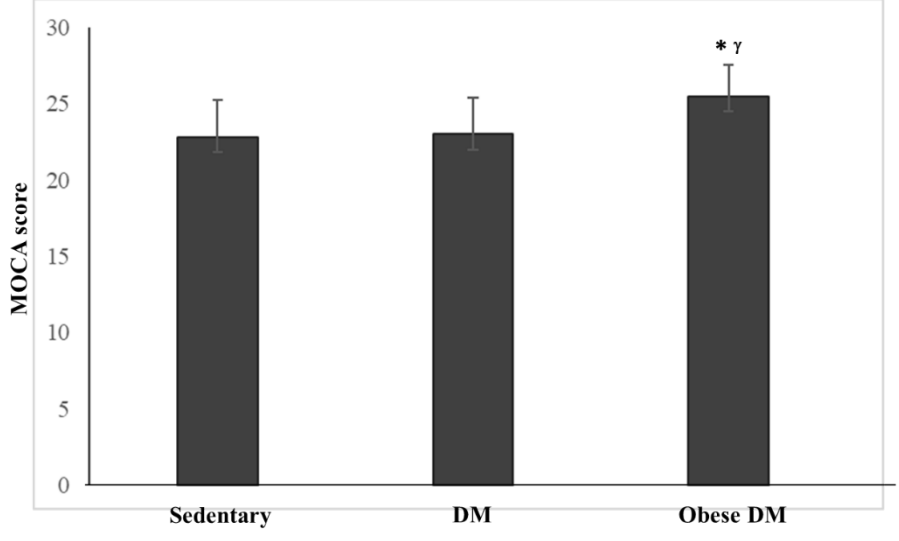

Figure 1 Montreal Cognitive Assessment (MOCA score)
Note: DM, diabetes; Values are means ± SD. *p-value < 0.05 versus sedentary; ᵞp-value < 0.05 versus diabetes.

Brachial-ankle pulse wave velocity (Figure 2) and waist circumference (Figure 3) were positively associated with MOCA score in the pooled population (r = 0.33, p-value < 0.05 and r = 0.35, p-value < 0.05 respectively). However, there were no relationship between BMI and MoCA score.

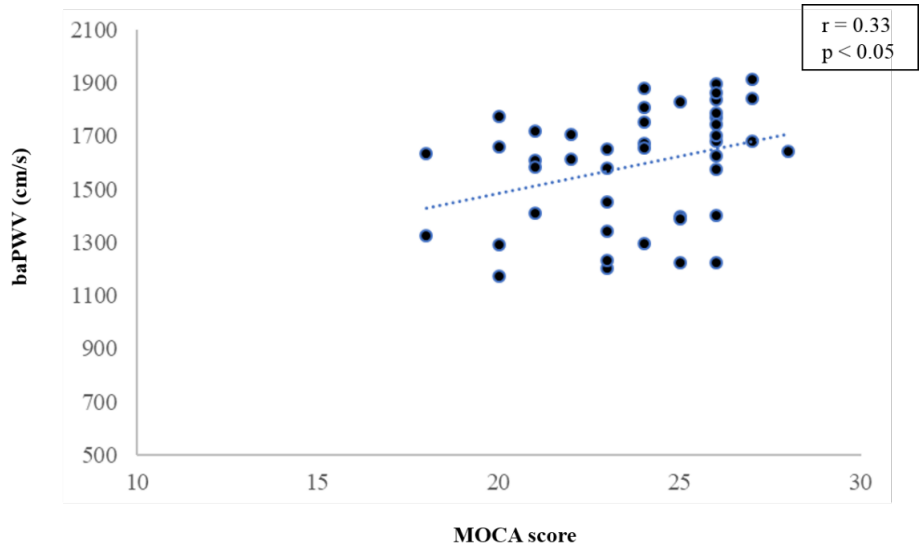

Figure 2 Association between brachial-ankle pulse wave velocity and Montreal Cognitive Assessment (MOCA) score

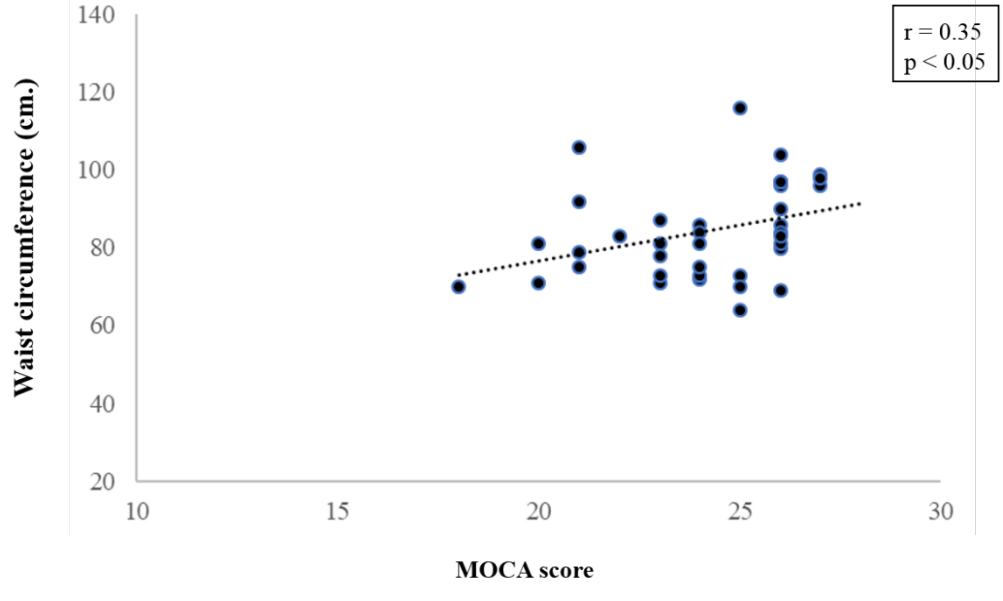

Figure 3 Association between waist circumference and Montreal Cognitive Assessment (MOCA) score

Discussion

This is the first study, to our knowledge, to determine whether diabetes with obesity exhibited higher cognitive function impairment than diabetes with normal weight. We found that diabetes with obesity group had higher MOCA score than diabetes with normal weight. This finding is in contrast with our hypotheses. The obese diabetic patients in our study showed the better cognitive ability than normal weight diabetes.

In the present study, middle-aged diabetic patients showed higher level of central artery stiffness than sedentary controls. This finding is in agreement with previous cross-sectional studies which reported high level of arterial stiffness in diabetic patients[18,19]. We first demonstrated

in the present study that carotid-femoral pulse wave velocity and brachial-ankle pulse wave velocity of diabetes with obesity tended to be higher than in diabetic patients (*p*-value = 0.07). Thus, obesity tended to show the coincidence effects with diabetes on central arterial stiffness level. In contrast with the central arteries, a lack of influence of high blood sugar and high BMI on peripheral arterial stiffness is attributed to the fact that peripheral arteries do not exhibit the same extent of pulsatile changes in diameter compared with central arteries.

It remains unclear why diabetic patients have high risk of cognitive impairment. The possible mechanism is that stiffening of elastic arteries decreases their buffering ability and increases the velocity of the propagating pressure wave which causes facilitation of pulsatile hemodynamic energy into the delicate microcirculation in the brain[20]. Recent evidence showed that elevated arterial stiffness and pulse pressure are associated with lower subcortical perfusion because of increased microvascular resistance[21]. Importantly, cerebral hypo-perfusion which leads to hypoxia is increasingly recognized as elevating the risk of dementia[22,23]. Nevertheless, it should be noted that not all individuals that present with these early cerebral abnormalities progress to dementia. In our study, the higher level of arterial stiffness in diabetic obesity group was not related to the level of cognitive impairment.

Different cardiovascular risk factors including diabetes, hypertension, and obesity were previously reported to convey a similar risk of dementia[24]. Imaging studies also showed similar cerebral changes across vascular risk factors, in particular more accentuated global atrophy and white matter hyperintensities and an increased occurrence of infarcts, although the magnitude of the effects may differ across factors[25]. The most consistent association of cardiovascular risk factors with cognitive decrements is founded for diabetes and hypertension. The previous study reported that higher pulse pressure is an important predictor of MCI[26]. Moreover, the results from previous studies for effects of obesity on cognitive function are less consistent[27].

The present study showed that the obese diabetic patients have better cognitive ability, measured by MOCA score than normal weight diabetes. However, the score differences among 3 group were small. To the best of our knowledge, there were no report about minimal clinical important difference (MCID) of the MOCA score in diabetes. Therefore, the interpretation of our results may be not generalized to other population.

The literature related to the effects of obesity on cognitive function emerged conflicting results. Some authors found the relationship between obesity as a risk of cognitive impairment[3,4]. In contrast, some evidence, which is along with our study, reported that higher body mass index (BMI) was associated with better cognitive performance[28,29]. A population-based study in 500 participants reported that the Mini-mental state examination (MMSE) score was significantly higher and the clock drawing task (CLOX) and Trail Making Test (TMT) Part A performances were better in subjects in the highest BMI (> 29.4 kg/m^2) and higher waist to hip ratio[30]. The possible pathophysiological explanation was that these subjects have greater sympathetic activation. Leptin and norarenalin level, a sympathetic nerve stimulator, is a potential cognitive enhancer[31,32].

The main limitation of our work is the cross-sectional design which did not directly determine the cause-effect relationship of cognitive function and arterial stiffness in obese diabetes patients. Moreover, magnetic resonance imaging of brain assessing white matter lesion burden has not been performed. Another potential limitation is that it was performed in a low-income bracket semi-rural area, and low statistical relationship between outcome variables level, making results not directly generalized to the population in different context.

However, some strengths merit to be emphasized. The participants are younger patients (< 65 years) and less likely to have cognitive impairment due to neurodegenerative disorder. Therefore, the other possible mechanisms of the impairment in cognitive functions in these middle-aged patients should be considered for health prevention issue.

Conclusion

In summary, the middle-aged diabetic patients showed higher level of central artery stiffness than sedentary controls. However, the arterial stiffness did not reach the statistically significant difference between T2DM with normal BMI and obese T2DM. The obese diabetic patients showed the better cognitive level measured by MOCA test than the normal BMI diabetes.

Take home messages

The results of this study showed that obese diabetes patients have higher level of central arterial stiffness than lean diabetes. The arterial stiffness and obesity are modifiable risk factors; therefore, the exercise intervention to improve vascular function and body mass index is critical to prevent vascular dysfunction in diabetes individual. Nevertheless, the population in all groups of our study showed cognitive impairment in their middle-aged. Therefore, the intervention to prevent future dementia should be considered.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We would like to thank the New Researcher Grant, Mahidol University for research funding. We also thank all diabetes and healthy subjects who participate in this study.

References

1. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 2011; 96(6): 1654-63.
2. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia 2005; 48(12): 2460-9.
3. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology 2008; 71(14): 1057-64.
4. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev 2008; 9(3): 204-18.
5. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 2011; 12(5): e426-37.
6. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav Immun 2014; 42: 10-21.
7. Schram MT, Euser SM, de Craen AJ, Witteman JC, Frolich M, Hofman A, et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc 2007; 55(5): 708-16.
8. Marioni RE, Strachan MW, Reynolds RM, Lowe GD, Mitchell RJ, Fowkes FG, et al. Association between raised inflammatory markers and cognitive decline in elderly people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes 2010; 59(3): 710-3.
9. Adeva-Andany MM, Ameneiros-Rodriguez E, Fernandez-Fernandez C, Dominguez-Montero A, Funcasta-Calderon R. Insulin resistance is associated with subclinical vascular disease in humans. World J Diabetes 2019; 10(2): 63-77.
10. Shah AS, El Ghormli L, Gidding SS, Bacha F, Nadeau KJ, Levitt Katz LE, et al. Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors. J Diabetes Complications 2018; 32(8): 740-5.
11. Tison GH, Ndumele CE, Gerstenblith G, Allison MA, Polak JF, Szklo M. Usefulness of baseline obesity to predict development of a high ankle brachial index (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2011; 107(9): 1386-91.

12. Aroor AR, Jia G, Sowers JR. Cellular mechanisms underlying obesity-induced arterial stiffness. Am J Physiol Regul Integr Comp Physiol 2018; 314(3): R387-R98.
13. Zeki Al Hazzouri A, Newman AB, Simonsick E, Sink KM, Sutton Tyrrell K, Watson N, et al. Pulse wave velocity and cognitive decline in elders: the Health, Aging, and Body Composition study. Stroke 2013; 44(2): 388-93.
14. Zeki Al Hazzouri A, Yaffe K. Arterial stiffness and cognitive function in the elderly. J Alzheimers Dis 2014; 42(4): S503-14.
15. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006; 29(1):S43-8.
16. Cortez-Cooper MY, Supak JA, Tanaka H. A new device for automatic measurements of arterial stiffness and ankle-brachial index. Am J Cardiol 2003; 91(12): 1519-22, A9.
17. Alagiakrishnan K, Zhao N, Mereu L, Senior P, Senthilselvan A. Montreal Cognitive Assessment is superior to Standardized Mini-Mental Status Exam in detecting mild cognitive impairment in the middle-aged and elderly patients with type 2 diabetes mellitus. Biomed Res Int 2013; 2013: 186106.
18. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002; 106(16): 2085-90.
19. De Angelis L, Millasseau SC, Smith A, Viberti G, Jones RH, Ritter JM, et al. Sex differences in age-related stiffening of the aorta in subjects with type 2 diabetes. Hypertension 2004; 44(1): 67-71.
20. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol 2008; 105(5): 1652-60.
21. Tarumi T, Shah F, Tanaka H, Haley AP. Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. Am J Hypertens 2011; 24(10): 1108-13.
22. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol 2005; 57(6): 789-94.
23. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1(7): 426-36.
24. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 2008; 585(1): 97-108.
25. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002; 33(1): 21-5.
26. Iadecola C, Gottesman RF. Neurovascular and Cognitive Dysfunction in Hypertension. Circ Res 2019; 124(7): 1025-44.
27. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim Biophys Acta 2009; 1792(5): 470-81.
28. Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. Arch Neurol 2007; 64(3): 392-8.
29. Bryant AN, Ford KL, Kim G. Racial/ethnic variations in the relation between body mass index and cognitive function among older adults. Am J Geriatr Psychiatry 2014; 22(7): 653-60.
30. Tikhonoff V, Casiglia E, Guidotti F, Giordano N, Martini B, Mazza A, et al. Body fat and the cognitive pattern: A population-based study. Obesity (Silver Spring) 2015; 23(7): 1502-10.
31. Harvey J. Leptin regulation of neuronal morphology and hippocampal synaptic function. Front Synaptic Neurosci 2013; 5: 3.
32. Welle S, Campbell R. Effect of overeating on plasma and urinary concentrations of norepinephrine. J Clin Endocrinol Metab 1984; 59(3): 531-4.