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Effect of carotid revascularization on Neural plasticity and cognition in patients with carotid stenosis.

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Abstract

Background: Severe carotid artery stenosis is accompanied by increased risk for cognitive impairment. A member of the neurotrophin family; BDNF is expressed in human and other mammalian brains. It plays an important role in the working memory of the prefrontal cortex. So far, the effect of carotid reperfusion by carotid artery stenting (CAS) and its effect on brain level of BDNF as a biomarker for brain neural palsticity is not studied well. So,this work aimed to analyze the impact of carotid revascularization through CAS on cognition and its effect on neuroplasticity in patients with carotid stenosis 70-99%. **Methods**: Prospective observational study done on 30 stroke patients with significant carotid stenosis (> 70%) underwent carotid stenting. Neurological, radiological and cognitive assessment: Paired Associate Learning (PALT), Benton Visual Retention Test (BVRT) , Paced Auditory Serial Addition Test (PASAT) and measurement of BDNF serum level were done for patients before and one-month post-intervention.**Results**: There was a statistically significant increase in cognitive test before and after carotid stenting mean value for PALT score before was 12.15 ±2.79 and after was 13.9 ± 2.155, The mean value for BVRT score before was 18.46±3.01 and after was 21.133 ± 3.02 , The mean value for PASAT Test score before 46.36 ± 6.58 after was 49.87 ± 2.11 with (P-value < 0.001). There was a statistically insignificant difference in BDNF serum level before and after carotid stenting. There was no effect of either age, gender, hypertension, DM, and IHD on BDNF serum level measured at baseline.**Conclusion**: Treatment of patients with carotid stenosis by stenting causes significant improvement in cognition but no effect on BDNF serum level.

Keywords: Carotid stenting; PALT; BVRT; PASAT, NIHSS; BDNF

Introduction:

Stroke is one of the leading causes of severe long- term disability and is one of the major causes of death in the world. According to official national statistics in Egypt, diseases of the circulatory system, including stroke, are one of the primary causes of death, responsible for one third of all deaths after heart and liver diseases [1] **.**Revascularization carotid endarterectomy (CEA) or carotid artery stenting (CAS) is the treatment of choice in patients with symptomatic carotid stenosis that exceeds 50% in order to reduce the risk of recurrent stroke (NASCET) North American Symptomatic Carotid Endarterectomy Trial Collaborators [2]**.**

Recently, carotid angioplasty and stenting (CAS) has been proposed as a valid alternative to CEA and is considered an option for patients at high risk of complications with endarterectomy. Moreover, CAS has the advantage that it can be done with the patient under mild sedation, requires no incision, carries no risk of cranial nerve palsy, and has fewer cardiovascular complications[3] **.**

Severe CAS is associated with increased risk for cognitive impairment [4], as it represent an indicator or marker for underlying multiple vascular risk factors that predispose patients to cognitive impairment [5] **.** Also, carotid stenosis may be a direct cause of a reduced level of cognitive functioning due to hypoperfusion and microemboli. Thus, reperfusion may improve cognitive impairment[6] **.** Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which is expressed in human and other mammalian brains [7] . It is associated with synaptic plasticity, synaptic connectivity formation and neuronal survival[8]**.**

A number of reports suggested a relationship between BDNF, and the functioning of certain brain areas involved in attention and cognition BDNF plays an important role in the working memory of the prefrontal cortex [9]. Indeed, the effect of carotid reperfusion by CAS and its effect on brain level of BDNF isn't studied yet. This work aimed to analyze the impact of carotid revascularization through CAS on cognition and its effect on serum BDNF as neuroplasticity biomarker in patients with carotid stenosis 70-99%.

Patients and Methods:

This observational study was carried out on 30 stroke patients with significant symptomatic carotid stenosis (stenosis ≥ 70 %) underwent carotid stenting .

Patients were recruited from neurology clinic, Beni-Suef university hospital from August 2019 to June 2021.

A written informed consent was obtained from each participant in this study. The study was ethically approved by Faculty of Medicine, Beni-Suef University Research Ethical Committee (FM-BSU-REC). The ethical approval number was FMBSUREC /16062019/Kamel

All the included patients were subjected to the following:

- History taking regarding: stroke risk factors age, gender, hypertension, diabetes mellitus, previous symptoms of cerebrovascular disease, tobacco smoking, cardiac troubles.
- Clinical assessment including National Institutes of Health Stroke Scale (NIHSS) was performed in one day before and 1 month post –intervention.
- Cognitive assessment**:** one day before and 1-month post-intervention using the following psychometric tests:

1. Paired Associate Learning test (PALT) score representing auditory verbal memory of the patients.

2. Benton Visual Retention Test (BVRT) score that represents visual perceptual, visual memory, visual motor and visuo-constructive abilities of the patients.
3. Paced Auditory Serial Addition (PASAT) Test score that represent assessment of attention and auditory working memory.

- Serum BDNF was measured one day before and 1 month post –intervention using commercial sandwich-ELISA kits **(Human BDNF ELISA Kit , SUNLONG BIOTECH).**
- Radiological assessment including: C.T. or MRI brain to detect the size and site of symptomatic infarction.
- Cardiovascular assessment using echocardiography to assess the presence of valvular disease, ejection fraction, left atrium dilatation and cardiomyopathy.
- Carotid and vertebrobasilar duplex confirmed by CT angiography to detect atherosclerosis or stenosis of the carotid and vertebrobasilar arteries.
- Carotid Revascularization Procedure: All the included patients were subjected to carotid artery stenting (CAS). The protocol for CAS included the following: general or local anesthesia (according to the anesthesiologist's preferences) . Patients were treated with 200 mg of aspirin and 75 mg of clopidogrel during the procedure. Patients were heparinized with heparin (80-100 IU/ kg), an arch angiogram was performed, and the target carotid was selectively cannulated. Seven- or eight- millimeter self-expanding stents were deployed and post-dilated to 5 or 6 mm.

Statistical methods: the data were coded and entered using the statistical package for social science version 18 (SPSS v 18). The following tests were used when appropriate: Student t- test, Chi square test, Paired sample t- test, and Mixed ANOVA test, P value ≥0.05: Not significant, while P value <0.05: Significant

Results:

Table (1): **Demographic &Baseline clinical characteristics of included patients**

Baseline clinical characteristics		**Patients (n=30)**
Age [mean ± SD]		**68.9 ± 6.9**
Sex	**Males [n (%)]**	**18 (60%)**
	Females [n (%)]	**12 (40%)**
Smoking	**Yes [n (%)]**	**13 (43.3%)**
	No [n (%)]	**17 (56.7%)**
DM	**Yes [n (%)]**	**22 (26.7%)**
	No [n (%)]	**8 (73.3%)**
HTN	**Yes [n (%)]**	**19 (63.3%)**
	No [n (%)]	**11 (36.7%)**
IHD	**Yes [n (%)]**	**7 (23.3%)**

	No [n (%)]	**23 (76.7%)**
Baseline NIHSS [mean ± SD]		**3.33 ± 2.64**
Percent of stenosis in carotid artery [mean ± SD]		**77.47 ± 5.22**

SD: Standard deviation, N: number, DM: Diabetes mellitus, HTN: Hypertension, IHD : ischemic heart disease, NIHSS : National Institutes of Health Stroke Scale

In our study, the mean value for age in the included patients was 68.9 ± 6.9 y 60% (n=18) of the patients were males and 40% (n=12) were females. 13 (43.3%) of the patients were smoker and 17 (56.7%) were not,19 (63.3%) of the patients were hypertensive and 11 (36.7%) were not hypertensive. 7 (23.3%) of the patients had ischaemic heart disease and 23 (76.7%) didn't have, The mean value of NIHSS in the patients was 3.33 ± 2.64 representing their disability before carotid stenting, carotid artery stenosis was 77.47 ± 5.22 %. Table (1)

Table (2): Pre and post carotid stenting cognitive assessment& BDNF serum level

	Pre-intervention	**Post-intervention**	**P-value**
PALT [mean (SD)]	**12.15 ± 2.79**	**13.9 ± 2.155**	**< 0.001 ***
BVRT [mean (SD)]	**18.46 ± 3.01**	**21.133 ± 3.02**	**< 0.001 ***
PASAT [mean (SD)]	**46.36 ± 6.58**	**49.87 ± 2.11**	**< 0.001 ***
BDNF [mean ± SD] ng /ml	**4.72 ±2.4**	**4.9 ±2.11**	**0.154**

(**p < 0.05 is considered significant***), PALT=Paired Associate Learning, BVRT =Benton Visual Retention Test, PASAT= Paced Auditory Serial Addition Test

The results showed that the mean value for Paired Associate Learning test (**PALT**) score representing auditory verbal memory of the patients before carotid stenting was 12.15 ±2.79 and after was 13.9 ± 2.155 , The mean value for Benton Visual Retention Test (**BVRT)** score that represent visual perceptual, visual memory, visual motor and visuo constructive abilities of the patients before carotid stenting was 18.46±3.01 and after was 21.133 ± 3.02 , The mean value for Paced Auditory Serial Addition (**PASAT**) Test score that represent assessment of attention and auditory working memory of the patients before carotid stenting was 46.36 ± 6.58 and after was 49.87 ± 2.11. There was a statistically significant difference between pre and post stenting in all cognitive scales done for the patients (P-value < 0.001). Also, the mean value for BDNF serum level before carotid stenting in all included subjects was 4.72 ±2.4 n*g*/ml and after was 4.9 ± 2.11 *ng*/ml. There was no statistically significant difference between pre and post stenting BDNF serum level (P-value = 0.154) Table (2)

Table (3): Effect of various clinical characteristics on baseline BDNF serum level in the included patients

clinical characteristics		**BDNF [mean ± SD] ng/ml**	**P-value**
Sex	**male**	**4.53 ± 1.9**	**0.627**
	female	**4.98 ± 3.1**	
Smoking	**Smokers**	**4.13 ± 1.74**	**0.248**
	Non-smokers	**5.16 ± 2.76**	

DM	**diabetics**	**4.49 ± 2.5**	**0.392**
	Non- diabetics	**5.35 ± 2.11**	
HTN	**Hypertensive**	**4.52 ± 2.65**	**0.566**
	Non-hypertensive	**5.05 ± 1.93**	
IHD	**Patients with IHD**	**3.04 ±1.17**	**0.032**
	Patients without IHD	**5.22 ±2.45**	

The results revealed that mean value for baseline BDNF serum level in all included female subjects was 4.98 ± 3.1 *ng/*ml and for all included male subjects was 4.53 ± 1.9 *ng/*ml. There was no statistically significant difference between females and males (P-value = 0.627) . The mean value for baseline BDNF serum level in all included smoker subjects was 4.13 ± 1.74 *ng/*ml and for all included non-smoker subjects was 5.16 ± 2.76 *ng/*ml. There was no statistically significant difference (P-value = 0.248). The mean value for baseline BDNF serum level in all included hypertensive subjects was 4.52 ± 2.65 *ng/*ml and for all included non-hypertensive subjects was 5.05 ± 1.93*ng/*ml. There was no statistically significant difference (P-value = 0.566). The mean value for baseline BDNF serum level in all included diabetic subjects was 4.49 ± 2.5*ng/*ml and for all included non-diabetic subjects was 5.35 ± 2.11 *ng/*ml. There was no statistically significant difference (P-value = 0.392). The mean value for baseline BDNF serum level in all included IHD subjects was 3.04 ±1.17*ng/*ml and for all included non-IHD subjects was 5.22 ±2.45 *ng/*ml. There was no statistically significant difference (P-value = 0.032) Table (2)

Table (4): Correlation between baseline BDNF serum level and various assessed parameters

	Baseline BDNF serum level	
	(r) coef.	**P-value**
Age in years	**-0.296**	**0.112**
Baseline NIHSS	**-0.114**	**0.548**
Percent of carotid stenosis	**-0.693**	**< 0.001***
Baseline PALT	**-0.009**	**0.963**
Baseline BVRT	**0.206**	**0.275**
Baseline PASAT	**0.088**	**0.645**

There was negative correlation between age & baseline NIHSS and BDNF serum level measured in patients before carotid stenting, but such correlations have no significant value (r coef.= -0.2960.182, P-value=0.112)& (r coef.= -0.114, P-value=0.548) respectively. As regards the cognitive functions; There was negative correlation between baseline Paired Associate Learning test (**PALT**) score representing auditory verbal memory and BDNF serum level measured in patients before carotid stenting . There was positive correlations between baseline Benton Visual Retention Test (**BVRT)** score that represent visual perceptual, visual memory, visual motor and visuo constructive abilities, Paced Auditory Serial Addition (**PASAT**) Test score that represent assessment of attention and auditory working memory of the patients and BDNF serum level measured in patients before carotid stenting, but this correlations has no statistically significant value (r coef.= -0.009, P-value=0.963) , (r coef.= 0.206, P-value=0.2750.963) and (r coef.= 0.088, P-value=0.645.) respectively Table (4)

Table (5): Correlation between post-intervention BDNF serum level and post-intervention assessed parameters

	Baseline BDNF serum level	
	(r) coef.	P-value
Age in years	**-0.296**	**0.112**
Post-intervention NIHSS	**-0.204**	**0.279**
Post-intervention PALT	**0.144**	**0.446**
Post-intervention BVRT	**0.246**	**0.190**
Post-intervention PASAT	**0.167**	**0.377**

There was negative correlation between patient serum BDNF one month after carotid stenting and NIHSS measured in patients after carotid stenting, but this correlation was statistical of a non-significant value (r coef.= -0.204, P-value =0.279). As regards the cognitive functions ; there was positive correlation between Paired Associate Learning test (**PALT**) score representing auditory verbal memory , Benton Visual Retention Test (**BVRT)** score that represent visual perceptual, visual memory, visual motor and visuo constructive abilities, Paced Auditory Serial Addition (**PASAT**) Test score that represent assessment of attention and auditory working memory of the patients after one month after carotid stenting with serum BDNF measured in the included subjects after one month of carotid stenting, but this correlations has no statistically significant value (r coef.= 0.144, P-value=0.446) , (r coef.= 0.246, P-value=0.190) and (r coef.= 0.167, P-value=0.377) respectively. Table (5).

Discussion:

Our study showed a statistically significant increase in all cognitive scales done for the patients between pre and post stenting including: PALT score representing auditory verbal memory of the patients, BVRT score that represent visual perceptual, visual memory, visual motor and visuo constructive abilities of the patients and PASAT Test score that represent assessment of attention and auditory working memory .

Similar to our study, ***Lin .et al (2016)*** showed that both aggressive medical therapy alone and combined carotid revascularization in 70% asymptomatic carotid stenosis similarly preserved cognition during 3-month follow-up. Moreover, only the stent-placement group showed interval improvement in the short-term verbal memory and visuospatial performance after 3 months[11].

In addition, **Wapp *.et al (2015)*** , showed improvement in all cognitive tasks after one year in patients of the CAS group[12]**.**

Similarly**, *Chang et al.(2013)* ,** and ***Lin et al.*** **(2016)** found that CAS could improve the global cognitive function as well as attention and psychomotor processing[13&11].

Same results regarding auditory verbal learning improvement **,*Yan et al. (2014), Xia et al. (2015)*** found that the scores of MMSE, MoCA, the alternating trail test, cube copying, clock-drawing, attention and delayed recall in the auditory-verbal learning test were significantly higher at different time points after CAS[14&15].

In agreement with our results, Mendiz ***et al. (2012)*** found that Executive function scores improved after CAS and the benefit of working memory was marginally significant[16]. ***Yoon et al*. *(2015)*** found that Symptomatic carotid stenosis patients exhibited improvements in visuospatial function when compared with asymptomatic carotid stenosis patients[17].

In contrast to our results, **Bo,.et al (2006)** showed cognitive decline in older patients after carotid endarterectomy[18].

On the other hand ***List ,.et al (2012)*** study revealed reperfusion (CEA) does not improve cognitive parameters in patients with severe stenosis of the internal carotid artery[19] .

In our study there was non-significant correlation between baseline cognitive function and percent of carotid stenosis.Similar to our study ***, Martinić-Popović I ., et al (2009),*** included 26 stroke-free patients, with advanced internal carotid artery stenosis or/and occlusion, Cognitive functions were tested by use of Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), performance scores were numerically reduced for executive/visuospatial function, but it was not statistical significance [20]**.**

Unlike our results, ***Framingham Offspring Study, showed*** that internal carotid stenosis ≥50% was associated with higher prevalence poorer performance on executive function [21]**.**

Additionally, ***Romero et al., (2009)*** regarding asymptomatic carotid stenosis and cognitive function found patients with stenosis had worse domain-specific scores in both learning/memory and motor/processing speed. Almost half of the patients were impaired in at least two cognitive domains [22]**.Wang et al .,(2015)** founded that patients with carotid stenosis often experienced subtle cognitive impairment using the Mini-Mental State Examination [6] **.**

The discrepancies in results might be due to the differences between sample populations, choices of cognitive tests, specific cognitive domains and analytic approaches.

Our study showed a negative correlation between the degree of carotid stenosis & baseline BDNF serum level measured in patients before carotid stenting which has statistically significant value.

Comparable to our results ***Wang et al .(2020)*** ,study found that the expression levels of serum BDNF and TrkB were significantly reduced by Chronic cerebral hypoperfusion induced by bilateral common carotid artery occlusion in rat model[23] .

In contrast to our study **, *Schmidt-Kastner et al.(2001)***, showed that Chronic bilateral common carotid artery occlusion (BCCAO) induces moderate ischemia (oligemia) in the rat forebrain and the result showed BDNF mRNA was significantly increased in the hippocampal granule cells at 6 h of occlusion[24] **.**

Our study showed non-significant Correlation between post-intervention BDNF serum level and post-intervention cognitive function (Paired Associate Learning, Benton Visual Retention Test and Paced Auditory Serial Addition Test)

Similar to our study, **Hitchner et al ,(2016)** study was on Patients underwent neuropsychological battery of measures to evaluate (executive function, motor speed and strength, visual and verbal memory, and language) prior to and at 1 month following carotid intervention and brain-derived neurotrophic factor (BDNF) gene polymorphism found that No significant associations were found between BDNF polymorphisms and its expression with decline in verbal or visual memory[25] .

In our study, there was no statistically significant difference between pre and post stenting BDNF serum level. In contrast to our study regarding carotid reperfusion on the level of BDNF ***Yali et al*****,(2019)** study which studied BDNF level post CEA and the results showed that Plasma levels of BDNF significantly increased at 72 hours postoperatively and 7 days postoperatively . However, the value of BDNF returned to baseline at *1 month postoperatively*, which agreed with our BDNF level 1 month postoperatively[26].

Comparing to the reperfusion effect on the level of BDNF ***Rodier et al (2015) study*** which was the first to be designed to assess the impact of rt-PA treatment on circulating BDNF levels in

stroke patients, revealed higher serum BDNF levels in rt-PA treated than in non-treated stroke patients at least from day 1 to 7 after stroke onset. Higher BDNF level after treatment with rTPA may be explained by the transformation of pro-BDNF to mature BDNF through plasmin activity[27].

Similar to our results regarding the effect of carotid stenting on neural plasticity, ***List et al (2012)*** found that decreased rapid-onset cortical plasticity in patients with severe stenosis of the ICA was not improved by reperfusion using CEA.

In contrast, ***Serra et al (2019)*** found that a statistically significant decrease of BDNF relative protein levels, amounting to 46%, occurred in bilateral common carotid artery occlusion followed by reperfusion (BCCAO/R) vs. control rats.

Additionally***, Wang et al (2020),*** study found that the expression levels of serum BDNF and TrkB were significantly reduced by Chronic cerebral hypoperfusion induced by bilateral common carotid artery occlusion followed by reperfusion in rat. In the current study there was non- significant correlation between baseline &post-intervention BDNF serum level and baseline& post-intervention NIHSS, respectively[23].

In agreement with our results ***Rodier et al. (2015)*** study showed that NIHSS results had no significant correlation with serum levels of BDNF at any time point[27].

On the other hand, ***Shan et al .(2021) ,*** found that serum BDNF levels were found to be negatively correlated with scores on the NIH Stroke Scale (NIHSS) , so lower serum BDNF levels were associated with increasing severity of stroke[28] .

Unlike our results***, Qiao et al. (2017)*** found a significant negative correlation between NIHSS and BDNF serum level and concluded that reduced serum level of BDNF was associated with worse neurological outcome[29].

In our study there was non-significant correlation between age and BDNF serum level measured in patients before carotid stenting.an

Similar to our study, ***Gajewska et al.(2014)*** also found that the concentration of BDNF did not differ in the investigated subjects regardless of age &sex[30].

On the other hand, ***Bus et al .(2011),*** showed older patients had higher levels of BDNF compared with younger patients and ***that*** women had lower levels of BDNF compared with males [31]**.** Additionally **Galle *et al. (2021)***, found that a higher plasma BDNF level at baseline was associated with higher age [32].

Unlike our study ***Golden et al. (2010),*** showed that a significant negative correlation was seen between BDNF and age, with older males and females having lower plasma BDNF levels.

Additionally, ***Ziegenhorn et al. (2007)***, showed that there was a negative correlation between serum BDNF levels and age in healthy old subjects.

The study made by ***Lommatzsch et al.(2005),*** also showed that there was a significant decrease of BDNF levels in plasma with increasing age.

That decrease in serum BDNF was illustrated that Since BDNF is readily crossing the blood–brain barrier in both directions ***(Pan W,.et al 1998),*** BDNF secretion in the central nervous system may also contribute to the amount of circulating BDNF ***(Poduslo JF,.et al 1996)***.There is some evidence indicating decreasing expression of the high-affinity BDNF receptor trkB in specific brain regions and peripheral ganglia during the normal aging process ***(Romanczyk TB,.et al 2002)***. However, a significant decrease of overall cerebral BDNF production during aging has not been found ***(Tanaka,. et al 1997).*** Besides, altered function of other cells such as vascular endothelial cells during aging may be of major importance in this regard ***(Nakahashi T,. et al 2000).***

In our study, there was no statistically significant difference between females and males in baseline BDNF serum level in all included subjects.

In agreement with our study***, Lang et al. (2004), and Ziegenhorn AA et al. (2007),*** study showed that no significant gender differences were detected when we compared BDNF serum concentrations between male and female participants. That may be explained by the increased number of menopausal females in study.

However, ***Golden et al. (2010)*** found that women had a higher mean plasma BDNF level than men[33] .

On the other hand, ***Galle S.et al (2021),*** found that a higher plasma BDNF level at baseline was associated with female sex[32].

The higher level of BDNF in females compared to males can be explained by the possible regulatory role of estrogen in BDNF expression and signaling [34]. Interestingly, higher BDNF serum level was observed in females with regular menses than females with amenorrhea. Also, BDNF serum level correlated negatively with the number of years since menopause[35] . In addition, In vitro studies discovered a role of estrogen in increasing the number of spine dendrites in hippocampal neurons [36] .

In our study, there was no statistically significant difference in the mean value for baseline BDNF serum level in all included smoker and non-smoker subjects.

Additionally, ***Chan et al. (2008)*** reported no significant difference in serum BDNF levels between smokers and non-smokers[37] .

Possible explanations for this difference may be due to different pathological conditions, different races, and biological heterogeneity or other factors. So far, it is unclear whether smoking or nicotine could affect the peripheral BDNF by acting on the blood cells or the platelets directly, and it is generally believed that changes in the periphery might be due to the effects of chronic nicotine exposure on the CNS, in particular the hippocampus[38].

In our study there was no statistically significant difference in mean value for baseline BDNF serum level in all included diabetic and non-diabetic subjects.

In the other hand, ***Rozanska O et al.(2020),*** showed that Plasma levels of BDNF decreased in humans with type 2 diabetes, The concentration of BDNF correlates positively with immunoreactive insulin and HOMA-IR (homeostatic model assessment for insulin resistance) [39].

In addition to ***Moushira Z et al (2022),*** declared in their pilot study that BDNF levels in serum decreased significantly in diabetic depressed women[40].

Other than our study, ***Fujinami et al. (2008),*** demonstrated that serum BDNF levels in patients with T2DM were significantly lower than in healthy control subjects[41].

However, ***Suwa et al .(2006) ,***have a similar opinion to that of ***Boyuk et al.(2014),*** They studied the relationship of BDNF concentration in Japanese women newly diagnosed with T2DM and a control group consisting of women with normal glucose tolerance. BDNF concentration was much higher in patients with type 2 diabetes than in the healthy control group[42&43].

In our study there was no statistically significant difference in mean value for baseline BDNF serum level in all included IHD and non-IHD subjects.

In the other hand, ***Ejiri et al. (2015)****,* showed that plasma BDNF was increased in the coronary circulation in patients with Unstable Angina, and BDNF expression was enhanced in coronary arteries of those patients, suggesting that BDNF may detrimentally influence atherosclerotic plaque stability[44].

Additionally, ***Hang et al (2015)***, observed that plasma BDNF level in MI patients was markedly enhanced compared with non-MI patients. Thus, these results suggested that circulating BDNF level was elevated in acute MI[45].

However, ***Sustar et al (2019)***, revealed lower plasma BDNF concentration in patients with CHD, suggesting that decreased plasma BDNF concentration might be associated with CHD pathogenesis[46].

Additionally, ***Manni et al. (2005),*** reported lower BDNF plasma levels in the acute coronary syndrome cases compared with the controls, suggesting a protective role of BDNF[47]. On the other hand, ***Kaess et al .(2015),***have also shown, that higher BDNF levels is associated with lower risk of cardiovascular disease events and death, independently of standard risk factors[48] .

In our study, there was no statistically significant difference in the mean value for baseline BDNF serum level in all included hypertensive and non-hypertensive subjects.

Prigent-Tessier et al. (2013), Found that essential hypertension was associated with decreased expression of the endothelial BDNF[49].

However, In a study of ***Nemcsik et al.(2017),*** BDNF serum levels were elevated in a chronic hypertensive patients, and it was suggested that BDNF could play a role in a compensatory mechanism targeting peripheral neurons and vascular cells[50]**.**

That could be explained as BDNF was found to have relaxing effects on pulmonary and aortic rings in animal studies. BDNF is evidenced to be secreted from vascular endothelial cells and mediate the arterial baroreceptors development and function. Also, BDNF participates in vessels smooth muscles relaxation and blood pressure reduction ***(Meuchel L. W., et al 2011).***

Limitations of our study*:* the relatively small study population that was affected by COVID-19 pandemic that caused postponing to many interventions is considered one of the limitations in our study. Also, the role of antiplatelet before and after intervention and its effect on platelet BDNF release to serum was not studied.

5.Conclusion: Treatment of patients with carotid stenosis by stenting causes significant improvement in cognition but no effect on BDNF serum level. Also, age , sex , diabetes mellitus , ischemic heart disease ,smoking or hypertension has no effect on baseline serum BDNF as a biomarker for neuralplasticity in the studied patients.

6.Conflict of interest: Nill

7.Funding: Nill

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