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Study of Possible Effect of Atorvastatin on Memory and Cognition in Normal and High Fat Diet Fed Adult Male Albino Rats

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ABSTRACT

Background: Atorvastatin reduces blood cholesterol levels, although there is evidence linking statins in general to memory loss. **Objective:** To evaluation of atorvastatin effects against memory and cognition in normal and hyperlipidemic male albino rats.

Materials and methods: 24 male adult albino rats, have been used and in random way divided into four groups with six rats in each group as follows; 1) Control group: normal diet group, 2) HFD group: orally HFD-fed group in a dose of (15 gram/animal/day) for 28 days, 3) Atorvastatin/ordinary diet group: treated with atorvastatin orally (10 mg/kg/day) for 14 days; from 29th day to 42nd day of the study, 4) Atorvastatin/HFD group: treated with atorvastatin orally (10 mg/kg/day) for 14 days; from the 29th day to the 42nd day of the study. Assessment of working memory and spatial learning was performed after the 42nd day of the experiment. **Results:** Treatments with atorvastatin were significantly ameliorated this lipid dysfunction as it significantly reduced cholesterol, LDL-C and VLDL levels, increased HDL-C levels but did not affect triglycerides. Atorvastatin exhibited beneficial effects against hyperlipidemia induced by HFD treatment. Administration of atorvastatin in atorvastatin/ordinary diet-fed group also induced a statistically significant increase in AchE level in comparison with control group, while administration of atorvastatin attenuated AchE in Atorvastatin/HFD group compared with non-treated HFD group.

Conclusion: Administration of atorvastatin in atorvastatin/ordinary diet-fed group also induced an oxidative status as indicated by disturbance of oxidative stress markers (GSH, and CAT), while administration of atorvastatin in Atorvastatin/HFD group improved both oxidative stress markers (GSH, and CAT) as well as inflammatory markers (TNF-α and IL-1β) compared with non-treated HFD group.

Keywords: Atorvastatin, Memory, High fat diet (HFD).

INTRODUCTION

Dementia is an illness of the nervous system that causes a slow but steady decline in mental abilities. Even though there are various types of dementia, Alzheimer's disease and vascular dementia account for the vast majority of cases **(1).**

Alzheimer's disease (AD) is characterized by the presence of extracellular senile plaques (SPs) composed of amyloid beta protein (A) as well as intracellular neurofibrillary tangles (NFTs) composed of tau proteins in regions of the brain critical for memory, behavior, and cognition, such as the basal forebrain as well as hippocampus **(2).**

Cholesterol as well as hyperlipidemia, thought that being Alzheimer's disease risk factor, are found to influence the deposition and elimination of amyloid peptide in the brain **(3).** Developing Alzheimer's disease has been related to high blood cholesterol levels, and several clinical studies have found that lipid lowering medications like statins may be effective in reducing this risk **(4).** Statins, of which atorvastatin is a member, work by blocking the enzyme 3-hydroxy-3-methyleglutaryl coenzyme A reductase, wherein the rate-limiting step in cholesterol synthesis is catalyzed. Statins help reduce inflammation and decrease the formation of harmful free radicals owing to their pleiotropic properties **(5).**

Atorvastatin reduces blood cholesterol levels, although there is evidence linking statins in general to memory loss. The question of whether statins help or hurt memory and other cognitive functions remains controversial **(6)**. Our study objective was evaluation of atorvastatin effects against memory and cognition among normal and hyperlipidemic male albino rats.

MATERIALS AND METHODS

Twenty-four male rats weighing between 120 and 150 grammes were used in the study, all of which were obtained from the animal unit at the Faculty of Veterinary Medicine at Zagazig University in Egypt, on 27/9/2021. In the week leading up to the studies, the rats were given time to adjust to life in the animal facility. For 42 days, the animals were housed in conventional settings (room temperature of 22.2 degrees Celsius; humidity of 50 to 55 percent; 12-hour light/12-hour dark cycle), fed a standard rodent diet (or HFD, depending on the group to which they belonged), and allowed free access to food and water.

Inclusion criteria: Adult male albino rat weighing 120-150 gm, at age of 6 weeks

Exclusion criteria: We excluded rats of body weight less than 120gm, above 150 gm.

- A total of 24 rats were split into 4 groups of 6 animals each:

- **Control group**: normal diet group**.**

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- **HFD group:** orally high fat diet fed group in a dose of (15 gram/animal/day) for 28 days without giving any drugs.
- **Atorvastatin/ordinary diet group:** atorvastatin is given orally by gavage in a dose of 10 mg/kg for 14 days; from the 29th day to the 42nd day of the study.
- **Atorvastatin/HFD group:** atorvastatin is given orally by gavage in a dose of 10 mg/kg for 14 days; from the 29th day to the 42nd day of the study.

➢ Behavioral tests were performed after the 42nd day of the experiment. Modified T maze test was utilized for screening of working memory and spatial learning **(7).**

After administering 75 mg/kg of intraperitoneal pentobarbital to put the rats to sleep, blood was taken from the retro-orbital plexus. Serum was separated from whole blood by centrifugation at 3000 rpm for 10 minutes, and then stored at -80°c until bioassay of lipid profile was performed. (total cholesterol, triglycerides, LDL, HD), tumor necrosis factor-α (TNF-α), reduced glutathione (GSH), catalase (CAT), acetylcholineestrase (AchE) and interleukin-1β (IL-1β).

➢ Tissue samples: The brains of sacrificed rats were extracted surgically from their bodies. Hippocampus is excised and rinsed thoroughly using cold salt water and dividing it in half, one part was preserved in formalin 10% for histopathological examination and other part was rapidly frozen by at -80°c, for later biochemical determination of superoxside dismutase (SOD) and catalase (CAT) levels.

➢ Histopathology: Hippocampus slides were stained by s immunohistochemical staining using synaptophysin and examined with light microscope under different magnification powers.

METHODS

Oral administration of atorvastatin:

Once a day, for 2 weeks, an oral gavage needle tube attached to a standard 5 ml syringe was used to deliver atorvastatin powder dissolved in carboxy methyl cellulose (0.5 percent) diluted in distilled water. The esophageal tube inserted to guarantee medicine administration and prevent vomiting back up.

Induction of dementia:

Rats were given an HFD consisting of 15 grammes of prepared mixture each day, which included 2% cholesterol, 1% cholic acid, 5% coconut oil, and 92.5% standard pellet diet powder. **(6).**

Assessment of working memory and spatial learning was performed after the 42nd day of the experiment using Modified T maze test. On the last day of the experiment, Rats were anesthetized then blood samples were collected from retro-orbital plexus for bioassay of lipid profile, AchE, oxidative stress markers and inflammatory markers. After that, rats were sacrificed by cervical dislocation, the whole brain was removed and the hippocampus was dissected to be used in estimation of GSH and CAT level. Representative hippocampal samples of each group were also used for histopathological examination using immunohistochemical stain with synaptophysin.

Ethical approval:

Zagazig University Institutional Animal Care and Use Committee (IACUC) granted ethical permission (ZU-IACUC/3/F/139/2021) for this investigation. Mice were handled according to National Institutes of Health (NIH) guidelines for animal experimentation. All experiments were carried out according to The Clinical and Laboratory Standards Institute (CLSI) guidelines and were approved by an institution responsible for animal ethics concerning care for animals and safe disposal of their wastes at Theodor Bilharz Research Institute.

Statistical Analysis

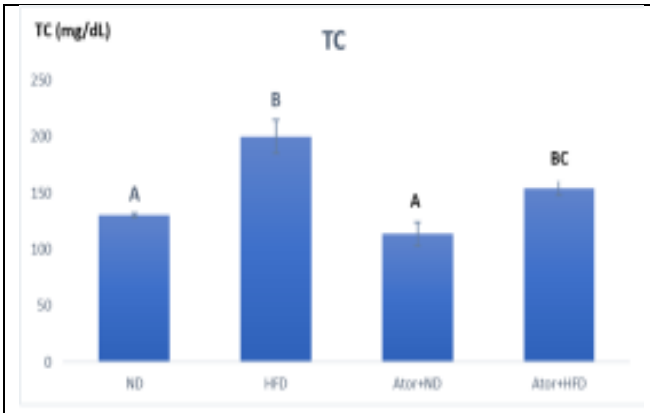
The Statistical Package for the Social Services (SPSS) version 20 was used to examine the data (SPSS). For parametric data, we used one-way analysis of variance (ANOVA) and the Post Hoc Tukey test to compare groups, whereas for non-parametric data, we used Kruskal-Wallis and the Duncan test. In this case, statistical significance was determined to exist at a P value of 0.05 or lower.

RESULTS

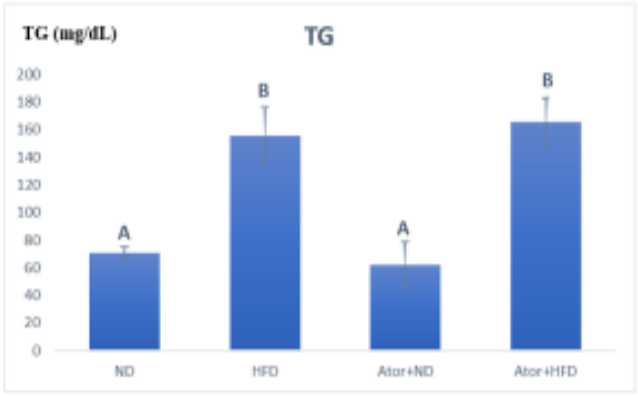
In the normal diet control group, total cholesterol (TC) was 130.07±2.17 mg/dL, (TG) level was 70.54±4.32 mg/dL, LDL level was 66.25±2.75 mg/dL, HDL level was 50.76±1.56 mg/dL, VLDL level was 14.26±0.74 mg/dL. In HFD group TC was 199.7±14.73 mg/dL, TG was 155.7±20.55 mg/dL, VLDL level was 30±3.77 mg/dL which all were significantly ($p<0.05$) increased in comparison to that of the normal diet control group while HDL level was 47.9±0.95, and LDL level was 139.59±16.22 which were not significantly ($p>0.05$) different in comparison to that of the normal diet control group **(Figure 1)**

In ND/atorvastatin-treated group, TC was 113.5±10.66 mg/dL, TG was 62.29±16.51 mg/dL, HDL level was 51.23±0.98 mg/dL, LDL level was 49.82±13.02 mg/dL, VLDL level was 12.46±3.3 mg/dL which did not differ significantly ($p>0.05$) when compared to that of normal diet control group **(Figure 1)**

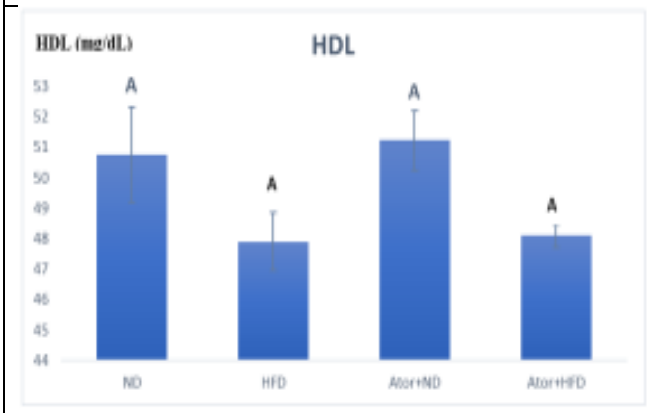
In HFD/atorvastatin-treated group, TC was 154.53±6.6 mg/dL, TG was 165.63±17.54 mg/dL, VLDL level was 33.13±3.51 mg/dL which were significantly increased ($p<0.05$) when compared to normal diet control and ND/atorvastatin-treated groups, but were not significantly different ($p>0.05$) when compared to that of HFD group. HDL level was 48.09±0.37 mg/dL, and LDL level was 73.31±10.47 mg/dL, that were not significantly different ($p>0.05$) when compared to normal diet control, HFD and ND/atorvastatin-treated groups **(Figure 1)**



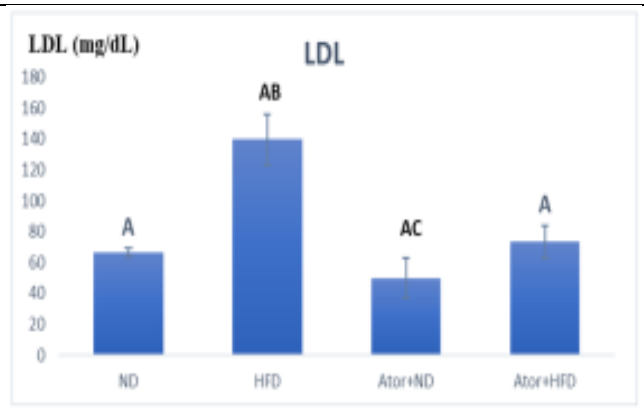
(A) **Total cholesterol**



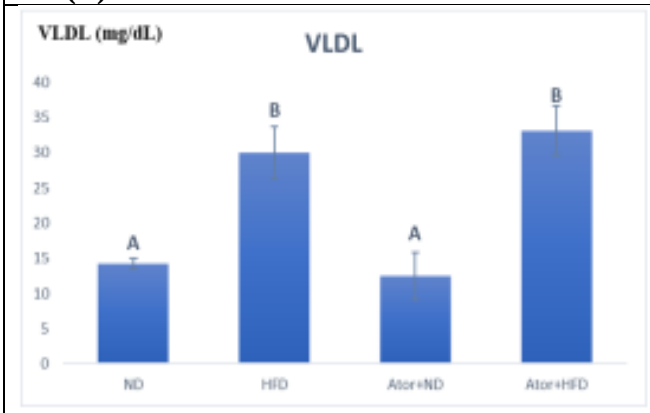
(B) Triglycerides level



(C) HDL



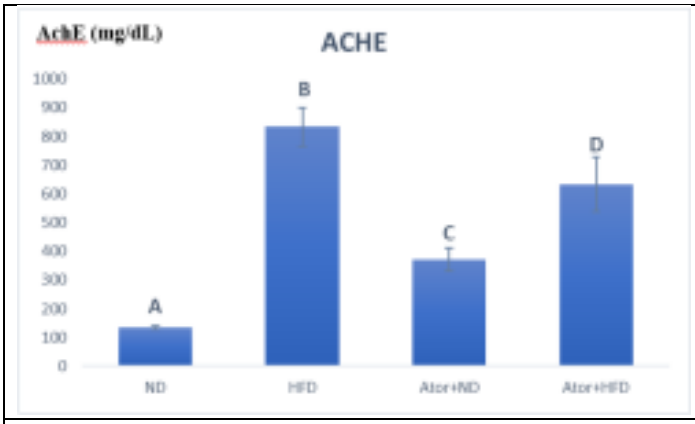
(D) LDL level



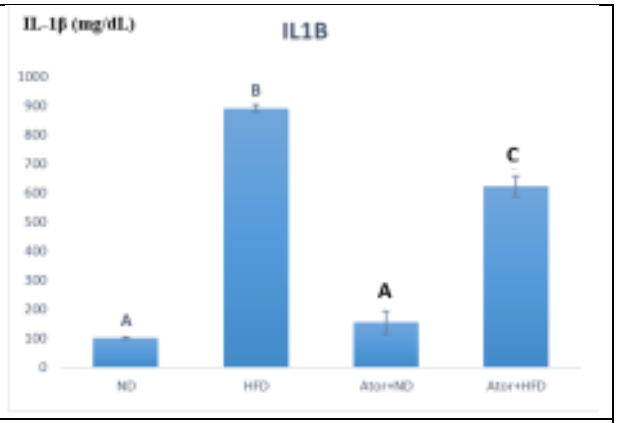
(E) VLDL level

Figure (1): Total cholesterol, TG, HDL, LDL, VLDL levels in ND, HFD, ND/Atorvastatin-treated with and HFD/Atorvastatin-treated with groups
ND: normal diet, HFD: high fat diet, Ator: Atorvastatin

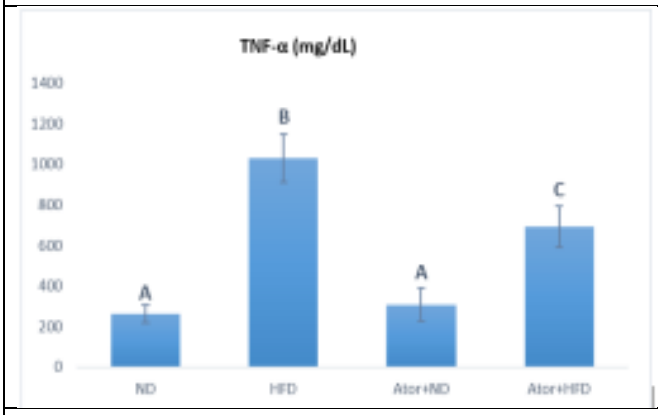
In comparison with control group, HFD group revealed a state of oxidative stress and inflammation as indicated by decreased hippocampal CAT, decreased serum GSH levels when compared with control group. Administration of atorvastatin in atorvastatin/ordinary diet-fed group also induced an oxidative status as indicated by disturbance of oxidative stress markers (GSH, and CAT), while administration of atorvastatin in Atorvastatin/HFD group improved both oxidative stress markers (GSH, and CAT) as well as inflammatory markers (TNF-α and IL-1β) compared with non-treated HFD group, Concerning AchE, there was a statistically significant elevation in concentration of HFD group compared to control group. Administration of atorvastatin in ND/atorvastatin group also induced a statistically significant increase in AchE level in comparison with control group, while administration of atorvastatin attenuated AchE in Atorvastatin/HFD group compared with non-treated HFD group **(Figure 2)**



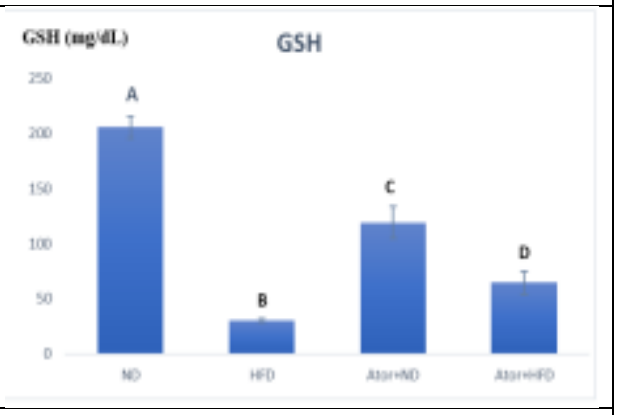
(A) AchE level



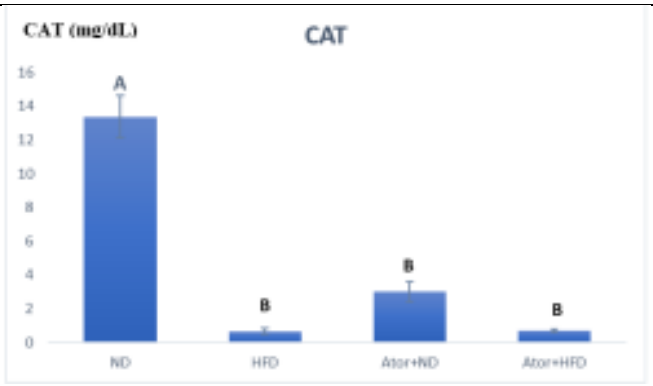
(B) IL-1β level



(C) TNF-α level



(D) (GSH level



(E)CAT level

Figure (2): Acetyl choline esterase enzyme (AchE), Interleukin-1-beta (IL-1β), Tumor necrosis factor alpha (TNF-α), Glutathione (GSH), Catalase (CAT) levels in ND, HFD, ND/Atorvastatin-treated with and HFD/Atorvastatin-treated with groups

Short and long-term memory were evaluated in the present study using modified T maze test, the T score was significantly reduced in HFD and atorvastatin/ordinary diet-fed group in relation to control group. However, the score still significant higher in Atorvastatin/HFD group when compared to HFD group. In the normal diet control group, Percentage of alternations was 90.0 (87.5-100.0). In HFD group Percentage of alternations was 50.0 (37.5-60.0), which was significantly ($p<0.05$) decreased in comparison to that of the normal diet control group.

In normal diet/atorvastatin-treated group, Percentage of alternations was 0.0 (0.0-10.0) which was significantly ($p<0.05$) decreased in comparison to normal diet control and HFD groups. In HFD/atorvastatin-treated group, Percentage of alternations was 75.0 (67.50-82.50), that decreased significantly ($p<0.05$) when compared to normal diet control group but increased significantly ($p<0.05$) when compared to HFD and ND/atorvastatin-treated groups **(figure 3)**

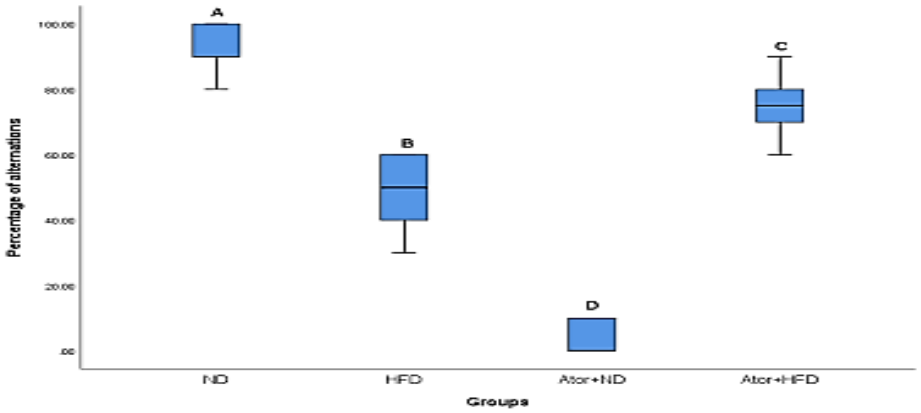


Figure (3): Percentage of alternations (correct choice) of T-maze test in ND, HFD, ND/Atorvastatin-treated with and HFD/Atorvastatin-treated with groups.

Histopathological examination of the hippocampus was done by using immunohistochemical stain with synaptophysin. The HFD and Atorvastatin/ordinary diet-fed groups showed significant signs of structural damage and neuronal loss in the hippocampus. However, the administration of Atorvastatin in atorvastatin/HFD group minimized this damage and improved HFD-induced neuronal degeneration

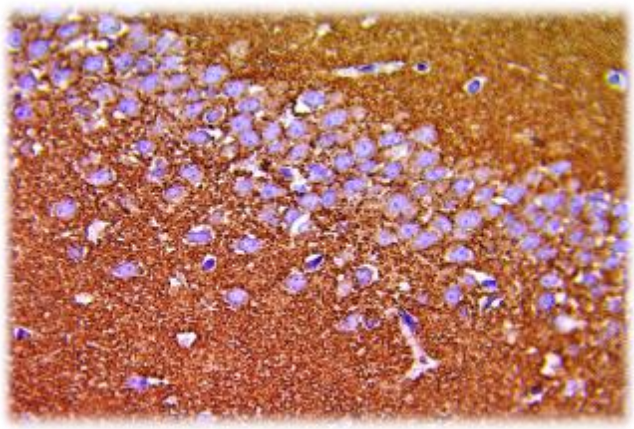
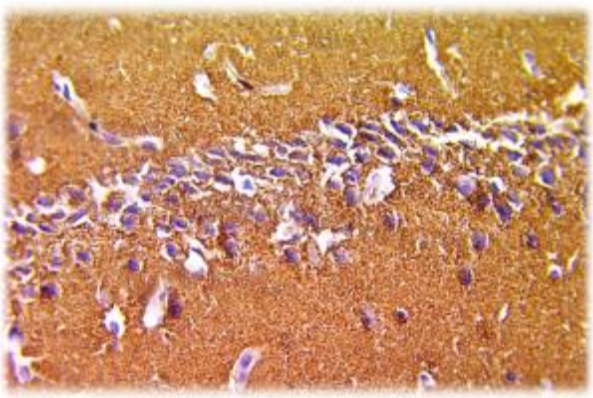
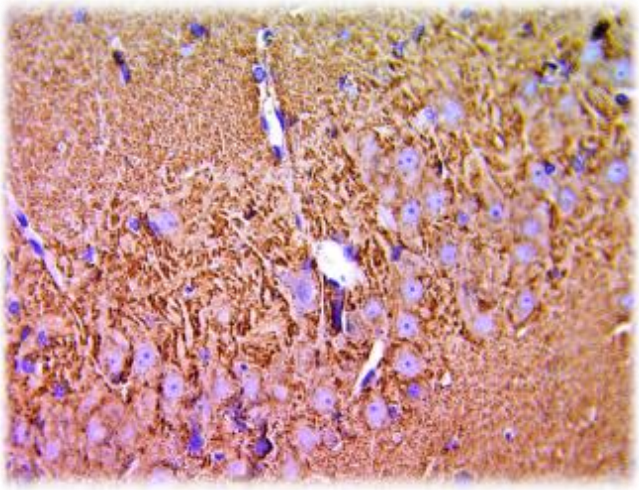
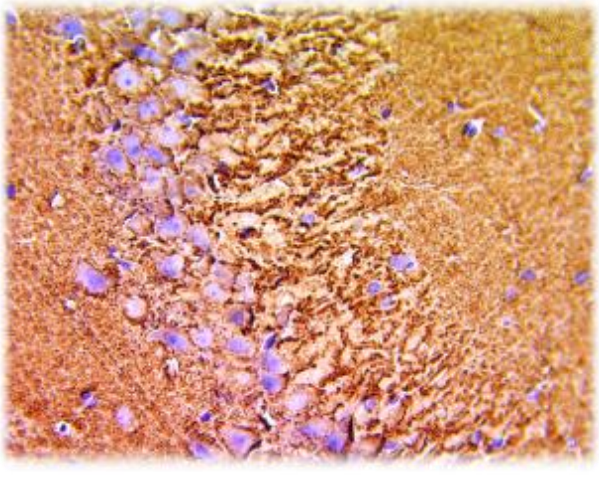
	
(A) Photomicrographs of normal diet control group showing diffuse strong Synaptophysin immunohistochemical expression (black arrows) in the synaptic processes in hippocampus. (Synaptophysin immunostaining, x400)	(B) Photomicrographs of high fat diet group showing moderate Synaptophysin immunohistochemical expression (asterisks) in the synaptic processes in hippocampus. (Synaptophysin immunostaining, x400).
	
(C) Photomicrographs of normal diet/Atorvastatin group showing moderate Synaptophysin immunohistochemical expression (asterisks) in the synaptic processes in hippocampus. (Synaptophysin immunostaining, x400).	(D) Photomicrographs of high fat diet/Atorvastatin group showing diffuse Synaptophysin immunohistochemical expression (black arrows) in the synaptic processes in hippocampus. (Synaptophysin immunostaining, x400)..

Figure (4): photomicrographs of immunohistochemical staining "synaptophysin" for microscopic changes in hippocampus within different groups

DISCUSSION

A high-fat diet may cause memory and cognitive decline [8]. Several physiological systems are adversely affected by a high-fat diet (HFD), with negative consequences for brain function. These include changes in brain lipid composition, insulin resistance, and neurotransmitter release [9].

A typical lipid-lowering medication, atorvastatin blocks the enzyme HMG co-A reductase, which is the bottleneck in the cholesterol-making process [10].

In the present results, HFD induced significant increments in the total cholesterol, TGs, LDL, and VLDL serum levels compared to control group while decreased the HDL level.

These results coped with **Jakobsdottir *et al.*** [11] who discovered that high-fat diet-induced inflammation, raised liver fat and cholesterol in male Wistar rats compared to rats fed a fiber-rich diet.

On the same approach, **Zhukova *et al.*** [12], Researchers in a recent study on male rats hypothesized that, in response to a high-fat diet (HFD), the liver would initiate two processes that are diametrically opposed to one another from a physiological standpoint buildup of external saturated lipids in the diet and internal synthesis of monounsaturated and polyunsaturated fatty acids.

Results like this may be explained by the elevated fat levels in the HFD. In addition, adipose tissue becomes resistant to insulin's effects on a high-fat diet, which in turn increases the breakdown and production of triglycerides (TG) [13].

Current study findings showed that administration of atorvastatin significantly decreased the serum levels of cholesterol, LDL and VLDL levels, increased the HDL level and did not affect triglycerides serum level compared with HFD group. In line with the present results, **Ji *et al.*** [14] found that the administration of 30 mg/kg of atorvastatin to rats with HFD-induced hepatic steatosis and hyperlipidemia had mild to moderate benefits for the NAFLD rats and could inhibit the progression of NAFLD and hyperlipidemia, as atorvastatin increased HDL cholesterol and HDL synthesis, decreased LDL cholesterol and HDL synthesis, and improved serum and hepatic lipid metabolism and liver function in HFD-induced hyperlipidemic and steatotic mice. In spite of the fact that high-density lipoprotein (HDL), the medication was found to decrease total cholesterol, LDL, and VLDL cholesterol in the blood.

A plaque formation and the progression of AD are both triggered by oxidative stress on brain cells. Damage to neurons' structure and function can also be brought on by reactive oxygen species (ROS) [15]. The present results showed decrements in serum levels of antioxidant parameters; GSH, and CAT.

The current work revealed that HFD/Atorvastatin-treated group had increments in GSH, and CAT compared with non-treated HFD group. These findings coped with **Kavalipati *et al.*** [16] they found that statins had effects on lipid peroxidation beyond lowering cholesterol and preventing FFAs - β oxidation. They do this by inhibiting the formation of reactive oxygen species (ROS) and decreasing the NAD+/NADH ratio.

The current study exhibited significant decline in both TNF-α and IL-1β serum levels by administration of atorvastatin in HFD/Atorvastatin-treated group compared with non-treated HFD group. These results might be attributed to the anti-inflammatory properties of atorvastatin. Statins can decrease levels of IL-1β and TNF-α in the bloodstream, which improves endothelial function and dampens the inflammatory response brought on by a high-fat, low-carbohydrate diet [17].

The present study, HFD group had increment in the level of AchE in comparison with normal diet control group. Indeed, similar findings were obtained with **Das** [18] who first hypothesized that people with Alzheimer's disease, type 2 diabetes, high blood pressure, insulin resistance, and high cholesterol levels would have raised plasma levels of the cholinesterase enzymes acetylcholinesterase and butyrylcholinesterase (BChE).

The present results demonstrated that administration of atorvastatin in ND/Atorvastatin-treated group induce significant increase in AchE in comparison with normal diet control group indicating memory loss associated with atorvastatin.

These results coincides with **King *et al.*** [19] who found that atorvastatin caused mitochondrial dysfunction and energy depletion in neurons by inhibiting coenzyme Q10. In addition, because Atorvastatin prevents new cholesterol from being synthesized, the central nervous system (CNS) gets stripped of myelin [20].

On the contrary, our research revealed that AchE level had been significantly decreased as a result of atorvastatin administration in HFD/Atorvastatin-treated group in comparison to HFD group.

In a line with the present work, **Kosowski *et al.*** [21] using statins improved rats' cognitive and behavioural outcomes by decreasing their AchE levels, and increasing the amount of ACh in their brain tissue.

It is possible to quantify rodents' spatial working memory by the use of a T-maze test, which is a behavioural test, by counting the number of their successful route selections. Current findings showed that rats of HFD group exhibited a decline in T maze score compared to normal diet control group. These findings are in agreement with **de Oliveira *et al.*** [22] where mice with high cholesterol in the family were studied to see if a high-fat diet affected their brain function.

Some hypotheses for these findings include that A plaque buildup, hyperphosphorylation of tau proteins, and gliosis are the result of hypercholesterolemia-

induced alterations to brain lipid composition, inflammation, immune system activation, and oxidative stress [23], making the connection between high cholesterol and memory loss in spatial contexts more clear

However, the present work exhibited that ND/Atorvastatin-treated group score was significantly decreased than other groups indicating that Atorvastatin has a passive effect on memory. Atorvastatin's negative impact on memory and thinking may be explained by the drug's ability to decrease de novo cholesterol synthesis [24], a sudden change in the balance of cholesterol in the central nervous system, which interferes with the development and maintenance of myelin [25].

On the contrary, current study findings showed that administration of atorvastatin in HFD/Atorvastatin-treated group generated significant improvement of memory and cognitive ability comparing to HFD group.

Immunohistochemical staining by synaptophysin is one of the most widely methods used protein markers of synaptic plasticity in the brain. In the current study HFD induced moderate synaptophysin immunohistochemical expression in the synaptic processes in hippocampus.

Indeed, **Samuel *et al.*** [26] reports of atorvastatin-induced hippocampus damage are consistent with these findings. Results from this study demonstrated that compared to the control group, atorvastatin caused moderate synaptophysin Immunohistochemical expression in hippocampal synaptic processes.

On contrary, the present work showed that administration of atorvastatin in HFD/Atorvastatin-treated group resulted in marked improvement of Hematoxylin and eosin-stained histopathological picture of the HFD-induced hippocampus damage, while photomicrographs of HFD/Atorvastatin-treated group showed diffuse synaptophysin immunohistochemical expression in the synaptic processes in hippocampus.

In accordance to our research, **Tian *et al.*** [27] studied the impact of intraperitoneal administration of 0.2 mg/kg of atorvastatin on survival and cognitive impairments following cecal ligation and puncture-induced sepsis, and discovered that atorvastatin pretreatment raises the proportion of survivors and boosts mental performance.

CONCLUSION

Oral administration of HFD induced an AD-like state with memory impairment, increased levels of both oxidative stress markers (GSH, MDA, SOD and CAT) and inflammatory markers (TNF-α and IL-1β) with apparent histopathological changes including neuronal degeneration and amyloid deposition in the hippocampus.

Atorvastatin alone was sufficient to produce a significant degree of oxidative stress, impairment of memory and cognitive performance and neuronal damage in the hippocampus suggesting that atorvastatin may have memory toxic effects on its own.

Animals receiving Atorvastatin on top of HFD had marked improvement of HFD-induced oxidative stress and inflammation, in addition to attenuation of memory impairment developed as result of neuronal degeneration caused by HFD due to its lipid lowering, anti-oxidant and anti-inflammatory effects.

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Competing interests: Nil.

REFERENCES

1. **Kumar A, Singh A (2015):** A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. Frontiers in Pharmacology, 6:206.
2. **Mehra R, Sodhi R, Aggarwal N (2015):** Memory restorative ability of clioquinol in copper-cholesterol-induced experimental dementia in mice. Pharmaceutical Biology, 53(9): 1250–1259.
3. **Mishra A, Reynolds J, Chen Y *et al.* (2016):** Astrocytes mediate neurovascular signaling to capillary pericytes but not to arterioles. Nature Neuroscience, 19(12): 1619–1627.
4. **Bagheri H, Ghasemi F, Barreto G *et al.* (2020):** The effects of statins on microglial cells to protect against neurodegenerative disorders: A mechanistic review. BioFactors (Oxford, England), 46(3): 309–325.
5. **Mollazadeh H, Tavana E, Fanni G *et al.* (2021):** Effects of statins on mitochondrial pathways. Journal of Cachexia, Sarcopenia and Muscle, 12(2): 237–251.
6. **Biswas R, Das M, Asr S *et al.* (2014):** Effect of atorvastatin on memory in albino mice. Journal of Clinical and Diagnostic Research, 8(11): 1-4.
7. **Schilling J, Cui W, Godoy J *et al.* (2014):** Long-term atorvastatin treatment leads to alterations in behavior, cognition, and hippocampal biochemistry. Behavioural Brain Research, 267: 6-11.
8. **Morris M, Tangney C (2014):** Dietary fat composition and dementia risk. Neurobiology of aging, 35: 59-64.
9. **Duarte A, Moreira P, Oliveira C (2012):** Insulin in central nervous system: more than just a peripheral hormone. Journal of Aging Research, 12: 384017. doi: 10.1155/2012/384017.
10. **Raghow R (2017):** Statins redux: a re-assessment of how statins lower plasma cholesterol. World Journal of Diabetes, 8(6): 230-34.
11. **Jakobsdottir G, Xu J, Molin G *et al.* (2013):** High-fat diet reduces the formation of butyrate, but increases succinate, inflammation, liver fat and cholesterol in rats, while dietary fibre counteracts these effects. PloS One, 8(11): e80476. doi: 10.1371/journal.pone.0080476.
12. **Zhukova N, Novgorodtseva T, Denisenko Y (2014):** Effect of the prolonged high-fat diet on the fatty acid metabolism in rat blood and liver. Lipids in Health and Disease, 13(1): 1-8.
13. **Bannerman D, Sprengel R, Sanderson D *et al.* (2014):** Hippocampal synaptic plasticity, spatial

memory and anxiety. Nature Reviews Neuroscience, 15(3): 181-192.

14. **Ji G, Zhao X, Leng L *et al.* (2011):** Comparison of dietary control and atorvastatin on high fat diet induced hepatic steatosis and hyperlipidemia in rats. Lipids in Health and Disease, 10(1): 1-10.
15. **Kumar A, Singh A (2015):** A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. Frontiers in Pharmacology, 6: 206. doi: 10.3389/fphar.2015.00206.
16. **Kavalipati N, Shah J, Ramakrishan A *et al.* (2015):** Pleiotropic effects of statins. Indian Journal of Endocrinology and Metabolism, 19(5): 554-62.
17. **Wen G, Wen C, Zhang B *et al.* (2018):** Effect of Atorvastatin on elderly patients with chronic kidney diseases complicated with hyperlipidemia. Chinese Journal of Geriatrics, 12: 779-782.
18. **Das U (2012):** Acetylcholinesterase and butyrylcholinesterase as markers of low-grade systemic inflammation. Annals of Hepatology, 11(3): 409-411.
19. **King D, Wilburn A, Wofford M *et al.* (2003):** Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 23(12): 1663-1667.
20. **Tan B, Rosenfeldt F, Ou R *et al.* (2019):** Evidence and mechanisms for statin-induced cognitive decline. Expert Review of Clinical Pharmacology, 12(5): 397-406.
21. **Kosowski M, Smolarczyk-Kosowska J, Hachuła M *et al.* (2021):** The effects of statins on neurotransmission and their neuroprotective role in neurological and psychiatric disorders. Molecules, 26(10): 2838. doi: 10.3390/molecules26102838.
22. **de Oliveira J, Engel D, de Paula G *et al.* (2020):** High cholesterol diet exacerbates blood-brain barrier disruption in LDLr–/–mice: impact on cognitive function. Journal of Alzheimer's Disease, 78(1): 97-115.
23. **Tan B, Norhaizan M (2019):** Effect of high-fat diets on oxidative stress, cellular inflammatory response and cognitive function. Nutrients, 11(11): 2579. doi: 10.3390/nu11112579.
24. **Jabir S, Salih Jaffat H (2018):** Effects of Atorvastatin Drug in Albino Male Rats. Journal of Pharmaceutical Sciences and Research, 10(11): 2924-2928.
25. **Anchisi L, Dessì S, Pani A *et al.* (2013):** Cholesterol homeostasis: a key to prevent or slow down neurodegeneration. Frontiers in Physiology, 3: 486. doi: 10.3389/fphys.2012.00486
26. **Samuel G, Ekong M, Akpanabiatu M (2018):** Atorvastatin misuse alters histological and protein expression in the hippocampal CA3 region of male rat models. Trends in Biomedical Research, 1(1): 1-7.
27. **Tian J, Tai Y, Shi M *et al.* (2020):** Atorvastatin relieves cognitive disorder after sepsis through reverting inflammatory cytokines, oxidative stress, and neuronal apoptosis in hippocampus. Cellular and Molecular Neurobiology, 40: 521-530.