Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.282691.3333 Volume 30, Issue 5, August 2024
Manuscript ID ZUMJ-2404-3333 (R2)
DOI 10.21608/ZUMJ.2024.282691.3333
ORIGINAL ARTICLE

Implication changes of Adiponectin and Brain derived neurotropic factor gene expression in chronic moderate and high intensity exercise in male albino rat model of Alzheimer

Sara G. Seada, Shereen El-Arabi Bdeer, Faten Fawzy Hadary Mohammed,Wesam M.R. Ashour,
Physiology Department, Faculty of Medicine, Zagazig university

Corresponding author:

Sara Gamal Seada

Email:

saragamal86@yahoo.com.

Submit Date 2024-04-13
Revise Date 2024-04-23
Accept Date 2024-05-25

ABSTRACT

Background: Alzheimer's disease (AD) is a neurodegenerative condition featuring by gradual degradation of the cortical and hippocampal neurons, which results in impaired cognitive and memory functions.**Objectives:** To assess the effect of chronic moderate and high intensity pattern of exercise on brain functions regarding memory and implication changes of adiponectin (APN) and brain derived neurotropic factor (BDNF) gene expression.**Subjects and methods:** Sixty adult male albino rats were subdivided randomly into two main groups (n=30), control group and AD group. Each main group was suballocated into three subgroups (n=10) according to intensity of exercise. Finally we had 6 groups: **Subgroup Ia:** vehicle only. **Subgroup Ib:** vehicle + Moderate intensity exercise. **Subgroup Ic:** vehicle + High intensity exercise. **Subgroup IIa:** $AlCl_3$. **Subgroup IIb:** $AlCl_3$ + Moderate intensity exercise. **Subgroup IIc:**$AlCl_3$+ High intensity exercise. APN and BDNF gene expression were assessed and histopathological examination of **cerebral cortex** and hippocampus was done. Evaluation of behavioral parameters was done using modified T-maze to evaluate short term and working memory. **Results:** Gene expressions of APN and BDNF were substantially decreased in the all AD subgroups compared to their corresponding control subgroups. However, they were remarkably elevated in moderately exercised subgroups compared to the sedentary subgroups. Moreover, in high intensity exercised subgroups**,** they were significantly higher than that of the sedentary and moderately exercised subgroups. **Conclusion:** APN & BDNF gene expression can be employed as a biomarker for early diagnosis of AD. Also regular exercise with increased intensity should be recommended for all patients with AD.

Keywords: Adiponectin, APN, Brain derived neurotropic factor, BDNF, exercise, Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) is a neurological condition that progresses over time. It is the most prevalent type of dementia, causing irreversible cognitive impairment and reduced learning capability. This is aggravated by a lack of sufficient treatment choices to reduce the disease's inevitable progression. There has recently been substantial scientific interest in developing non-pharmacological therapies for managing or curing AD [1]. Several investigations have shown that exercising following the onset of AD can induce neurological protection [1]. Several additional investigations examined the positive impacts of exercise in the context of AD, with positive findings [2].

Adiponectin (APN) is an adipocyte-derived hormone first extracted from rat adipocytes. It

regulates glucose and lipid catabolism and sensitizes the cell to insulin. APN was reported to be negatively correlated with T2DM, IR, BMI, and cardiovascular conditions. All of these variables can increase the possibility of dementia. Furthermore, APN has anti-inflammatory impacts by reducing pro-inflammatory cytokine synthesis [3].

Brain-derived neurotropic factor (BDNF) is a protein present in high amounts throughout the central nervous system, particularly in the cerebral cortex, hippocampus, cerebellum, and hypothalamus. Peripheral tissues can also synthesize BDNF. BDNF has been linked to brain growth and function, particularly dendritic development, neurogenesis, and long-term neuron potentiation [4].

Physical exercise elevates circulating concentrations of BDNF in healthy individuals. There is a variety of proof that exercise enhances both mental and emotional functioning. Evidence suggests that BDNF activation could regulate these impacts [5].

We aimed for assessing the effect of chronic moderate and high intensity pattern of exercise on brain functions regarding short term and working memory and the implication changes of APN and BDNF gene expression.

MATRIALS AND METHODS

Animals:

This study was approved by The Institutional Animal Care and Use Committee Zagazig University (ZU-IACUC) (ZU-IACUC/2/f/94/2022). This experimental prospective cohort study was carried out on a total number of 60 healthy adult male albino rats weighing 180-200g. The rats were housed in sanitary stainless-steel wire cages (7-8/cage) at Zagazig University's Faculty of Medicine. Rats had water ad libitum, were housed at room temperature, and followed a 12-hour light/dark cycle.

After one week of acclimatization, rats were randomized based on ELT (escape latency) and allocated into two main equal groups (30 rats each).

Group I (Control group, n=30): in which the rats received the vehicle orally (distilled water 0.5 ml/100g body weight) [6], then divided into 3 subgroups:

Subgroup Ia (Sedentary group): received the vehicle only.
Subgroup Ib (moderate intensity exercise): received the vehicle + moderate intensity exercise (from day 32 to day 74).
Subgroup Ic (high intensity exercise): received the vehicle + high intensity exercise (from day 32 to day 74).
Group II (induced-AD groups, n=30): in which the rats received aluminium chloride ($AlCl_3$) orally for 25 days from day1 to day 25 (175 mg/kg orally). This dose of $AlCl_3$ was reported to have low mortality and increased induction rate [7] $AlCl_3$ was dissolved in distilled water and were orally administered (0.5 ml/100g body weight) [6]. Then it was divided into 3 subgroups:

Subgroup IIa: $AlCl_3$.
Subgroup IIb: $AlCl_3$ + moderate intensity exercise (from day 32 to day 74).
Subgroup IIc: $AlCl_3$+ high intensity exercise (from day 32 to day 74).

Exercise regimen:

Swimming was chosen as our exercise routine since it is similar to rodents' normal actions and is less exhausting.

The swimming program has two phases: training and adaptation. The training was graded over the first week to allow for adaptation, starting with 15 minutes on the first day and ending with 60 minutes on the last day. After that, exercise regimen was started lasting for six weeks as following:

Moderate intensity exercise regimen: 60 minutes/day, five days/week [8]**.**
High intensity exercise regimen : 90 minutes/day, five days/week [8].

A period of six weeks is the limit for the period of the entire training, with short-term physical activity < 6 weeks and long-term exercise extending 6 weeks or longer [8]. Rats of sedentary subgroups were kept in pools filled with water with 5 cm depth, while rats of the exercised subgroups practiced swimming in pools (in the form of plastic tanks with 70 cm height and diameter of 90 cm) and filled with water to a depth of 50cm [9]**.** The water temperature was 32±1°C. Rats were regularly observed while swimming to keep them from drowning. After each daily swimming period, each rat was toweled and warmed under a heat lamp prior the rats were put back in their cages [10].

Evaluation of Behavioral Parameters:

Modified T-maze:

A manually operated T-maze with a central division and guillotine doors at each goal arm was built. The maze pattern was formed according to Deacon and Rawlins [11]**.** The novelty of the maze encouraged spontaneous exploration/alteration, hence no habituation was permitted. Over two days, each rat received one sample trial and 5 option runs, for an overall of 12 trials and 10 possible variations. Each of the rats in the sample run had the option to select a goal arm after being placed in the starting area at the bottom of the T. Gently moving the guillotine door down kept the rat in the assigned arm for thirty seconds. After that, it was taken out and left in its cage for ten minutes. The middle barrier was taken down and the guillotine door of the arm that was chosen in the sample run was elevated once more throughout the choice runs. After being moved to face away from the goal arms, the rat was free to choose one of the two open goal arms. Each trial took 1-2 minutes. An alternation (right choice) was defined as a rat choosing the opposite arm from the previous trial. The proportion of alternation per animal was computed as follows [12]:

$$\frac{Number\ of\ correct\ choices\ (Alternations)}{Total\ possible\ alterations} x100$$

Blood sampling and brain isolation:

Animals were originally sedated with ether, then blood specimens were obtained from the retro-orbital sinus and allowed for 30 minutes to clot. Then samples were centrifuged for 10 min at 3000 rpm and the obtained serum was stored at -80°C until assayed for APN and BDNF gene expression. After decapitation, brains were immediately removed from the skull, weighed and placed in 2 ml microtubes. Samples were placed in liquid nitrogen then preserved to -80°C freezer [13]. Histopathological examination was done with collaboration of Pathology department, Zagazig University. Brain samples were fixed in 10% formal saline, processed to make paraffin blocks, stained with H&E for assessment [14].

Quantitative real-time PCR

Total RNA was extracted from serum utilizing Trizol (Invitrogen; Thermo Fisher Scientific, Inc.).The NanoDrop® ND-1000 Spectrophotometer (NanoDrop Technologies; Wilmington, Delaware, United States) was used to measure the A260/A280 ratio of 1.5µl of RNA to assess its quality. To synthesize cDNA, a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems™, USA) was utilized. RT-PCR was done in a Mx3005P Real-Time PCR System (Agilent Stratagene, USA) using TOPreal™ qPCR 2X PreMIX (SYBR Green with low ROX) (Cat. # P725 or P750) (Enzynomics, Korea) according to the manufacturer's instructions. The primer set of *BDNF* was,forward,5'-CCCGCACACTCTGTGTAGTT -3' and reverse,5'-CAGCCTTCATGCAACCGAAG -3' , *Adiponectin* was,forward,5'- GGACAAGGCCGTTCTCTTCA -3' and reverse,5'- CCCCATACACTTGGAGCCAG -3' compared to the reference gene *GAPDH*, forward, 5'- GCATCTTCTTGTGCAGTGCC -3' and reverse,5'- TACGGCCAAATCCGTTCACA -3'. The PCR cycle settings included 12 minutes of first denaturation at 95°C, then 40 cycles of denaturation at 95°C for 20 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. Sangon Biotech (Beijing, China) developed the oligonucleotide-specific primers. The fold changes in gene expression were assessed employing cycle threshold (Ct) method through the calculation of $2^{-\Delta\Delta Ct}$ [15].

STATISTICAL ANALYSIS

Data was analyzed utilizing the Statistical Package for Social Sciences (SPSS) version 19. Data with a normal distribution was presented as mean ± SD. To compare many sets of numerical (parametric) data, the analysis of variance (ANOVA) was used, then by the post-hoc turkey test (p-value < 0.05).). Also, independent sample t-test was used to compare the mean of each control group with its corresponding AD group.

Data was displayed graphically using Microsoft Excel for Windows (Microsoft Inc. USA.

RESULTS

Regarding body weight(g) in control group, it was significantly lower in subgroup Ic than subgroups Ia &Ib (140±9.43,191±8.75&191±8.76 respectively). Also in AD group, body weight was significantly lower in subgroup IIc than subgroups IIa &IIb (140±9.4, 191±8.8, and 191±8.77 respectively). No remarkable variances were detected between control subgroups and their corresponding AD subgroups. (Table1)

Concerning gene expression (fold change) of APN in control group, subgroup Ib(1.08±0.05) was significantly higher than subgroup Ia (1.00±0.12,p<0.05). Also subgroup Ic(1.18±0.02) was substantially elevated than subgroup Ib (p<0.05) and subgroup Ia (p<0.001). While in AD group, subgroup IIb (0.38±0.07) was substantially increased than subgroup IIa (0.30±0.03, p<0.05). Also subgroup IIc (0.79±0.06) was notably elevated than subgroup IIb (p<0.001) and subroup IIa (p<0.001). Moreover, all AD subgroups were significantly less than their corresponding control subgroups (p<0.001). (Table 2)

Concerning gene expression (fold change) of BDNF in control group, subgroup Ib(1.93±0.59) was substantially elevated than subgroup Ia(1.5±0.47,p<0.05). Also subgroup Ic(2.52±0.71) was substantially elevated than subgroup Ib (p<0.05) and subgroup Ia (p<0.001). While in AD group, subgroup IIb(0.53±0.03) was substantially elevated than subgroup IIa (0.15±0.02,p<0.05). Also subgroup IIc(0.91±0.05) was substantially elevated than subgroup IIb (p<0.001) and subgroup IIa (p<0.001). Moreover, all AD subgroups were significantly less than their corresponding control subgroups (p<0.001). (Table 3)

Regarding modified T-maze test (%), no substantial variance were found between control subgroups. However in AD group, subgroup IIb (33±4.38) was significantly higher than subgroup IIa (24±5.16,p<0.05). Also, subgroup IIc (57±4.83) was substantially elevated than subgroup IIb and IIa (p<0.001). Moreover, all AD subgroups were significantly less than their corresponding control subgroups (p<0.001). (Table 4)

Histopathological Examination:

The hippocampus of control group (Group I) showed intact neurons arranged closely with orderly arranged pyramidal neurons (Fig.A). The cortex of control group showed normal brain parenchyma and normal neuronal morphology (Fig.B). The hippocampus of $AlCl_3$-treated group (subgroup II a) showed decreased thickness of the hippocampus with increase in number of degenerated neurons with pyknotic nuclei and irregular and indistinct nuclear membrane (red arrows) (Fig.C). The cortex of $AlCl_3$-treated group (subgroup II a) revealed multiple neurodegeneration with small pyknotic nuclei, vacuolated cytoplasm and extracellular eosinophilic deposits (arrows) (Fig.D). The hippocampus of (subgroup IIb) revealed moderate improvement in the structural changes induced by $AlCl_3$ with increased thickness of hippocampus and decrease number of degenerated neurons (Fig.E). The cortex of subgroup IIb revealed mild improvement in the structural changes induced by $AlCl_3$ with decreased number of pyknotic nuclei and eosinophilic deposits (Fig.F). The hippocampus of subgroup IIc revealed remarkable improvement in the structural changes induced by $AlCl_3$ with almost normal thickness and arrangement of pyramidal neurons (Fig.G). The cortex of subgroup IIc revealed marked improvement with near normal brain parenchyma and remarkable decrease in the number of pyknotic nuclei and eosinophilic deposits (Fig.H).

Table (1): Body weight (in grams) among all studied groups:

		Sedentary	Moderate intensity exercise	High intensity exercise
Control groups	**Groups**	**Ia**	**Ib**	**Ic**
	Range (g)	180-200	180-200	130-150
	Mean ± SD (g)	191±8.75	191±8.76	140±9.43
	P of LSD vs. group Ia		**NS**	**<0.001**
	P of LSD vs. group Ib			**<0.001**
AD groups	**Groups**	**IIa**	**IIb**	**IIc**
	Range (g)	180-200	180-200	130-150
	Mean ± SD (g)	191±8.8	191±8.77	140±9.4
	P of LSD vs. group IIa		**NS**	**<0.001**
	P of LSD vs. group IIb			**<0.001**
P-value of unpaired t-test		**NS**	**NS**	**NS**

NS: Non significant (P>0.05) Significant (P<0.05)

Table (2): Shows gene expression (fold change) of APN in all studied groups:

		Sedentary	Moderate intensity exercise	High intensity exercise
Control groups	**Groups**	**Ia**	**Ib**	**Ic**
	Range	0.91-1.18	1.03-1.12	1.16-1.19
	Mean ± SD	1.00±0.12	1.08±0.05	1.18±0.02
	P of LSD vs. group Ia		**<0.05**	**<0.001**
	P of LSD vs. group Ib			**<0.05**
AD groups	**Groups**	**IIa**	**IIb**	**IIc**
	Range	0.26-0.35	0.30-0.45	0.71-0.86
	Mean ± SD	0.30±0.03	0.38±0.07	0.79±0.06
	P of LSD vs. group IIa		**<0.05**	**<0.001**
	P of LSD vs. group IIb			**<0.001**
P-value of unpaired t-test		**<0.001**	**<0.001**	**<0.001**

Table (3): Show gene expression (fold change) of BDNF in all studied groups:

		Sedentary	Moderate intensity exercise	High intensity exercise
Control groups	**Groups**	**Ia**	**Ib**	**Ic**
	Range	0.93-1.99	1.01-2.5	1.18-3
	Mean ± SD	1.5±0.47	1.93±0.59	2.52±0.71
	P of LSD vs. group Ia		**<0.05**	**<0.001**
	P of LSD vs. group Ib			**<0.05**
AD groups	**Groups**	**IIa**	**IIb**	**IIc**
	Range	0.14-0.19	0.48-0.59	0.82-0.99
	Mean ± SD	0.15±0.02	0.53±0.03	0.91±0.05
	P of LSD vs. group IIa		**<0.05**	**<0.001**
	P of LSD vs. group IIb			**<0.05**
P-value of unpaired t-test		**<0.001**	**<0.001**	**<0.001**

Table (4): Shows result of T Maze test in percentage in all studied groups:

		Sedentary	Moderate intensity exercise	High intensity exercise
Control groups	**Groups**	**Ia**	**Ib**	**Ic**
	Range (%)	70-80	70-80	70-80
	Mean ± SD (%)	75±5.27	76±5.16	75±5.27
	P of LSD vs. group Ia		**NS**	**NS**
	P of LSD vs. group Ib			**NS**
AD groups	**Groups**	**IIa**	**IIb**	**IIc**
	Range (%)	20-30	30-40	50-60
	Mean ± SD (%)	24±5.16	33±4.38	57±4.83
	P of LSD vs. group IIa		**<0.05**	**<0.001**
	P of LSD vs. group IIb			**<0.001**
P-value of unpaired t-test		**<0.001**	**<0.001**	**<0.001**

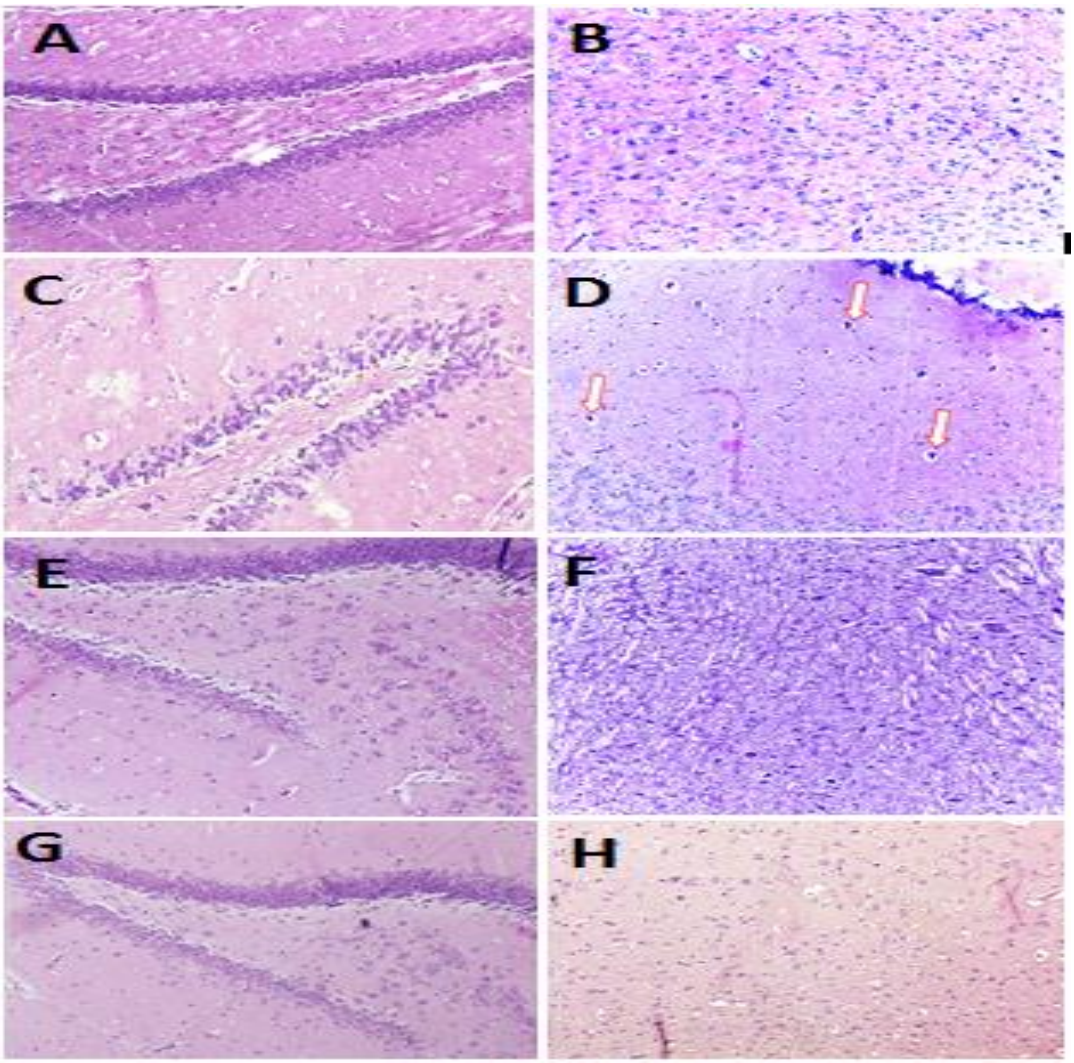

Figure A: The hippocampus of control group (Group I)intact neurons arranged closely with orderly ranged neurons.
Figure B: The cortex of control group with normal brain parenchyma and normal neuronal morphology.
Figure C: Hippocampus of $AlCl_3$-treated group(subgroup II a) showed decreased thickness of the hippocampus wit increase in number of degenerated neurons with pyknotic nuclei and irregular and indistinct nuclear membrane(red arrows).
Figure D: Cortex of $AlCl_3$-treated group (subgroup II a) revealed multiple neurodegeneration with small pyknotic nuclei, vacuolated cytoplasm and extracellular eosinophilic deposits (arrows).
Figure E: Hippocampus of (subgroup IIb) revealed moderate improvement in the structural changes induced by $AlCl_3$ with increased thickness of hippocampus and decrease number of degenerated neurons.
Figure F: Cortex of (subgroup IIb) revealed mild improvement in the structural changes induced by $AlCl_3$ with decreased number of pyknotic nuclei and eosinophilic deposits.
Figure G: Hippocampus of (subgroup IIc) revealed remarkable improvement in the structural changes with induced by $AlCl_3$ with almost normal thickness and arrangement of pyramidal neurons.
Figure H: Cortex of (subgroup IIc) revealed marked improvement with near normal brain parenchyma and remarkable decrease in the number of pyknotic nuclei and eosinophilic deposits .

DISCUSSION

AD is a neurological disorder and the leading cause of dementia. AD is featured by β-amyloid (Aβ) plaque formation, intraneuronal hyperphosphorylated tau aggregation, neuronal apoptosis, synapse loss, and neuro-inflammation [16].

In this study, we used $AlCl_3$ as Aluminum worsens brain damage caused by oxidative stress, triggers neuronal inflammatory processes, and impairs working and semantic memory, visuoperception,

and focus [17]. It also effectively modifies the blood-brain barrier, causing alterations in noradrenergic and cholinergic neurotransmissions. It involves reduced glucose consumption, elevated free radical production and lipid peroxidation, and alterations in protein phosphorylation, resulting in severe neurotoxicity [18].

The current investigation revealed a remarkable decline in APN gene expression levels in the AD group compared to control group and this agreed with ***Texixeira et al.***[19] who observed lower serum APN values in mild cognitive impairment and AD cases with equal subject sizes. This may be explained by the increased pro-inflammatory cytokine TNF-α level and its gene expression which is a suppressor of APN gene transcription [20]. Contrary to prior results, another investigation found no substantial variation in APN concentrations between a non-demented group and cases with dementia [21].

Our study showed that moderate to high intensity exercise, even in lack of weight loss, leads to a notable rise in APN gene expression. Our findings imply that a significant alteration in body weight caused by exercise training is not always necessary to elicit enhanced APN expression and this agreed with ***Garekani*** whose study provided the first indication that high to moderate aerobic exercise training, even in lack of weight reduction, improves the APN level in adipose tissue and blood of male rats [22]. However, a previous report suggested that weight loss is essential for elevating circulating APN values, but certain investigations have found that exercise training paired with a decrease in body mass has no impact on APN levels [22].

By the study end, the body weights of moderately exercised subgroups were similar but APN expression was higher in these subgroups than sedentary subgroups. While in groups with high intensity exercise, APN expression was significantly greater than those in the sedentary groups but their body weights were reduced. This was against a previous study that showed that physical activity accompanied by body mass loss did not influence APN levels [23].

Moreover, we found that APN expression was higher in high intensity exercised than moderately-exercise subgroups. Thus, the exercise training intensity appears to be a potential parameter affecting the APN expression. This agreed with prior reports that showed elevation in APN concentrations in highly trained male rowers with maximal exercise [22,24]. Blüher et al. similarly showed that prolonged exercise for four weeks led to elevated circulating APN concentrations among cases [25].

This increase in APN expression with exercise can be explained by decreased TNF-α (APN suppressor) where there is a proof that exercise may decrease circulating TNF-α values. And there is a substantial negative association between plasma APN and TNF-α [26].

Regarding BDNF there is significant decline in its gene expression in the AD group compared to control group. This is in line with Forlenza [27] who reported that AD cases have reduced BDNF serum values than healthy individuals. The most substantial BDNF decreases in AD have been revealed in the hippocampus, parietal, frontal, and entorhinal cortex. This may be explained by Aβ monomers, produced and released at firing synapses, play a critical effect in synaptic control and neuronal activity, making them neuroprotective rather than harmful. Aβ monomers control synaptic activity by activating cAMP response element-binding protein (CREB) via the PI3K/AKT pathway, resulting in prolonged transcription and BDNF production [28].

In AD, increased amounts of Aβ neurotoxic oligomers can hinder CREB activity in the brains of AD cases and mice models, as they fail to trigger the PI3K/AKT pathway [29]. Soluble Aβ oligomers can affect signal transduction pathways involved in memory and cognition, including CREB-regulated transcription [30].BDNF values in AD may be linked to CREB transcription instability caused by Aβ accumulation [31].

The current investigation assumed that with moderate to high intensity exercise there is an improvement in BDNF gene expression, as the moderately exercised AD group level of serum BDNF was significantly higher than the sedentary AD group and this agree with Cechetti et al. [32] who found out that running on treadmill (for 2 weeks) by rats with moderate intensity, significantly increased BDNF in hippocampal region compared with other regions of the brain.

In high intensity exercised AD subgroup, we found that BDNF expression was significantly higher than

that of the sedentary and moderately exercised AD subgroups. This was in line with Jeon and Ha that found long-term aerobic exercise at high to moderate intensity levels may have an advantageous impact on blood concentrations of BDNF and cognitive performance [33].

Our findings indicate that the higher the intensity of the exercise the more positive effect on BDNF expression.

The rise in BDNF is one of the most persistent alterations recorded after exercise, as reported by Wrann and colleagues [34] who assumed that exercise induces BDNF upregulation in the hippocampus through the PGC-1α/FNDC5 pathway. Durability of exercise increased the expression of the Fndc5 gene in the hippocampus, along with the expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α). This co-regulated the expression of neuronal fibronectin type III domain-containing protein 5 (FNDC5) with estrogen-related receptor α [35].

Overexpressing FNDC5 in the periphery raised BDNF expression in the hippocampus. This suggests that exercise-induced elevated levels of BDNF in the hippocampus were controlled by both muscle-derived irisin (FNDC5 secreted form) and the neuronal PGC-1α/FNDC5 pathway [34]. In contrast to the current study, Nofuji et al. [36] revealed that exercise reduced the levels of BDNF. The reason of lack of alignment between their findings and those of present study might be difference in type, intensity, duration of exercise or type of tested subjects.

In our study, modified T Maze test was used for testing short term and working memory. The AD group revealed a significant lower T maze score compared to control group. This finding agreed with Davis et al. [38] who showed significant decline in T maze score in 3xTg AD mice.

However, the moderately exercised AD subgroup score was significantly higher than the sedentary AD subgroup. And in the high intensity exercised AD subgroup, the result was significantly higher than that of the sedentary and moderately-exercised AD subgroups. These findings indicate that the higher the intensity of the exercise the more positive effect on memory**.** Chronic exercise has been widely proven to improve the memory of AD cases [39].

Following the onset of AD, exercise training has been shown in numerous trials to provide neuroprotection through reducing Aβ deposition, reducing inflammation, improving synaptic plasticity, and preventing neuronal apoptosis [40].

Histopathological examination of hippocampus and cortex tissue of the sedentary AD subgroup showed multiple neurodegeneration with small pyknotic nuclei, vacuolated cytoplasm, extracellular eosinophilic deposits, and decreased number of neurons with widely spaced irregular shaped neurons with loss of pyramidal neurons. These results were in consistent with Lakshmi et al. [18].

Moderately exercised AD subgroup revealed mild improvement in the structural changes induced by $AlCl_3$ with decreased number of pyknotic nuclei and eosinophilic deposits.

While high intensity exercised AD subgroup showed remarkable improvement in the structural changes induced by $AlCl_3$ with nearly normal brain parenchyma, almost normal thickness and arrangement of pyramidal neurons and remarkable decrease in the number of pyknotic nuclei and eosinophilic deposits. These findings supported by Hegazy et al. who showed that exercise training almost reversed the neurodegenerative hippocampal changes [41].

CONCLUSION

This study demonstrated that exercise improved short term and working memory in AD. And as the intensity of exercise increases, its effect increases. Also this study revealed that APN and BDNF expression decreased with AD and increased with exercise. It also provided the evidence that the intensity of exercise training appears to be a potential parameter affecting APN and BDNF expression. Thus, APN & BDNF gene expression can be employed as a biomarker for AD diagnosis. Also regular exercise should be recommended for all patients with AD.

CONFLICTS OF INTEREST

No potential conflict of interest was reported by the authors.

REFRENCES

1. Lu Y, Dong Y, Tucker D, Wang R, Ahmed ME, Brann D, et al. Treadmill Exercise Exerts Neuroprotection and Regulates Microglial Polarization and Oxidative Stress in a Streptozotocin-Induced Rat Model of Sporadic Alzheimer's Disease. JAD. 2017;56:1469–84.

2. Gratuze M, Julien J, Morin F, Marette A, Planel E. Differential effects of voluntary treadmill exercise and caloric restriction on tau pathogenesis in a mouse model of Alzheimer's disease-like tau pathology fed with Western diet. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79:452–61.

3. Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD, Palin M-F. Adiponectin action from head to toe. Endocr. 2010;37:11–32.

4. Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci. 2005;6:603–14.

5. Heyman E, Gamelin F-X, Goekint M, Piscitelli F, Roelands B, Leclair E, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—Possible implications for reward and depression. Psychoneuroendocrinology. 2012;37:844–51.

6. Liu L, Liu Y, Zhao J, Xing X, Zhang C, Meng H. Neuroprotective Effects of D-(-)-Quinic Acid on Aluminum Chloride-Induced Dementia in Rats. Evid Based Complement Alternat Med. 2020;2020:5602597.

7. McGeer PL, McGeer EG. Inflammation, autotoxicity and Alzheimer disease. Neurobiol Aging. 2001;22:799–809.

8. Wang R, Tian H, Guo D, Tian Q, Yao T, Kong X. Impacts of exercise intervention on various diseases in rats. J Sport Health Sci. 2020;9:211–27.

9. Liu YQ, Duan XL, Chang YZ, Wang HT, Qian ZM. Molecular analysis of increased iron status in moderately exercised rats. Mol Cell Biochem. 2006;282:117–23.

10. Lee H-H, Kim H, Lee J-W, Kim Y-S, Yang H-Y, Chang H-K, et al. Maternal swimming during pregnancy enhances short-term memory and neurogenesis in the hippocampus of rat pups. Brain and Development. 2006;28:147–54.

11. Deacon RMJ, Rawlins JNP. T-maze alternation in the rodent. Nat Protoc. 2006;1:7–12.

12. Wu CYC, Lerner FM, Couto E Silva A, Possoit HE, Hsieh T-H, Neumann JT, et al. Utilizing the Modified T-Maze to Assess Functional Memory Outcomes After Cardiac Arrest. JoVE. 2018;56694.

13. Delrobaei F, Fatemi I, Shamsizadeh A, Allahtavakoli M. Ascorbic acid attenuates cognitive impairment and brain oxidative stress in ovariectomized mice. Pharmacol Rep. 2019;71:133–8.

14. Gadelmawla MHA, Alazzouni AS, Farag AH, Gabri MS, Hassan BN. Enhanced effects of ferulic acid against the harmful side effects of chemotherapy in colon cancer: docking and in vivo study. JOBAZ. 2022;83:28.

15. Livak KJ, Schmittgen TD. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2−ΔΔCT Method. Methods. 2001;25:402–8.

16. He K, Nie L, Ali T, Wang S, Chen X, Liu Z, et al. Adiponectin alleviated Alzheimer-like pathologies via autophagy-lysosomal activation. Aging Cell. 2021;20:e13514.

17. Campbell A. The potential role of aluminium in Alzheimer's disease. Nephrol Dial Transplant. 2002;17:17–20.

18. Lakshmi BVS, Sudhakar M, Prakash KS. Protective Effect of Selenium Against Aluminum Chloride-Induced Alzheimer's Disease: Behavioral and Biochemical Alterations in Rats. Biol Trace Elem Res. 2015;165:67–74.

19. Teixeira C, Garzotto F, Piccinni P, Brienza N, Iannuzzi M, Gramaticopolo S, et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care. 2013;17:R14.

20. Igbokwe IO, Igwenagu E, Igbokwe NA. Aluminium toxicosis: a review of toxic actions and effects. Interdiscip Toxicol. 2019;12:45–70.

21. Dukic L, Simundic A-M, Martinic-Popovic I, Kackov S, Diamandis A, Begcevic I, et al. The role

of human kallikrein 6, clusterin and adiponectin as potential blood biomarkers of dementia. Clin Biochem. 2016;49:213–8.

22. Garekani ET, Mohebbi H, Kraemer RR, Fathi R. Exercise training intensity/volume affects plasma and tissue adiponectin concentrations in the male rat. Peptides. 2011;32:1008–12.

23. O'Leary VB, Marchetti CM, Krishnan RK, Stetzer BP, Gonzalez F, Kirwan JP. Exercise-induced reversal of insulin resistance in obese elderly is associated with reduced visceral fat. J Appl Physiol. 2006;100:1584–9.

24. Jürimäe J, Purge P, Jürimäe T. Adiponectin is altered after maximal exercise in highly trained male rowers. European journal of applied physiology. 2005;93:502–5.

25. Blüher M, Bullen Jr JW, Lee JH, Kralisch S, Fasshauer M, Klöting N, et al. Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: associations with metabolic parameters and insulin resistance and regulation by physical training. J Clin Endocrinol Metab. 2006;91:2310–6.

26. Page ST, Herbst KL, Amory JK, Coviello AD, Anawalt BD, Matsumoto AM, et al. Testosterone administration suppresses adiponectin levels in men. J Androl. 2005;26:85–92.

27. Forlenza OV, Diniz BS, Teixeira AL, Ojopi EB, Talib LL, Mendonça VA, et al. Effect of brain-derived neurotrophic factor Val66Met polymorphism and serum levels on the progression of mild cognitive impairment. The World Journal of Biological Psychiatry. 2010;11:774–80.

28. Zimbone S, Monaco I, Gianì F, Pandini G, Copani AG, Giuffrida ML, et al. Amyloid Beta monomers regulate cyclic adenosine monophosphate response element binding protein functions by activating type-1 insulin-like growth factor receptors in neuronal cells. Aging Cell. 2018;17:e12684.

29. Bartolotti N, Segura L, Lazarov O. Diminished CRE-Induced Plasticity is Linked to Memory Deficits in Familial Alzheimer's Disease Mice. JAD. 2016;50:477–89.

30. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci. 2019;13:363.

31. Pugazhenthi S, Wang M, Pham S, Sze C-I, Eckman CB. Downregulation of CREB expression in Alzheimer's brain and in Aβ-treated rat hippocampal neurons. Mol Neurodegener. 2011;6:1–16.

32. Cechetti F, Fochesatto C, Scopel D, Nardin P, Gonçalves CA, Netto CA, et al. Effect of a neuroprotective exercise protocol on oxidative state and BDNF levels in the rat hippocampus. Brain Research. 2008;1188:182–8.

33. Jeon YK, Ha CH. The effect of exercise intensity on brain derived neurotrophic factor and memory in adolescents. Environ Health Prev Med. 2017;22:27.

34. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise Induces Hippocampal BDNF through a PGC-1α/FNDC5 Pathway. Cell Metab. 2013;18:649–59.

35. Liu Y, Yan T, Chu JM-T, Chen Y, Dunnett S, Ho Y-S, et al. The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. Laboratory Investigation. 2019;99:943–57.

36. Nofuji Y, Suwa M, Moriyama Y, Nakano H, Ichimiya A, Nishichi R, et al. Decreased serum brain-derived neurotrophic factor in trained men. Neuroscience letters. 2008;437:29–32.

37. Canales JJ, Corbalán R, Montoliu C, Llansola M, Monfort P, Erceg S, et al. Aluminium impairs the glutamate-nitric oxide-cGMP pathway in cultured neurons and in rat brain in vivo: molecular mechanisms and implications for neuropathology. J Inorg Biochem. 2001;87:63–9.

38. Davis KE, Burnett K, Gigg J. Water and T-maze protocols are equally efficient methods to assess spatial memory in 3xTg Alzheimer's disease mice. Behav Brain Res. 2017;331:54–66.

39. Dare LR, Garcia A, Alves N, Dias DV, de Souza MA, Mello-Carpes PB. Physical and cognitive training are able to prevent recognition memory deficits related to amyloid beta neurotoxicity. Behavioural brain research. 2019;365:190–7.

40. Nigam SM, Xu S, Kritikou JS, Marosi K, Brodin L, Mattson MP. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. J Neurochem. 2017;142:286–96.

41. Hegazy MA, Abdelmonsif DA, Zeitoun TM, El-Sayed NS, Samy DM. Swimming exercise versus L-carnosine supplementation for Alzheimer's dementia in rats: implication of circulating and hippocampal FNDC5/irisin. J Physiol Biochem. 2022;78:109–24.

To Cite:

Seada, S., Bedear, S., Hadary, F., Ashour, W. Implication changes of serum adiponectin in chronic Moderate aerobic and resistant pattern of exercise in male albino rat model of Alzheimer. ***Zagazig University Medical Journal*****, 2024; (1804-1814): -. doi: 10.21608/zumj.2024.282691.3333**