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Histological Alterations Induced by Hypercholesterolemia Diet in Central Nervous System of Male Rats

Hadeel Gani Rafash *[1], Wefak Jbori Albazi [1] and Muna Hussain Al-Aameli[2]

[1] *Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Kerbala, Karbala, Iraq.*

[2] *Department of Anatomy and Histology, College of Veterinary Medicine, University of Kerbala, Karbala, Iraq.*

Abstract

HYPERCHOLESTEROLEMIA is a risk factor for neurodegenerative diseases that impairs neuronal function and reduces the neurogenesis. In light of its association with neurodegenerative disease, the current investigation set out to clarify how elevated cholesterol levels could impact oxidant and antioxidant, which necessitated the importance of studying the histopathological changes in the nervous tissue of the central system that resulting from excess dietary fats. Twenty adult albino male rats weighing 178-200 grams were included in this study. Animals were randomly divided into two equal groups with 10 rats each group. Control group was fed on regular normal diet, while the treated groups were received the addition of 1% cholesterol in their food for the period of 28 days. Examination of the neurological sections revealed that the pattern of disruption of nerve tissue cells with varying degrees of deposition of neurofibrillary tangles on nerve cells, manifested by intracellular and extracellular deposition of beta-amyloid plaques of the central nervous system, which permeate cerebral layers and are less permeable than in the cerebellum and spinal cord parts. As it turns out, neuronal atrophy nuclei with neuroglia proliferation and inflammatory infiltration cells of neural tissues. In conclusion, our results indicated that hypercholesteremia had a negative impact. Elevated levels of oxidative stress lead to damage to the biochemical structural integrity of neurons and Glial cells in the cerebral cortex in a significant way, the restoration of which is often fundamental in neurodegenerative diseases.

Keywords: Hypercholesterolemia, Oxidative stress, Amyloid β-protein.

Introduction

The disorder of lipoprotein metabolism known as familial hypercholesterolemia (FH) is a well-known cause of atherosclerosis and cardiovascular disease. It has been associated with cognitive abnormalities [1]. Elevated cholesterol levels can promote neuro-inflammation, a chronic inflammatory state in the brain. Subsequently, this inflammation can damage neurons leading to the formation of amyloid plaques and tau tangles, hallmarks of Alzheimer's disease (AD) [2]. The pathogenesis of Alzheimer's disease (AD) involves the build-up of amyloid-β (Aβ) peptides in senile plaques and protein aggregates, together with the localized build-up of hyperphosphorylated tau in neurofibrillary tangles [3].

The cerebellum, spinal cord, and brain are integral components of the central nervous system. Acting as both a relay station and a control center, these structures consist of neurons, the fundamental building unit of the nervous system, and neuroglia cells, which provide support [4].

Amyloid plaques in the brains of patients suffering other neurodegenerative diseases are primarily composed of peptides called beta amyloid [5], which have an amino acid composition ranging from 36 to 43 [3]. Many types of cell membranes include the β amyloid precursor protein, which usually releases β-amyloids into the plasma and cerebrospinal fluid at a fast pace [6, 7].

The amyloid hypothesis states that when beta-amyloid aggregations occur, immune cells are activated, causing inflammation by interfering with cell-to-cell communication [8]. Within the cerebral tissues, a patch of compact amyloid nuclei is generated, neuroglia proliferates, nerve cells deform, and the layer of pyramidal cells is disorganized with

*Corresponding authors: Hadeel Ganai Rafeash, E-mail: hadeel.g@uokerbala.edu.iq,Tel.: 9647830382195
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edematous exudate, all of which highlight the author's [9]. A β-peptide accumulation in the cerebral cortex has been linked to several known symptoms of AD, including acetylcholine esterase and choline acyltransferase modulation, neuronal and morphological deterioration, and cognitive decline, according to numerous studies [10, 11].

In cognitive diseases the process of neuro-degeneration may be attributed to the toxicity of β-amyloid (Aβ), which has been shown to occur in vitro and appears to involve oxidative stress. This process underpins the characteristic feature of AD, which is the progression of neuro-degeneration [12].

Oxidative damage can alter the structure of the protein, which can change the amino acids and result in the creation of cross-linked protein aggregates [13]. Thus, the creation of protein-bound carbonyl groups as a consequence of direct oxidation of amino acid side chains by reactive oxygen species (ROS) or lipid peroxidation end products, like advanced glycation end products, malondialdehyde (MDA), and 4-hydroxynonenal (HNE), is widely employed as a marker of protein oxidation or modification [14, 15]. The diagnosis of amyloidosis relies on the demonstration of amyloid deposits in tissue sections. Traditionally, the positively stain with Congo red stain is considered the criterion standard for diagnosing amyloid [16]. Our study aims to investigate the histological changes in the brain and spinal cord of male rats given a 1% w/w cholesterol diet every day for 28 days.

Material and Methods

Experimental protocol

In this investigation, twenty white male ratsuses because male rats are not more affected by hormones such as estrogen and progesterone, which may affect the results of the study, weighing 178 ± 200 g and age 10–14 weeks, were employed from the University of Karbala's College of Veterinary Medicinin Iraq. The animals were kept in hygienic, purpose-built plastic cages. They were kept in the right environment (good ventilation, temperature (22-25°C), 55% relative humidity and a 12-hour light cycle). For the purpose of allowing them to acclimate to the standard testing settings, they were held for two weeks with a frequent monitoring. Then, rats were randomly divided into two groups (10/group) and administered the ensuing medical interventions: for a month, rats receiving 1% cholesterol (w/w) and the control group were fed a regular diet [16].

Collecting blood samples

Once the animals were sedated and given a chloroform inhalation, sterile medical syringes containing 5 mL were inserted into the heart. The samples were then centrifuged for five minutes at 4000 revolutions per minute in a dedicated gel tube. The isolated serum samples were stored in Eppendorf tubes at -30°C for further tests.

Glutathione levels measurement

Glutathione spectrophotometric measurement of serum and homogenized brain tissues were conducted using Ellman's reagent [17]. In order to extract all of the proteins from the tissue homogenate and determine the GSH concentrations. For analysis, clean supernatants were used after centrifugation at 11000 x g for 15 minutes at 4°C.

Malondialdehyde levels measurement

Malondialdehyde was estimated by Thiobarbituric acid (TBA) assay method of [18] on spectrophotometer, it was measured using serum and brain tissue.

Organs collection for histological section

Rats were euthanized by given a chloroform inhalation at the conclusion of the experiment [19]. And the animals were dissected to remove samples (cerebellum, cerebrum, and spinal cord). The organs were then preserved in formalin at a concentration of 10% in clean plastic containers after being numbered until the histological section was performed.

Histological changes study

After extracting organs from formalin washing with tap water, the samples were followed up with classical techniques for routine histological procedures, including dehydration with serial concentrations of alcoholic solution, and embedded in paraffin after being cleaned with xylene, and finished by sectioning 5 micrometers thickness microtome sections. The histological sections were stained with different stains. Hematoxylin and eosin as a routine histological stain (morphological structures) [20]. The structural and pathological characteristics of brain tissue were examined using histochemical Congo-red staining (to detect beta amyloid accumulation). Histological sections were photographed by a Chinese OMAX 20-megapixel tube microscope camera equipped with image processing software [21].

Statistical analysis

The statistical program Graph Pad Prism 8.0 the t-test and correlation was used, $P \leq 0.05$ was chosen as the standard of significance. The data points were shown as mean± SD [22].

Results

The results of the present study revealed that the control group showed a normal design architect of

the nervous tissues (neuron, neuropil and neuroglia) of brain (cerebral, cerebellum) and spinal cord, which composed from neo-cortex and neo-medulla. The cortex was formed six strata variable thickness that are blended with each other, in cerebral involve (molecular, external granular, external pyramidal, internal granular, internal pyramidal and multiform cells layers. Furthermore, the cerebellum has three well demarcated layers, these are the molecular, purkinje and granular cells layers, whereas gray and white matter makes up the spinal cord (Figures 1, 2).

As for the hypercholesterolemic rats (treatment group), we noticed a disorder pattern of nerve tissue cells evident by different degree of neurofibrillary tangles neurons (Neuro necrosis) by deposits a beta-amyloid plaque leads in neural and morphological degeneration in the neural tissues, specified from severe to mild, that permeates or spreads through the strata of the brain (cerebrum) and cerebellum, spinal cord represented mild, as it turns out, deeply stained a pyknotic nuclei, nicroptic karyorrhexis of degenerated neurons and purkinje cells with infiltration of inflammatory cells and proliferation of neuroglial cells (gliosis), (Figures 3- 5).

In Figure 6, the results of the current investigation indicate a significant ($P<0.0001$) decrease in brain GSH (22.07±0.31) with a significant ($P<0.0001$) increase in the MDA concentration (7.91±0.17) in the hypercholesteremic diet group as compared with the control group; 52.36±0.48, and 5.84± 0.19, respectively.

Figure (7) showed a significant ($P<0.0001$) increase in the serum MDA (0.344±0.008) in the hypercholesteremic diet group as compared with the control group (0.142± 0.003) and a significant ($P<0.0001$) decrease in the GSH concentration (2.90±0.14) in the hypercholesteremic diet group as compared with the control group (4.02 ± 0.02).

Discussion

The results of the present study observed in Figures (1, 2) were in agreement with other studies in which they mentioned that the basic structure including neuron and neuroglia of the central nervous system [4, 23].

Hypercholesterolemia caused by diet accelerates rat Aβ accumulation in their brain tissues. Our finding agree with the previous published studies [6, 10, 24] which showed that the deposition of beta amyloid on the nervous tissue clearly in cerebral cortex and mildly in cerebellum and spinal cord; furthermore, amyloid fibrils in several proteins react positively with Congo red amyloid dye ultrastructure of biofilms found inside cells (purkinje cells) and excreta cellular in cerebrum and spinal cord tissues, which represented a test for confirmation of the amyloid nature of protein aggregates, when bound to it will show a red color [25-26]. Additionally, one of the main causes of cell damage is oxidative stress, which is brought on by an excess of ROS and poor metabolism. In particular, the brain is represented the more vulnerable site to oxidative damage [27]. We observed neuro-corona necrosis with strongly marked pyknotic nuclei, nicroptic karyorrhexis of degenerated neurons and purkinje cells, and infiltration of inflammatory markers into the cells [28]. Disorders of cholesterol homeostasis in the brain affect several neurodegenerative diseases, as well as the proliferation and accumulation of fats in glial cells [29]. This is sporting our research findings that the increased number of neuroglia cells (gliosis) and distortion of the neurocytes of the nervous tissues lead to the neuroglia divergence to provide a higher proportion of the cholesterol needed to form synapses.

Cholesterol is a strong indicator of lipid peroxidation, a known mechanism of oxidative stress, as shown by a considerable decrease in brain and serum glutathione (GSH) concentrations and a marked increase in malondialdehyde (MDA) levels relative to the control group. That is why we call anything that can lower MDA levels a free radical scavenger [30-31]. Cholesterol-mediated reduction of mitochondrial glutathione (GSH) is worsened by elevated cholesterol levels caused by poor mitochondrial GSH transfer [32-33]. This, in turn, alters mitochondrial function and increases ROS generation. By amplifying the mitochondrial oxidative damage induced by Aβ. The results of the current study indicate a significant ($P<0.0001$) decrease in GSH and a considerable increase in MDA concentration in the group after a hypercholesteremic diet when compared to the control group.

However, the ROS directly interact with lipids to form aldehydes, dienals, or alkanes, including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA)[34]. We investigated the consequences of a high-cholesterol diet, which results in the release of significant amounts of MDA that builds up in protein and phospholipids due to the action of free radicals caused by the oxidation of cholesterol, thereby causing a chain reaction of fat oxidation, which results from neuronal damage, It's one of the causes of CNS weakness.

Conclusion

Hypercholesteremia diet (1% cholesterol) that was given for 28 days to male rats caused a case of oxidative stress and a significant elevation in the serum and homogenies brain tissue in MDA level and a significant decrease in serum and homogenies brain tissue in GSH level. Histologically, the brain (cerebrum and cerebellum) and spinal cord show signs of inflammation and the accumulation of beta amyloid, which damage the biochemical structural integrity of neurons and glial cells in the cerebral

cortex in a significant way, which often leads to neurodegenerative diseases.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

This study is a part of Msc in the college of Veterinary Medicine (University of Kerbala).

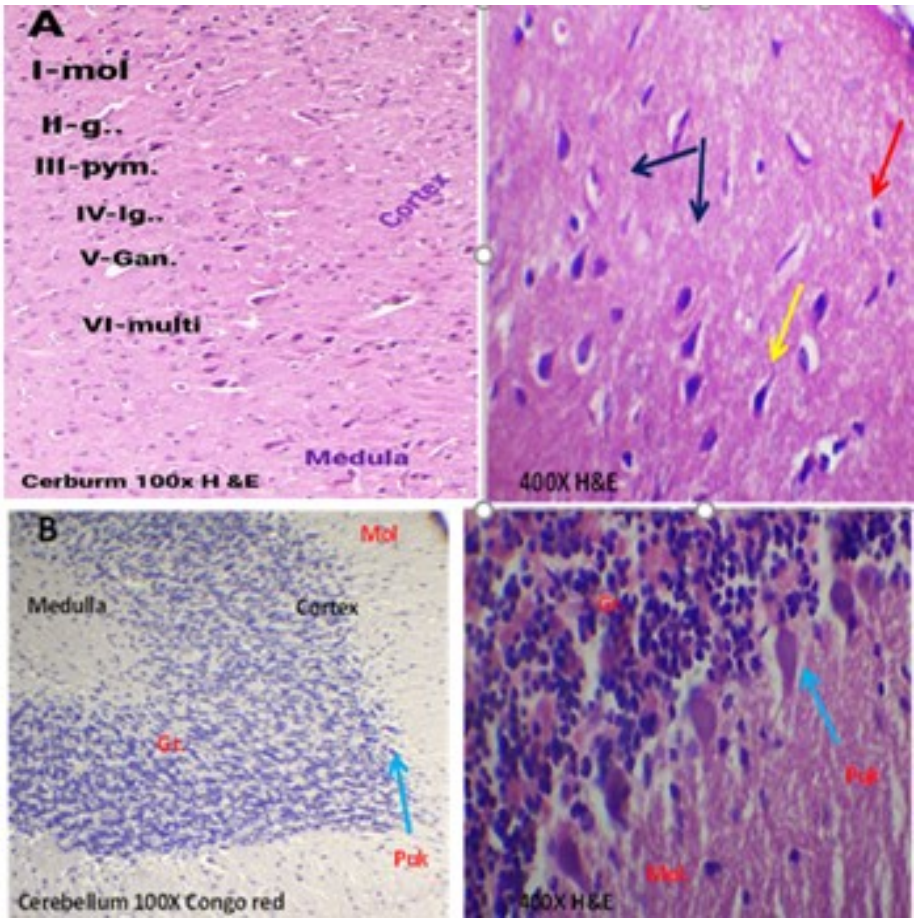

Fig 1. Photomicrograph of H and E and Congo red Magnification Power 100x, 400x: Represented normal histological sections. In control male rats of cortex layers with medulla in cerebrum (A) cerebellum (B): Cerebral-cortex is consist from six layers there are Molecular (I-Mol.), external granular (II- Eg), external pyramidal (III-Pym.), internal granular (IV-Ig.), ganglionic (V-Gan) and multiform (VI- multi) cells layers. Furthermore, cerebellar-cortex which is formed three strata; Molecular (I-Mol.), Purkinje (blue arrow) and granular (Gn.) cells layers and medulla. The (Red, Yellow and Black arrows) represented neuroglia, neuron and neuropil respectively.

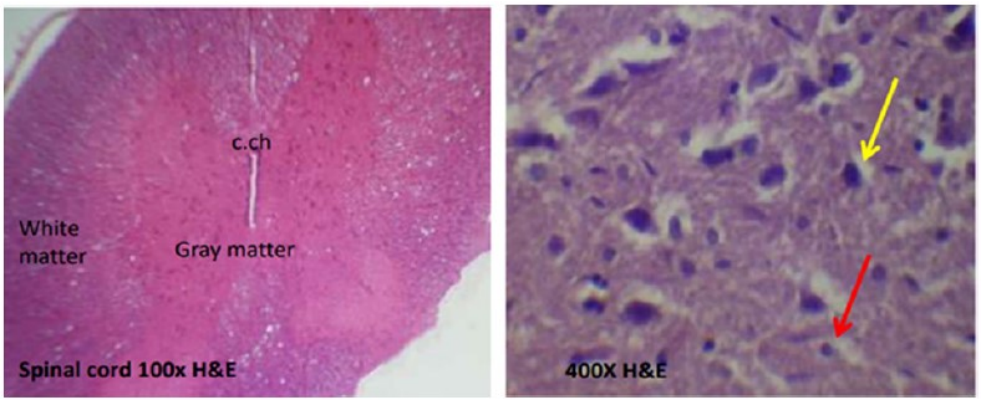

Fig. 2. Photomicrograph in control male rats group in hematoxylin and eosin stain and Magnification Power 100x, 400x: reveal the normal architecture of spinal cord tissues which is consist from the white and gray matter with central canal (c.ch) mediate it, the (Red and Yellow arrows) represented neuroglia and neuron respectively.

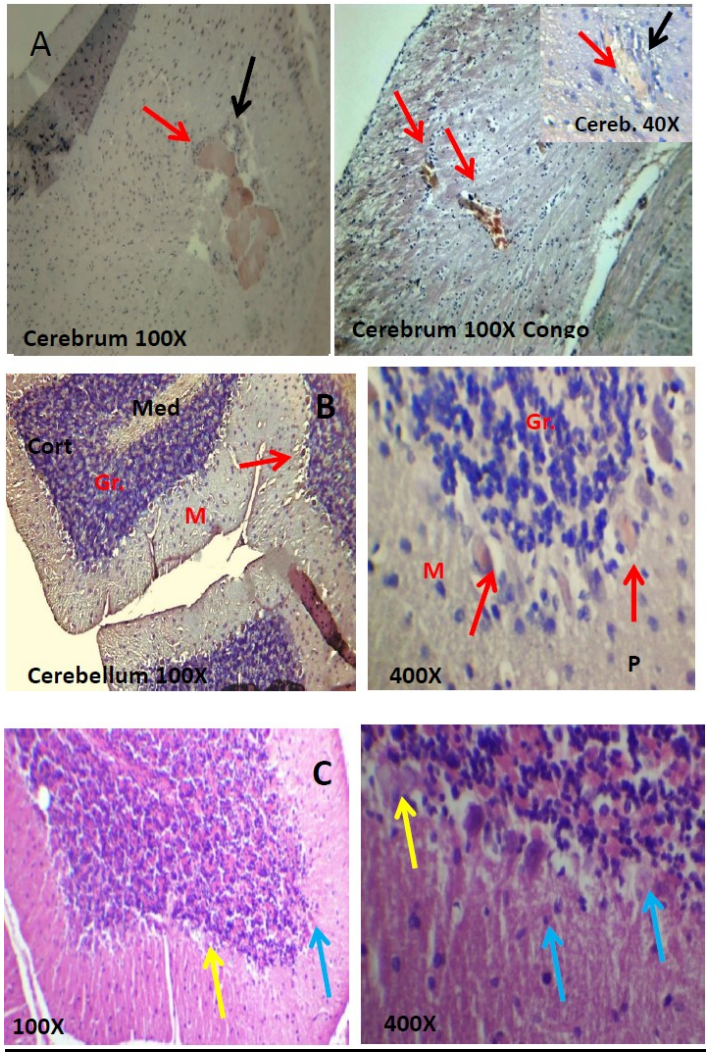

Fig. 3. Photomicrograph represented brain (cerebral and cerebellum) section of hypercholesterolemic male rats in CR and H and E stain and Magnification Power 100x, 400x: Reveal disorder pattern of neocortex and nero necrosis by significant deposits a beta-amyloid plaque in the neural tissues remarkable by highlight red color (Red arrow) protruding in the cerebral cortex strata but, mild in cerebellar cortex. In Addison Inflammatory cells infiltrations (Black arrow).Furthermore, necrotic neuronal karyorrhexis of degenerated Purkinje cells (yellow arrow) with deformity of structure (blue arrow).

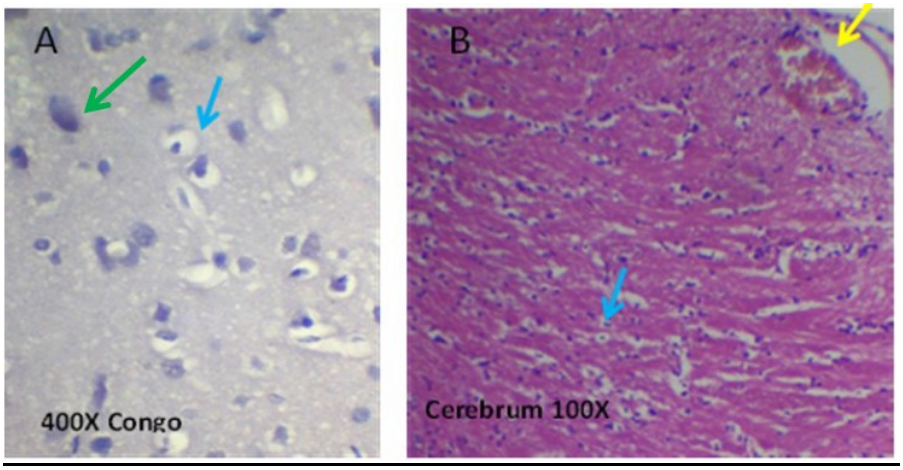

Fig. 4. Photomicrograph represented cerebral hypercholesterolemic male rats in CR and H and E stain and Magnification Power 100x, 400x: Showing changes occur disarrangement of neuro-cortical cells with significant increase of neuroglia cells and shrunken and degeneration (blue arrows) with congestion of blood vessel (yellow arrow),and pyknotic nuclei (green arrow).

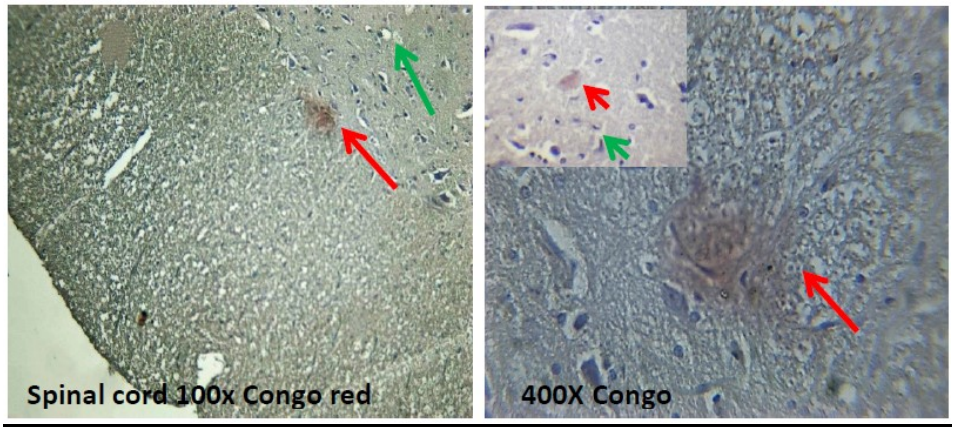

Fig. 5. Photomicrograph represented spinal cord section of hypercholesterolemic male rats in CR stain and Magnification Power 100x, 400x: Reveal mild deposition of beta –amyloid in highlight red color of the gray matter (red arrows) with significant glia cells and neuronal karyorrhexis (green arrow).

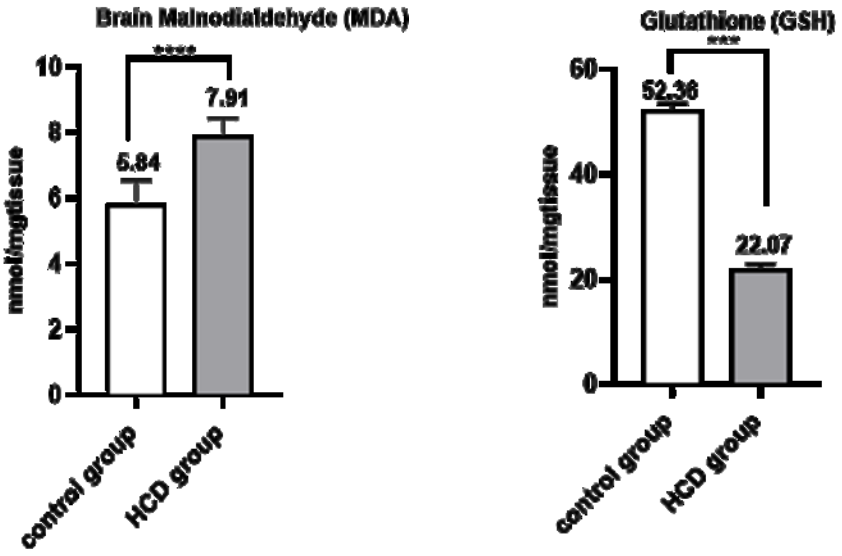

Fig. 6. Effect of 1% hypercholesteremic diet for 4 weeks on the brain tissue Malondialdehyde (MDA) and GSH concentration in the male rats.

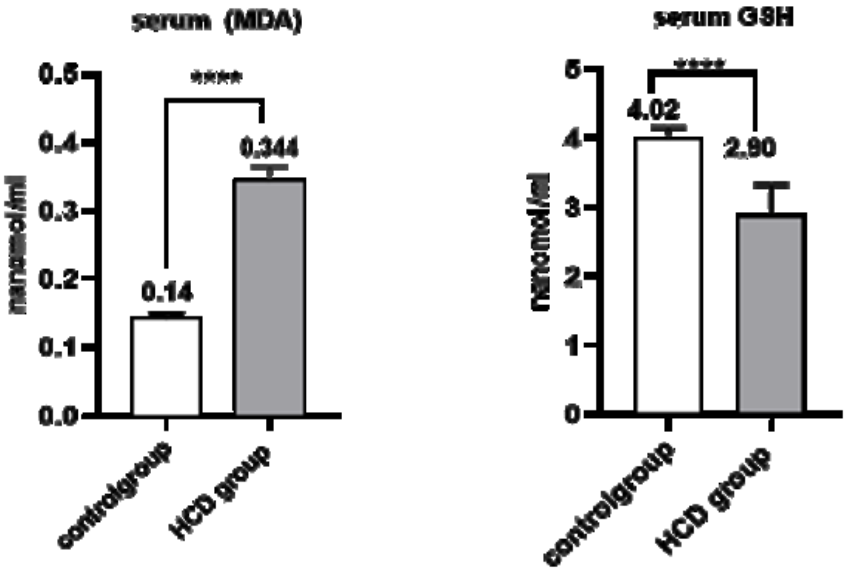

Fig. 7. Effect of a 1% hypercholesteremic diet on serum MDA and GSH concentrations in male rats after four weeks of feeding

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التغيرات النسيجية الناجمة عن النظام الغذائي لفرط كوليستيرول الدم في الجهاز العصبي المركزي لذكور الجرذان

هديل غني رفش [1]، وفاق جبوري البازي [1] و منى حسين العاملي [2]

[1]فرع الفسلجة والادوية - كلية الطب البيطري - جامعة كربلاء - كربلاء - العراق .

[2]فرع التشريح والانسجة - كلية الطب البيطري - جامعة كربلاء - كربلاء - العراق .

الملخص

فرط كوليستيرول الدم هو عامل خطر للإصابة بالأمراض التنكسية العصبية التي تضعف وظيفة الخلايا العصبية وتقلل من تكوين الخلايا العصبية. وفي ضوء ارتباطه بمرض التنكس العصبي، يهدف البحث الحالي إلى توضيح مدى تأثير ارتفاع مستويات الكولسترول على المواد المؤكسدة ومضادات الأكسدة، مما استدعى أهمية دراسة التغيرات النسيجية المرضية في الأنسجة العصبية للجهاز المركزي الناتجة عن زيادة الدهون الغذائية. شملت هذه الدراسة عشرين فأراً بالغاً من الذكور البيضاء تراوحت أوزانهم ما بين 178-200 غرام قسمت الحيوانات عشوائياً إلى مجموعتين متساويتين، كل مجموعة تحتوي على 10 فئران. تم تغذية المجموعة الضابطة على نظام غذائي عادي منتظم، في حين تم إضافة 1% كوليسترول في غذائها للمجموعات المعالجة لمدة 28 يوماً. كشف فحص المقاطع العصبية أن نمط تمزق خلايا الأنسجة العصبية بدرجات متفاوتة من ترسب التشابك الليفي العصبي على الخلايا العصبية، يتجلى في ترسب لويحات بيتا أميلويد داخل وخارج الخلية في الجهاز العصبي المركزي، والتي تتخلل طبقات المخ وتكون أقل نفاذية مما كانت عليه في أجزاء المخيخ والحبل الشوكي. كما اتضح، نواة ضمور الخلايا العصبية مع انتشار الخلايا الدبقية العصبية وخلايا التسلل الالتهابية للأنسجة العصبية. وفي الختام، أشارت نتائجنا إلى أن ارتفاع الكولسترول في الدم كان له تأثير سلبي. تؤدي المستويات المرتفعة من الإجهاد التأكسدي إلى إتلاف السلامة الهيكلية البيوكيميائية للخلايا العصبية والخلايا الدبقية في القشرة الدماغية بطريقة كبيرة، وغالبًا ما يكون استعادتها أمرًا أساسيًا في أمراض التنكس العصبي.

الكلمات الدالة : فرط كوليستيرول الدم، الإجهاد التأكسدي، بروتين الأميلويد بيتا ، العراق.