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Positive and Negative Aspects of Copaxone (Glatiramer acetate) Action on TC, TG HbA_{1c} and Iron Levels in The Sera of Iraqi Women with Multiple Sclerosis in Baghdad

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Abstract:

The aim of the present study is to highlight the role of total cholesterol (TC), triacylglycerol (TG), Glycated hemoglobin A_{1c} and iron in Iraqi women with multiple sclerosis and also to examine the biochemical action of copaxone (which is the most widely used in the 21st century to treat multiple sclerosis) on these biochemical parameters. This is the first study in Iraq which deals copaxone action on TC , TG , HbA_{1c} and iron. Ninety women in their fourth decade suffering from multiple sclerosis were enrolled in this study. They were divided into: the first (group B) composed of (30) women without any treatment related to multiple sclerosis or any treatment linked with chronic or inflammatory diseases. The second (group A_1) included (30) women under treatment with copaxone for 1 year, whereas the third group (group A_2) involved (30) women under treatment with copaxone for 2 years. Patients groups were compared with a healthy control group (group C) composed of (30) healthy women, TC, TG, HbA_{1c} and iron levels were determined in the sera of patients and control groups. Results of the present study has revealed that TC was high significantly increasing in the sera of group B (250.68±9.76) mg/dl compared with group C (175.36±8.81) mg/dl, while it was high significantly decreasing in the sera of groups A1 (211.88±5.90) mg/dl and A2 (212.12±5.60) mg/dL compared with group B (250.68±9.76) mg/dl. Beside, a non-significant difference was suggested between groups A_1 (211.88±5.90) mg/dl and A_2 (212.12±5.60) mg/dl. The present study also reported that TG was high significantly increasing in group B (224.84±10.76) mg / dl compared with group C (131.36±7.53) mg/dL whereas a significant decrease was shown in group A_1(142.48±4.63) mg/dl and group A_2 (195±4.20) mg/dl compared with group B (224.84±10.76) mg / dl. Surprisingly, a highly significant increase was reported in group A_2 (195±4.20) mg/dl compared with group A_1(142.48±4.63) mg/dl. The present study also suggested that HbA_{1c} level was high significantly increasing in the sera of group B (6.53±0.57) mg/dl compared with group C (4.99±0.07) mg/dl. Oppositely, it was high significantly decreasing in the sera of groups A1 (4.72±0.42) mg/dl and A2 (4.53±0.35) mg/dl compared with group B (6.53±0.57) mg/dl.

Futhermore, a non-significant difference was noted between groups A1 (4.72±0.42) mg/dl and A2 (4.53±0.35) mg/dl. This study also reported that iron level was high significantly decreasing in the sera of group B (37.31±4.24) µg / dl compared with group C (98.23±9.21) µg/ dl, whereas it was significantly increasing in the sera of groups A1 (44.05±6.32) µg/dl and A2 (45.31±6.82) µg/dl compared with group B (37.31±4.24) µg/dl . A non significant difference was shown between groups A1 (44.05±6.32) µg / dl and A2 (45.31±6.82) µg / dl.

Key words: *Multiple Sclerosis, Copaxone, TC , TG.*

Introduction:

Multiple sclerosis is a chronic autoimmune neurodegenerative disease of the central nervous system (CNS) [1,2]. Indeed, this disease causes chronic neurological features, particularly in "young and middle" age adults [3]. Anyway, multiple sclerosis is characterized as an inflammatory disease associated with inflammation, demyelination and destruction of oligodendrocytes and axons [1,4]. This autoimmune inflammatory disease is characterized by at least two demyelinating lesions presentation as distinct events affecting different parts of the central nervous system (CNS) [5]. Although multiple sclerosis is classified as an autoimmune disease, the cause of its pathology has not been yet fully established [6]. Nevertheless, there is a strong evidence suggesting that multiple sclerosis etiology is related to the combination of genetic causes and exposure to environmental factors as well a series of biochemical modifications affecting different extent neuronal functions [3,6]. Moreover, the immuno-pathology of multiple sclerosis is complex including autoreactive Th1 and Th17 lymphocytes, innate immune system cells involving dendritic natural killer, microglia cells in addition to vascular endothelial cells [4]. In view of biochemical factors, cholesterol is an essential membrane component for the maintenance of cell integrity and fluidity and for a wide variety of biochemical activities [7]. At this point, a recent study suggests a strong relationship between cholesterol metabolism and immunity [8]. On the other hand , triacylglycerols are commonly found as storage fats or oils and are described as neutral or non polar lipids differentiating them from polar membrane lipids [9]. Glycated hemoglobin A_{1c} (HbA_{1c}) is known as a compound consisting of of glycated hemoglobin A and glucose bond at the N-terminal valine. Indeed, hemoglobin glycation is not an enzymatic process, driven primarily by ambient glucose concentrations occuring post synthetically within red blood cells [10]. Iron is an essential element for the composition of several serum proteins and for the central nervous system, definitely , HbA is likely to be affected by iron deficiency .[11] As revealed by [10], at one end of impaired β-chains of normal adult hemoglobin (HbA), there is an available amino- group known as (N-terminal valine). [10]. Recently, several anti-inflammatory biochemical drugs play an important role in ameliorating this disease [3]. Glatriamiod derivatives are widely used for the treatment of multiple sclerosis. The first glatiramer and the best studied one is "glatiramer acetate" (GA) , the active ingredient in the copaxone chemical structure approved for the treatment of multiple sclerosis [12]. Glatiramer acetate is a class of compounds classified as a synthetic heterogeneous copolymer, it is composed of a mixture of four naturally occurring amino acids: "L-glutamic acids", "L- alanine", "L – lysine" and

"L- tyrosine", in a molecular ratio (0.14: 0.43 : 0.09 : 0.34) respectively [1,12]. It has an average MW in the range of 5000-9000 Daltons [12]. Copaxone (a traditional name for glatriamer acetate is a strong immunomodulatory) studied for the first time in 1987 [1]. In fact, copaxone is currently successful treatment for multiple sclerosis patients. Its dosage is daily 20 milligram as (injection approved in the Unites State in 1996) and recently approved in 2014 as40 milligram (injection administration three times / week) [1]. The aim of this work is to highlight the role of total cholesterol (TC), triacylglycerol (TG), Glycated hemoglobin A_{1c} and iron level in the sera of Iraqi women in multiple sclerosis and also to examine the biochemical action of copaxone on these biochemical parameters.

Materials and Methods:

In the present study, (90) multiple sclerosis women in their fourth decade were enrolled , all of them have attended private clinic in Baghdad with reports of magnetic radiation image (MRI) revealing that they are suffering from multiple sclerosis, Virtually, (30) of patients (group B) were newly diagnosed (they have not taken any treatments linked with multiple sclerosis or other chronic or inflammatory diseases) On the other hand, (group A1) was under treatment with Glatiramer acetate (copaxone) injection (20 mg/dl) daily for one year, while (group A2) was under treatment with the same dose of copaxone for two years. Glatiramer acetate (copaxone) comes as a solution to inject in the fatty layer just under the skin (subcutaneously). Women with multiple sclerosis were compared with a control group (group C) consisting of (30) healthy women with the same range of age. In the clinical laboratory, five milliliters (5 mL) of venous blood were collected from subjects enrolled in this work, the serum was separated from blood cells by centrifugation at 4000 round / minute for 5 minutes , kept frozen (-20 ^{o}C) until analysis. This work was performed in private laboratories in Baghdad. TC and TG were determined by enzymatic methods, TC was measured after enzymatic hydrolysis of cholesterol esters and oxidation of free cholesterol, whereas TG was determined by lipolysis, HbA_{1c} was evaluated by a high performance liquid chromatography (HPLC). Lastly, iron level was determined by flameless spectrophotometry. The results were described as mean ± SD (standard deviation). "Student t. test" was applied for comparison significance of the difference between all the studied groups. P value ($p\leq0.001$) , ($p\leq0.05$) and ($p\geq0.05$) were considered statistically "high significantly, significantly and non-significanlty" respectively, as suggested in the division of results.

Results:

Table (1): Copaxone Action on TC, TG, HbA_{1c} and Iron Levels in Sera of Multiple Sclerosis Patients and Control Groups.

Parameters	Group C Mean±SD	Group B Mean±SD	Group A_1 Mean±SD	Group A_2 Mean±SD	P B/C	P A_1/B	P A_2/B	P A_2/A_1
TC (mg/ dL)	175.36 ±8.81	250.68 ±9.76	211.88 ±5.90	212.12 ±5.60	H.S	H.S	H.S	N.S
TG (mg/dL)	131.36 ±7.53	224.84 ±10.76	142.48 ±4.63	195 ±4.20	H.S	H.S	S	H.S
HbA_{1c} (mg/dL)	4.92±0.07	6.53±0.57	4.72±0.42	4.53±0.35	H.S	H.S	H.S	N.S
Fe (µg/dL)	98.23±9.21	37.31±4.24	44.05±6.32	45.31±6.82	H.S	S	S	N.S

H.S : "high significantly" , S : "significantly" , N.S: "non significantly"

Data in Table (1) revealed a highly significant increase in TC level in the sera of group B (250.68±9.76) mg/dl compared with group C (175.36±8.81) mg/dl , Conversely, TC level was highly significant decreasing in sera of groups A_1 (211.88±5.96) mg/dl and A_2 (212.12±5.60) mg/dl compared with group B (250.68±9.76) mg/dl. Additionally, there was non-significant difference in TC level between groups A_2 (212.12±5.60) mg/dl and A_1 (211.88±5.96) mg/dl. Similarly, Table (1) show that TG level was highly significant increasing in the sera of group B (224.84±10.76) mg/dl compared with group C (131.36±7.53) but it was highly significant decreasing in the sera of group A_1 (142.48 ±4.63) mg/dl compared with group B (224.84±10.76) mg/dl. On the other hand, results of Table (1) revealed a significant decrease in TG level in the sera of group A_2 (195±4.2) mg/dl compared with group B (224.84±10.76) mg/dl. Unexpectedly, TG level was highly significant increasing in the sera of group A_2 (195±4.2) mg/dl compared with group A_1 (142.48 ±4.63) mg/dl. Likewise, HbA_{1c} was highly significant increasing in the sera of group B (6.53±0.57) mg/dl compared with group C (4.92±0.07) mg/dl , Table (1), whereas highly significant decreasing was reported in the sera of groups A_1 (4.72±0.42) mg/ dl and A_2 (4.53±0.35) mg/dl compared with group B (6.53±0.57) mg/dl, under those circumstances, there was non-significant difference in HbA_{1c} level between groups A_1(4.72±0.42) mg/ dl and A_2(4.53±0.35) mg/dl. Moreover , the results suggested that iron level was highly significant decreasing in the sera of group B (37.31±4.24) µg/dl compared with group C (98.23±9.21) µg/dl, while there was a significant increase in the sera of groups A_1 (44.05±6.32) µg/dl and A_2 (45.31±6.82) µg/dL compared with group B (37.31±4.24) µg/dl. A non significant difference was shown between groups A_1 (44.02±6.32) µg/dl and A_2 (45.31±6.82) µg/dl.

Discussion:

Multiple sclerosis is characterized by a sequence of biochemical modifications affecting different extent neuro-physiological functions. In this regard, great attention has been paid to lipid profile [4,6]. Occasionally, pathophysiology of multiple sclerosis has not been completely mapped out and appears to include different factors [3]. Indeed, autoreactive behavior of the immunological system in multiple sclerosis patients is accompanied by inflammatory lesions in central nervous system and axonal demyelination [3].

One of the accepted mechanisms reveals that myelin basic protein autoantigens trigger in inflammatory respond to towards the host tissue [3]. Interestingly, autoantigens and autoantibodies are known to cause devastation of myelin through up regulation of T cells and cytokines, which penetrate through the blood brain barrier to cause inflammation and myelin destruction [13]. Actually, myelin basic protein in human bodies is not a homogenous type of molecules and found itself as a group of charge isomers. This diversity in charge results from the deamination of the side chain of arginine, producing a citrulline residue. Accordingly, the positive charged side chain is important in forming contact with the negative charged membrane lipids, and in certain structural features of myeloid basic protein, these modifications in the content of citrulline may affect the membrane association of myeloid basic protein, promoting structural changes that expose epitopes of value for the auto-immune recognition and generate novel epitopes recognized by the immune system [3]. Cholesterol is one of the most common means that trigger inflammation by inducing pro-inflammatories secretion such as interleukin1-α and interleukin1-β [14]. Likewise, a study (Cunnane et al., 1989) has reported that more than 95% of the brain cholesterol is synthesized de novo from acetate, the hydroxyl methyl glutarate CR mediates with the rate limiting step of cholesterol biosynthesis, excess cholesterol is converted into cholesterol ester in neurons [13]. Consequently, total cholesterol is increased in the sera of multiple sclerosis patients (group B) compared with healthy control (group C). Indeed, cholesterol is a substational component of intact myelin, involved in the regulation of neural actions in the central nervous system (CNS) through specific mechanisms that are associated with lipid metabolism [15]. On the other hand , apolipoproteins play a major role in cholesterol recycling process-reverse cholesterol transport within the central nervous system and in the periphery production of cholesterol in the brain , loose cholesterol producing capacity and rely instead on cholesterol delivering lipoproteins to maintain ongoing needs [13]. Although the central nervous system has its own cholesterol production and transport system in multiple sclerosis, the blood – brain barrier is often compromised and apolipoproteins can easily carry cholesterol synthesized in the periphery to the central nervous system, thus altering cholesterol homeostasis behind the barrier [13]. A correlation is found between total cholesterol and the number of active plaques (contrast enhancing lesions) on the brain magnetic radiation image, it is possible to consider plasma cholesterol as a biochemical marker of multiple sclerosis [4,15]. Results show that the copaxone has a positive effect on the total cholesterol level, the high significant decrease in TC level in groups A1 and A2 compared with group B reflects the reactive role of copaxone in re-balancing total cholesterol level. Many studies highlight the reactive role of copaxone (as an immune-modulator), one of them (Aharoni et al., 2012) shows that the copaxone has unique immune-modulatory mechanisms leading to the distribution of the etiological process in multiple sclerosis by reinforcing immunoregulatory networks [16]. Also it has been reported that copaxone leads to a modification in the properties of the functional outcome of T cell signaling from Pro-inflammatory type(I) monocytes to anti-inflammatory type(II) monocytes, modulates immune responses [1,2]. In this regard, numerous effects of copaxone on the immune system have been identified [1]. Generally, the

suggested mechanisms can largely be divided into three groups. The three mechanisms deal with the possible influences of the copaxone on the adaptive and innate immune system, two of that are related to the influence of the inflammatory response, the last mechanism is linked with neuroprotective effects which also appear to include cells of the immune system [17]. The non-significant difference in the total cholesterol level between groups A1 and A2 reveals that the duration of treatment (for two years) has no side effect on TC level. Similarly, results show that triacylglycerol level is highly significant increasing in the sera of multiple sclerosis patients (group B) in comparsion with the healthy control group, Table (1). Accordingly, lipid profile such as the increased triacylglycerol (TG) levels is linked with the increased progression in multiple sclerosis [15]. Lipoproteins rich with triacylglycerol (VLDL and chylomicrons) are components of innate non adaptive host immune response to infection [18]. The recruitmet and extravasation of immune cells across the activated vascular endothelium of the blood brain is considered as a crucial step in the pathogenesis of multiple sclerosis. This study also suggest a negative effect of high triacylglycerol on multiple sclerosis cases [15] .Virtually, macrophages have an enormous capacity to store lipids , the absence of adipose triglyceride lipase (ATGL) in macrophages results in decreasing triacylglycerol hydrolysis activity and concomitantly in intracellular triacylglycerol accumulation [9]. Furthermore, results reveal that triacylglycerol level is highly significant decreasing in the sera of patients (treated for one year) (group A1) and also patients (treated for two years) (group 2) compared with patients without treatment (group B). Likewise, a study reveals that copaxone inhibits monocytes activation and production of tumor necrosis factor alpha(an important pro-inflammatory) by dendritic cells compared with untreated patients. Dendritic cells and monocytes isolated from multiple sclerosis patients receiving copaxone (for one year) show less activation, in addition to the reduced risk of replace[19]. Unexpectedly, results show that triacylglycerol level is significantly increasing in group A2 (patients under treatment with copaxone for two years) compared with group A1 (patients under treatment with copaxone for one year). Virtually, mannitol (monosaccharide) is found as one of copaxone ingredients [20, 21]. During the metabolism of mannitol, it should be converted into fructose as an intermediate compound [21]. Fructose will be converted into glucose [22]. Subsequently, glucose will be converted to triacylglycerol [23]. As a result, high triacylglycerol will be noticed as a side effect of the treatment with copaxone (but the increase not reaching the level of group B). The present study suggested that duration of treatment has an adverse effect on triacylglycerol level. In this regard, another study (Robert., 2010) agrees with results, reveals that hepatic fructose serve as substrate for de novo lipogenesis [24]. An association between multiple sclerosis and anemic syndromes (results from a decrease in iron level) has been reported. In this regard, a previous study (Deleva et al., 2012) has suggested that the coincidence of anemia with multiple sclerosis has been consider to impact seriously on clinical presentation, therapeutic strategy and the patients quality of life [25]. Another study (Sinha et al., 2012) has investigated the effect of iron deficiency anemia on HbA_{1c} levels, they observed that HbA_{1c} levels are higher in iron deficiency anemia patients. However, mechanisms

leading to the increased glycated HbA_{1c} levels are not obviously understood. Actually, it is suggested that in iron deficiency, the quaternary structure of hemoglobin chemical structure was modified, and the glycation of globin chains became more readily in the deficiency of iron (anemia) [26]. The two studies above are in agreement with our results related to the highly significant increasing in HbA_{1c} level in patients with multiple sclerosis (without treatment) in comparison with healthy control, Table (1). Moreover, it has been reported that patients with multiple sclerosis experience various complications, depending on the number of locations of lesions in the brain, erythrocytes with impaired membrane fluidity as shown in multiple sclerotic patients[27]. Furthermore, a recent study has suggested that iron is an essential element used for basic and specialized cellular functions throughout the body and in the central nervous system [28]. Another study (Kumar et al., 2010) indicates that iron deficiency is associated with impairment of cell mediated immunity [29]. Accordingly, the combination between [25], [26] and [29] supports the lower level of iron and the higher level of HbA_{1c} in multiple sclerosis patients. Consequently, the present study indicates the opposite correlation between (hemoglobin / Fe) and glycated hemoglobin A_{1c} levels, Table (1). The decrease in HbA_{1c} level in multiple sclerosis patients under treatment with copaxone (groups A_1 andA_2) compared with multiple sclerosis patients without any treatment (group B) reflects that copaxone (which is a reactive immune-modulator) improves iron and hemoglobin levels , in this regard, a relationship between erythrocytes, hemoglobin and immune system suggesting a reactive role in immune responds to pathogens. A study (Monera et al., 2010) reports that erythrocytes is a direct participant in the immune complex reaction [30]. In this regard, a recent study reveals a relationship between hematology and innate and acquired immune responses [31]. The non-significant difference in (HbA1c and iron levels) between groups A_1 and A_2 indicates that the duration of treatments (through two years) has no adverse effect on HbA_{1c} level.

Conclusions:

From this study we have concluded that:

1) Copaxone (glatiramer acetate) has a positive effect (good action) on TC level through the two years of treatment
2) Copaxone has a positive effect on TG level through the first year of treatment but it has an inverse effect through the second year of treatment.
3) Copaxone has a positive effect on HbA_{1c} level through the two years of treatment.
4) Copaxone has a positive effect on iron level through the two years of treatment.

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التأثيرات الإيجابية و السلبية لعمل الكوباكزون (كلاتيراماير أسيتيت) على مستويات الكوليسترول الكلي و الدهون الثلاثية و الهيموغلوبين السكري A_{c1} و الحديد في مصل دم نساء عراقيات مصابات بتصلب الأعصاب في بغداد

رشا زهير جاسم

قسم الكيمياء، كلية التربية للعلوم الصرفة إبن الهيثم، جامعة بغداد.

الخلاصة :

إن الهدف من الدراسة الحالية هو تسليط الضوء على دور الكوليسترول الكلي و الدهون الثلاثية و الهيموغلوبين السكري و الحديد لدى نساء عراقيات مصابات بتصلب الأعصاب و كذلك لإختبار تأثير الكوباكزون (الذي يعد من أهم الأدوية المستعملة على نطاق واسع لمعالجة تصلب الأعصاب في القرن الحادي و العشرين) على هذه المتغيرات الكيموحيوية. تعد هذه الدراسة هي الأولى في العراق و التي بدورها تبحث عن مفعول الكوباكزون على كل من الكوليسترول الكلي و الدهون الثلاثية و الهيموغلوبين السكري و الحديد. أخذت تسعون مريضة مصابة بتصلب الأعصاب في العقد الرابع من العمر و تم تقسيمهن إلى ثلاث مجاميع: حيث تضمنت المجموعة الأولى (group B) ثلاثين مريضة لم يخضعن لأي علاج فيما يخص مرض تصلب الأعصاب أو أي مرض مزمن أو إلتهابي، أما المجموعة الثانية (group A_1) فتضمنت (30) مريضة تحت العلاج بالكوباكزون لمدة سنة، بينما المجموعة الثالثة (group A_2) تضمنت (30) مريضة تحت العلاج بالكوباكزون لمدة سنتين. تمت مقارنة المجاميع المرضية بمجموعة ضابطة متكونة من (30) من النساء الأصحاء و تم تقدير مستويات الكوليسترول الكلي و الدهون الثلاثية و الهيموغلوبين السكري في مصل دم كل من المجاميع المرضية و المجموعة الضابطة. إن نتائج هذه الدراسة أثبتت أن مستوى الكوليسترول الكلي قد إرتفع بشكل معنوي عالي في مصل دم المجموعة B (250.68±9.76) ملغم/ ديسي لتر مقارنة مع المجموعة C (175.36±8.81) ملغم/ ديسي لتر بينما إنخفض بشكل معنوي عالي لدى المجموعةA_1(211.88±5.96) ملغم/ ديسي لتر و المجموعة A_2 (212.12±5.60) ملغم/ ديسي لتر مقارنة مع المجموعة B (250.68±9.76) ملغم/ ديسي لتر فضلا عن ذلك أظهرت هذه الدراسة فرقا غير معنويا بمستوى الكوليسترول الكلي مابين المجموعتين A_1 (211.8±5.96) ملغم/ ديسي لتر و (212.12±5.60) A_2ملغم/ ديسي لتر. إن الدراسة الحالية أثبتت أن مستوى الدهون الثلاثية إرتفع بشكل معنوي عالي لدى المجموعة 10.76) B±224.84) ملغم/ ديسي لتر مقارنة مع المجموعة C (131.36±7.53) ملغم / ديسي لتر بينما أظهر إنخفاضا معنويا لدى المجموعتين (4.63_1) A±142.48) ملغم/ ديسي لتر و (4.2_2) A ±195)) ملغم/ ديسي لتر بالمقارنة مع المجموعة B (224.84±10.76) ملغم/ ديسي لتر و بشكل غير متوقع أظهرت هذه الدراسة إرتفاعا معنويا عاليا في مستوى الدهون الثلاثية لدى المجموعة A2 (4.2 ±195)) ملغم / ديسي لتر مقارنة مع المجموعة (4.63_1) A±142.48) ملغم / ديسي لتر و كذلك أثبتت الدراسة الحالية أن مستوى الهيموغلوبين السكري إرتفع بشكل معنوي عالي لدى المجموعة B (0.57±6.53) ملغم / ديسي لتر مقارنة مع المجموعة 0.07) C±4.99) ملغم / ديسي لتر و على العكس نلاحظ أن مستوى الهيموغلوبين السكري إنخفض بشكل معنوي عالي لدى كل من المجموعتين A_1 (0.42±4.72) ملغم / ديسي لتر و (0.35_2) A±4.53) ملغم / ديسي لتر مقارنة مع المجموعة B (0.57±6.53) ملغم/ ديسي لتر، فضلا عن ذلك لوحظ إختلاف غير معنوي مابين المجموعتين A_1 (0.42±4.72) ملغم/ ديسي لتر و (0.35_2) A±4.53) ملغم / ديسي لتر. إن هذه الدراسة أثبتت أيضا أن مستوى الحديد إنخفض بشكل معنوي عالي في مصل دم المجموعة B (37.31±4.24) مايكروغرام/ ديسي لتر بالمقارنة مع المجموعة C (98.32±9.21) مايكروغرام/ ديسي لتر بينما إرتفع بشكل معنوي في مصل دم المجموعتين A_1 (44.05±6.32) مايكروغرام/ ديسي لتر و A_2 (45.31±6.82) مايكروغرام/ ديسي لتر بالمقارنة مع المجموعة B (37.31±4.24) مايكروغرام/ ديسي لتر. كما يظهر وجود فرقا غير معنويا مابين المجموعتين A_1 (44.05±6.32) مايكروغرام/ ديسي لتر و A_2 (45.31±6.82) مايكروغرام/ ديسي لتر.

الكلمات المفتاحية: تصلب الأعصاب، الكوباكزون، الكوليسترول الكلي، الدهون الثلاثية.