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(RESEARCH ARTICLE)

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The histological assessment of Anabolic Androgenic Steroids (Nandrolone Decanoate) administration on brain and liver of male albino rats

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Abstract

Nandrolone Decanoate is an anabolic androgenic steroid as testosterone derivatives which was commonly used in several diseases anemia, osteoporosis and muscle atrophy as well as its use by bodybuilders. The aim of this study to assessment the role of Nandrolone Decanoate administration on histological architecture of brain and liver and serum SOD, GSH Adropin in albino rats. Fifteen male albino rats, random distributed into three groups, 1st group I, 2nd group II where subcutaneous injection with (0. 5 and 0.15) ml/kg/ day / four times a week, for 45 day respectively and control group were injected with normal saline. The result of The group I showed congestion of meningeal and cortex hemolyzed blood vessels, cortex foamy appearance, neurons degeneration of inner pyramidal layer, pyramidal cells atrophy. axonal atrophy, myelin sheath degeneration and glial cells degeneration. The results of Group II, revealed infiltration of inflammatory cells within meningeal membrane, showed pyramidal cells degeneration within outer layer of cortex, atrophy of neuron cells and apoptosis of glial cells of inner cortex. Foamy appearance of white matter. The results of liver histological examinations of group I showed aggregate of fibroblast and inflammatory cells around central vein, infiltration of inflammatory cells in sinusoids vessels in between hepatocytes, cytoplasmic vacuolation of hepatocytes, pyknosis of degenerative hepatocytes, pyknosis of hepatocytes, hemorrhage in between hepatocytes with hemosiderin deposition and necrosis. The results of group II showed vacuolation within engorged hemolyzed RBCs within central vein, Infiltration of fibroblast cells adjacent portal bile duct, massive necrosis of hepatocytes. The results of Prussian blue staining in liver samples of group I and II showed iron deposit adjacent central vein, and between hepatocytes and increased iron accumulation between hepatocytes related with dosage of given dose. On the other hand the results of the present study revealed significant increasing of malondialdehyde and Adropin serum level otherwise there is a significant decreased superoxide dismutase and Glutathione when compared with control group on level P≤ 0.05.

Keywords: Nandrolone Decanoate; Brain; Necrosis; Adropin; Rat

1. Introduction

Nandrolone Decanoate are belongs to the anabolic androgenic steroids, especially group of Nor testosterone derivatives. The anabolic androgen steroids which basically represent a wide range of synthetic androgens used both legally and illegally medication (Sagoe et al. 2014). Moreover, Nandrolone Decanoate has been used for various medication, such as chronic renal diseases, osteoporosis in postmenopausal women (Federico et al, 2020). Nandrolone Decanoate as Breast cancer as an adjuvant drug for patients receiving corticosteroid administration (Salem2020), it is also used to maintain muscle body mass for individuals with muscle strain associated with losing weight caused by HIV and AIDS (Llewellyn, 2011). In the United States, about 2.9-4.0% of Americans have used anabolic androgenic steroids, and similarly high rates have been reported in various other regions, including Scandinavia, Brazil, the United Kingdom, and Europe (Basaria *et al*, 2001). The global prevalence of anabolic androgenic steroid use is 3.3% over a lifetime, with a

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higher prevalence of 6.4% in males when compared with 1.6% in females (Pope *et al*, 2014). The using of anabolic androgenic steroids is more common among adolescents (Rogol and Yesalis, 1992). Long-term use of anabolic androgenic steroids may lead to many adverse effects such as, lack of concentration, memory impairment, lethargy, and even increased mortality, acne and breast enlargement, increased risk of heart disease, liver cancer, hormonal disorders, lipid disorders in the blood, genital changes, infertility, cardiovascular disorders, sleep disorders, anxiety, musculoskeletal disorders, urinary disorders and digestive disorders (Patanè *et al*, 2020 ; Nieschlag, and Vorona, 2015) .It is important to be aware of these potential risks associated with the use of anabolic androgenic steroids, especially in the context of long-term and continuous use.

Adropin plays an important role in regulating lipid and glucose metabolism and thus regulating obesity (Kumar *et al*, 2008). The active Adropin protein similar in both rats, mice and humans (Mariami *et al*, 2020). The hormone Adropin is encoded by a gene related to the regulation of energy balance, and is expressed mainly in the brain and liver. As well as its detection in other tissues including the heart, lungs, kidneys, muscles, blood cells and breast cancer cells (chen *et al*, 2024).

The aim of study

The current study is designed to assessment the subcutaneously injection of Nandrolone Decanoate on histological texture of brain, liver and Malondialdehyde, superoxide dismutase, Glutathione and Adropin serum level in albino rats.

2. Materials and methods

Fifteen healthy albino male rats weighing (150-160 gm) were used for this experiment, placed in plastic cages under standard laboratory conditions, temperature of 22 ± 2 C^{o}, they had free access to rat food and water. All procedures related to animals were carried out in accordance with the approved animal testing protocols for the care and use of animals at Tikrit University. Animals leaved for a week before beginning the study, the experimental animals are randomly divided into three groups, five males each group, the 1st group I and second group II were injected with, nandrolone Decanoate 0.1, 0.15 ml/kg/day four times a week / 45 dayand control group were subcutaneously with normal saline. At the end of the study, blood samples are collect by Intracardiac (IC) bleeding, blood samples for biochemical tests. Brain and liver samples were fixed immediately with 10% buffered formalin then paraffinized into paraffin block, sectioning slices five micrometers thickness then mounted on slide staining Hematoxylin and eosin of brain and liver (Jasim et al 2022), Silver nitrate deposition for brain (savantha et al, 2018) and Prussian blue staining of liver (Reza et al 2015).

The level of malondialdehyde, superoxide dismutase, Glutathione were estimated by Using a diagnostic kit, blood serum samples of rats, the procedure done with the French business Biolabo. Adropin in the blood serum was estimated by using a Chinese-origin Eliza measurement kit (Sun Red Biotechnology, China), and the results were analyzed using the statistical program Duncan polynomial test with a probability level of $P \leq 0.05$.

3. Results

The results of the histological examination of both routine stain and silver nitrate stain of control group showed the cerebral cortex was covered with meninges membrane (pia mater) and it vascularized with blood vessels, that extended throughout the cortex, which subdivided into the molecular layer (contain pyramidal neurons and surrounded with glial cells), granular layer, outer portion contain multipolar pyramidal neurons cells surrounded by vacuoles surrounding by glial cells. Subcortical layer (fig 1, 2, 3 and 4).

The histological examination of group I, showed thickening and detachment of meningeal membrane which contained congested blood vessels and represent into outer layer (Arachnoid mater) and inner meninges membrane (pia mater) with spread of fibroblast in between these membranes (fig 5). The outer layer of the cerebral cortex, showed the molecular layer, decreased of pyramidal neurons in number. In deep layer of the cortex degenerated pyramidal neurons and blood vessels surrounded by caves with the presence of glial cells scattered within the cortex tissue. degeneration of neuron in inner layer of pyramidal and multipolar cells, apoptotic, and atrophic pyramidal neurons surrounded by concavities (fig 6). The medulla of the brain showed deformity of neurons surrounded by a clear zone, karyomegaly glial cells, disorganization of neurons fibers (fig 7).

silver nitrate stain of group I showed the cortex of the brain, thickening of meningeal layer, detachment of meningeal, external molecular layer appeared as foamy appearance, vacuolation around blood vessels, (fig 8). The cortex of the

brain showed, the cortex of the brain, cavitation around neuron (A) of internal pyramidal layer, cavitation around neuron and around atrophied neuron in polymorphic layer. Silver nitrate (fig 9). Shrinkage of neuron, atrophy of neuron of meningeal, disappearance of neuron (fig 10).

The results of group II, revealed infiltration of inflammatory cells in meningeal membrane, congestion of hemolysis blood vessels and degeneration of neuron (fig11). The outer part of cortex results showed The outer layer of the cortex showed an aggregate of degenerated pyramidal neurons which surrounded by glial cells, congested hemolyzed blood surrounded by cavitation zones(fig 12). The multipolar layer revealed an aggregation of different sizes of pyramidal appeared surrounded by cavitation zones. The medulla has a foamy appearance, with a decreased of glial cells in number, astrocytes surround the congested blood vessels (fig 13).

The results of silver nitrate impregnation of group II showed extensive cavitation around neuronal cells , disappearance of neuron, degeneration of neuron, shrinkage of neuron and diffused of glial cells (fig 14). Atrophy of neuron, shrinkage of neuron, hyperplasia of glial cells and disappearance of neuron (fig 15). Degeneration of nerve fibers, degeneration of basal ganglia, diffused with hypertrophy of glial cells and cavitation around basal ganglia cells (fig 16). Discontinuation of pia membrane, clumping nerve fibers, dissociation of granular, degeneration of dendrite of purkinje cells in molecular (fig 17). Dissociation of clumping nerve fibers, atrophy of purkinje cells, dissociation of granular (fig 18).

Histological examinations of liver sections of group I showed aggregate of fibroblast and inflammatory cells around central vein(fig19), infiltration of mononuclear cells in sinusoids of hepatocytes, cytoplasmic vacuolation of hepatocytes(fig 20), degeneration of hepatocytes, vacuolation of cytoplasm of hepatocytes, inflammatory cells in sinusoids (fig 21). vacuolation of cytoplasm of hepatocytes, pyknosis of degeneration of hepatocytes (Fig 22). Hemosiderin deposition between degeneration of hepatocytes, Pyknosis of degeneration of hepatocytes and necrosis in some area (fig 23).

The results of liver sections of group II showed vacuolation within engorged hemolyzed RBCs within central vein, cytoplasmic vacuolation of hepatocytes, Infiltration of inflammatory cells in between hepatocytes, degenerative hepatocytes, Infiltration of mononuclear cells (fig27),. Infiltration of fibroblast cells adjacent portal bile duct, congestion of blood vessel, other section revealed necrosis of hepatocytes. (Fig 28, 29). Infiltration of mononuclear cells, hemolysis of RBCs, pyknosis of hepatocytes, degeneration of hepatocytes (30).

The results of Prussian blue staining in liver samples of group control group showed normal archeteuter of liver section (fig 24). The results of group I showed iron deposit adjacent central vein, and between hepatocytes (fig25, 26) other sections of group II showed increased iron accumulation between hepatocytes related with dosage of given dose (fig 31, 32).

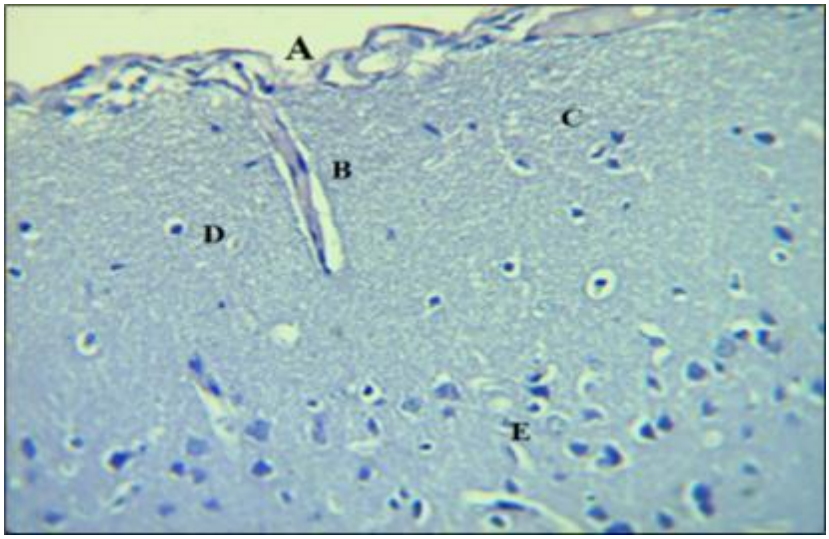

Figure 1 Control group brain tissue, cerebral cortex, in which the membranes of the meninges (A) appear . Meningeal blood vessel (B). Pyramidal neurons within the molecular layer (C). Glial cells (D). H&E X40

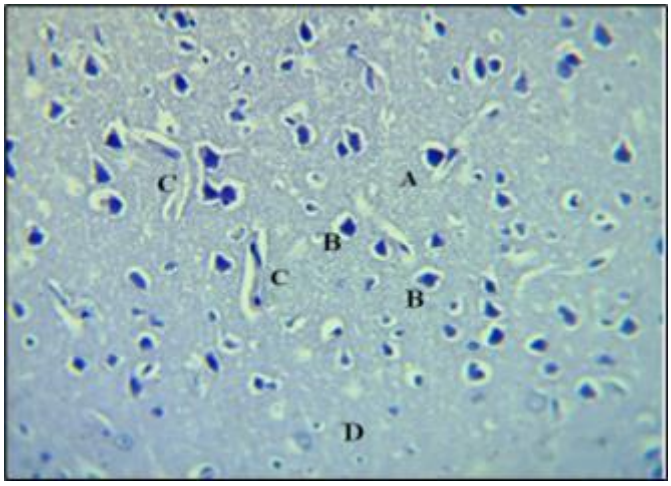

Figure 2 Control group brain tissue, pyramidal neurons (A) surrounded by vacuole Zones (B). blood vessels (C). Neuronal glial cells (D). H&E X40

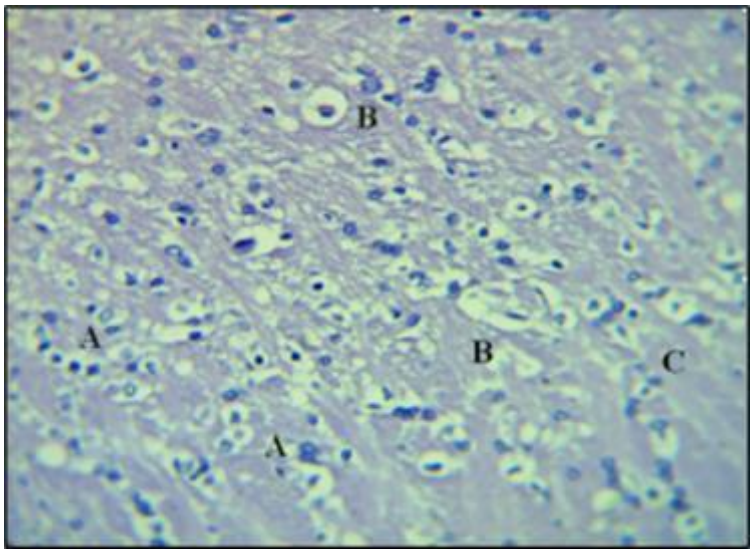

Figure 3 Control group brain tissue, white matter of the brain, glial cells (A). Vacuole Zones (B). Medullary nerve fibers (C). H&E X40

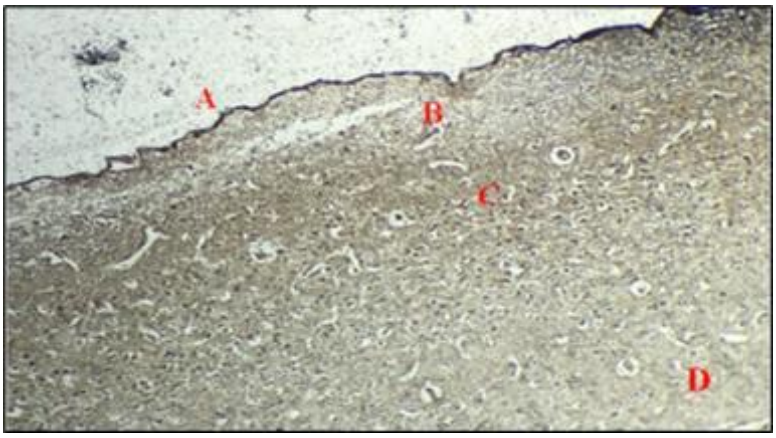

Figure 4 Control group brain tissue, cerebral cortex, meninges (pia membrane) (A). Molecular layer (B). External molecular layer (C). External Pyramidal layer (D). H&E X10

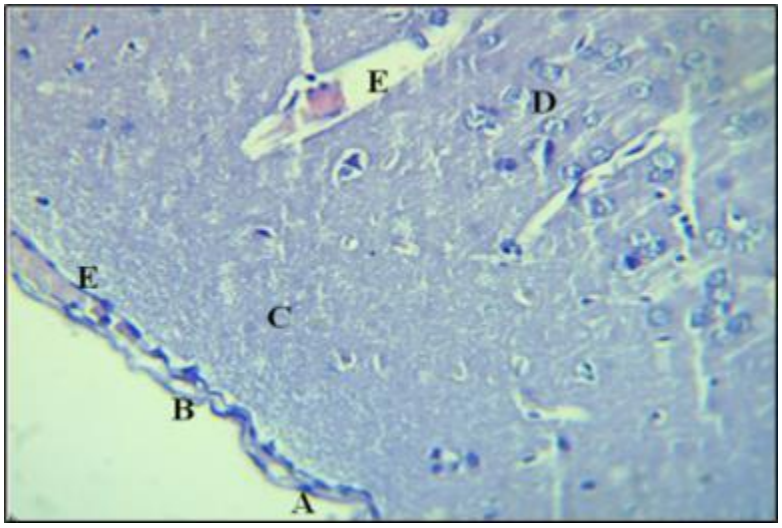

Figure 5 Group I, the cortex of the brain, the membranes of the meninges appear (A). Arachnoid membrane (B). Molecular layer (C). Pyramidal neurons (D). and congested blood vessels (E) H&E X40

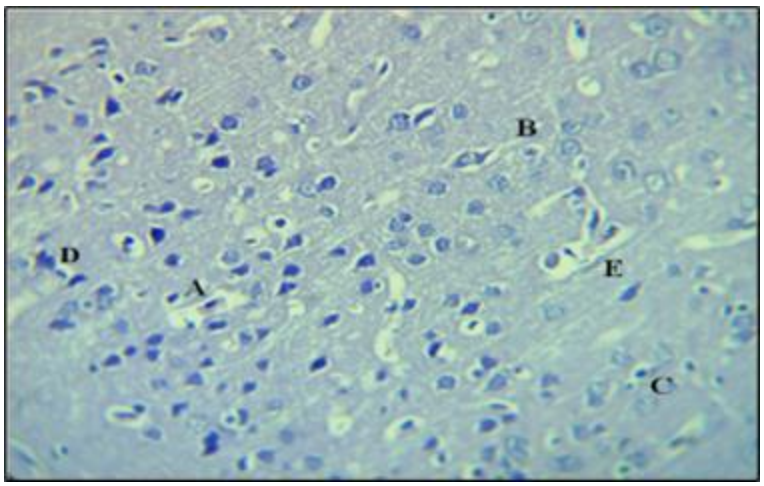

Figure 6 Group I : inner pyramidal neuron layer (A). Multi-layer (B) . Apoptotic Glial cells (C). atrophy of neuron (D)

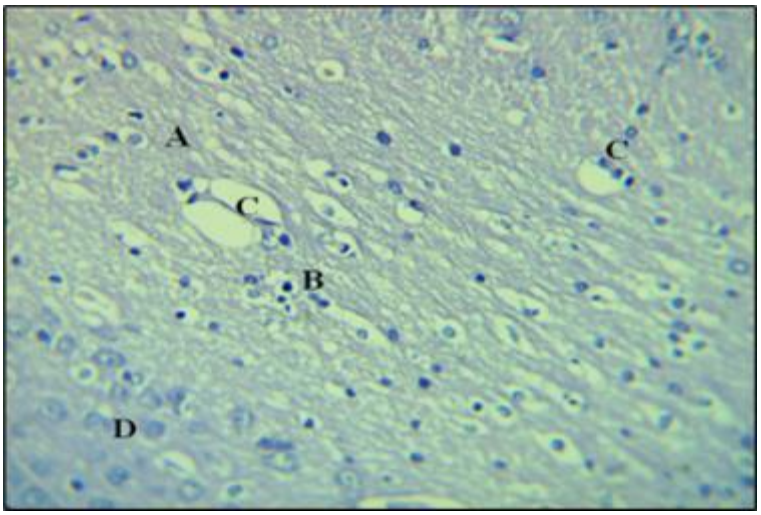

Figure 7 Group I, white matter of the brain, medullary nerve fiber (A). clear zones (B) around the cells. Multiple neurons (C). H&E X40

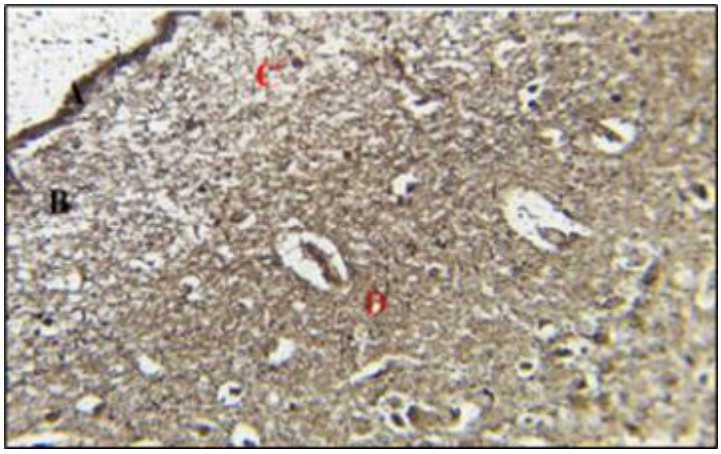

Figure 8 Group I: the cortex of the brain, thickening of meningeal layer (A) . detachment of meningeal (B). external molecular layer appeared as foamy appearance (C). vacuolation around blood vessels (D). Silver nitrate. 40X

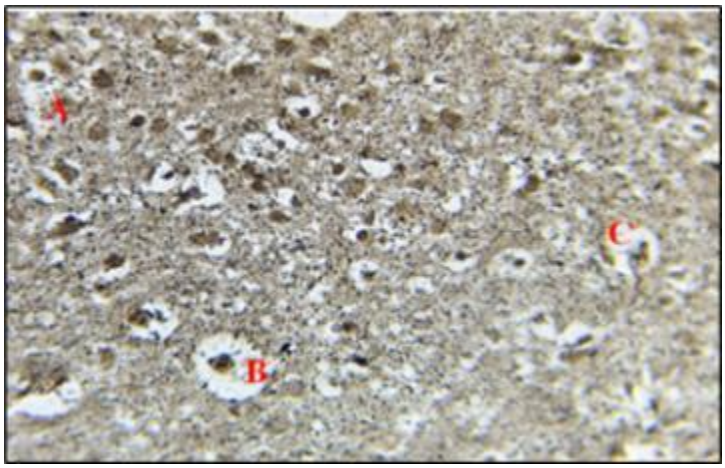

Figure 9 Group I, the cortex of the brain, the cortex of the brain, cavitation around neuron (A) of internal pyramidal layer . cavitation around neuron (B) and around atrophied neuron (C) in polymorphic layer. Silver nitrate. 40X

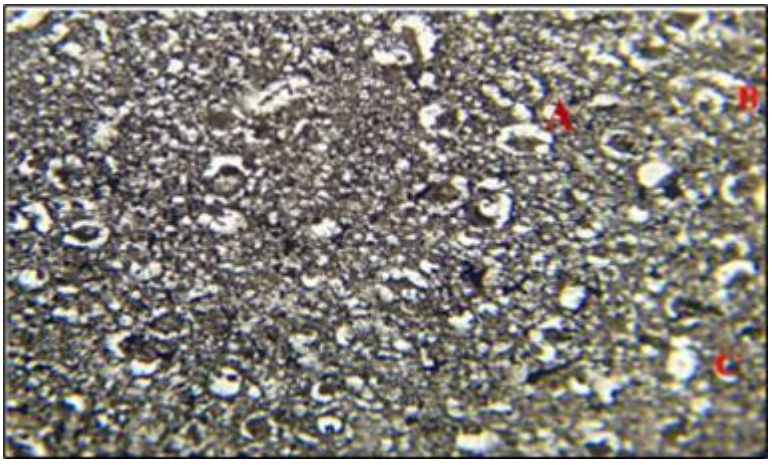

Figure 10 Group I, the cortex of the brain, shrinkage of neuron (A) . atrophy of neuron of meningeal (B). disappearance of neuron (C). Silver nitrate. 40X

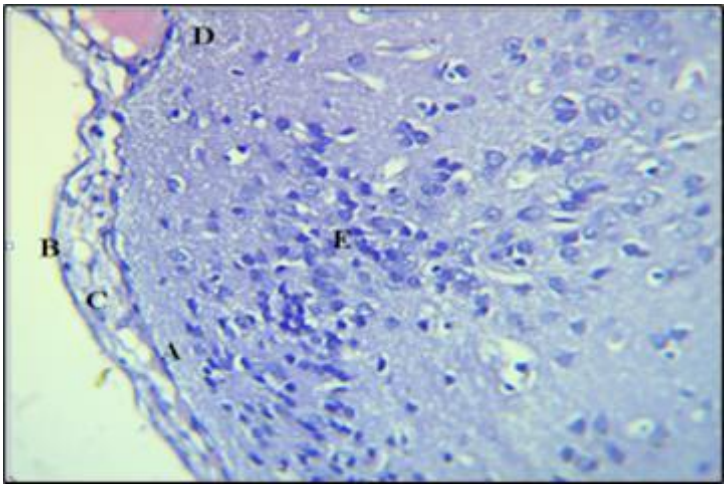

Figure 11 Group II, cerebral cortex, the membranes of the meninges appear (A) . Arachnoid membrane (B). Lymphocytes (C). Hemolysis within the meningeal blood vessel (D). Degenerated nerve cells (E). H&E X40

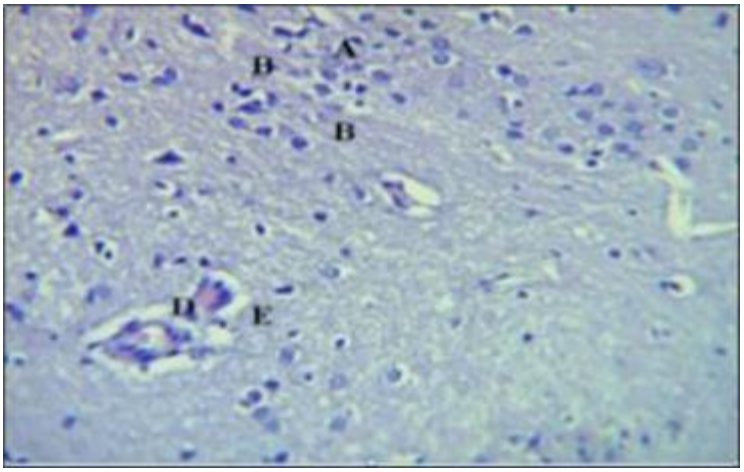

Figure 12 Group II, pyramidal neurons of different sizes (A). Atrophic cells (B). The medulla has a foamy appearance (C). congested blood vessels (D) are surrounded by astrocytes**.** H&E X40

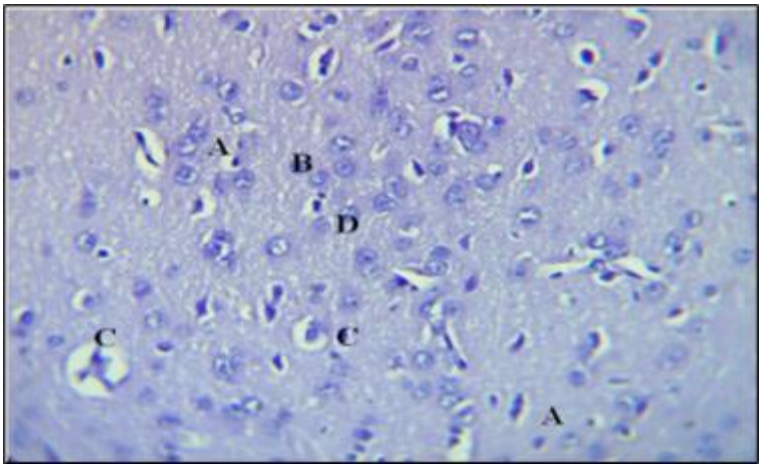

Figure 13 Group II, pyramidal neurons (A) within the inner pyramidal layer. apoptosis of neurons (B). Blood vessel (C).Glial cells (D). H&E X40

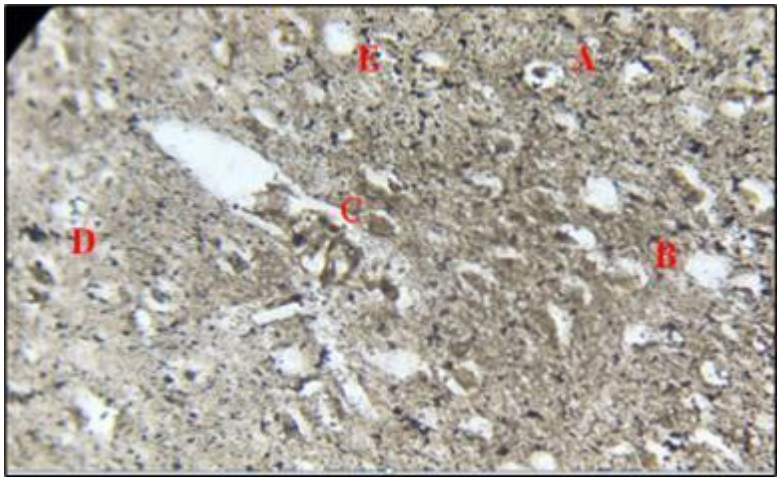

Figure 14 Group II, extensive cavitation around neuronal cells (A) . disappearance of neuron (B). degeneration of neuron (C). , shrinkage of neuron (D) and diffused of glial cells (A) Silver nitrate. 40X

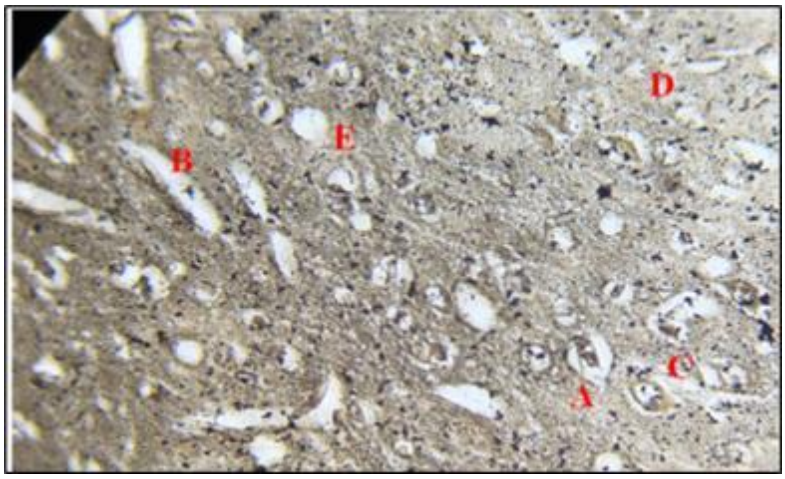

Figure 15 Group II, extensive cavitation around neuronal cells (A) . atrophy of neuron (B). shrinkage of neuron (C). hyperplasia of glial cells, (D), disappearance of neuron (C) Silver nitrate. 40X

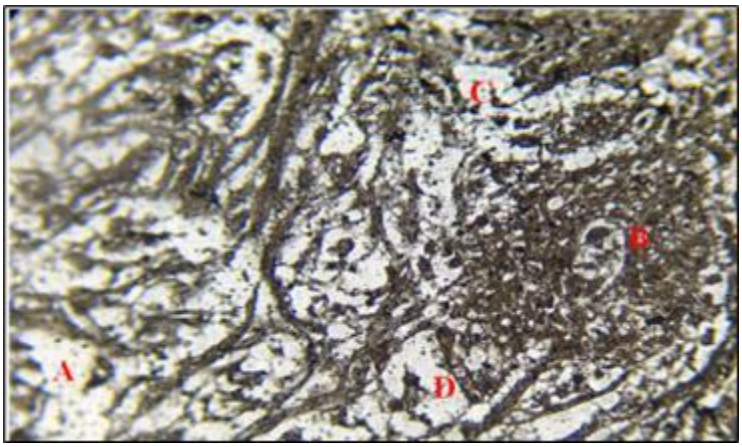

Figure 16 Group II, degeneration of nerve fibers (A). degeneration of basal ganglia (B). diffused with hypertrophy of glial cells (C). cavitation around basal ganglia cells (D). Silver nitrate. 40X

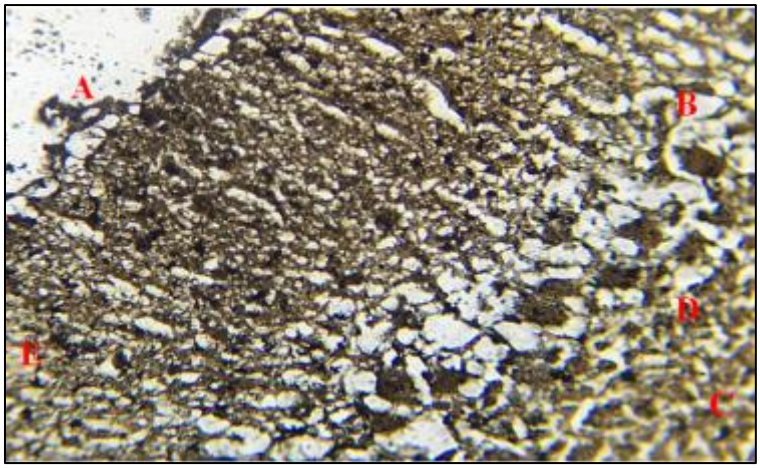

Figure 17 Group II, discontinuation of pia membrane (A). clumping nerve fibers (B). dissociation of granular (C). , degeneration of dendrite of purkinje cells (D) molecular (E) Silver nitrate. 40X

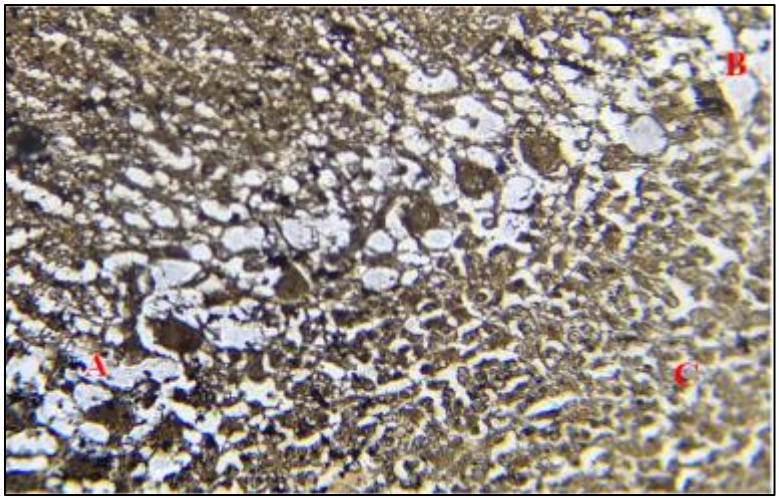

Figure 18 Group II, dissociation of clumping nerve fibres (A). atrophy of purkinje cells (B). dissociation of granular (C). Silver nitrate. 40X .

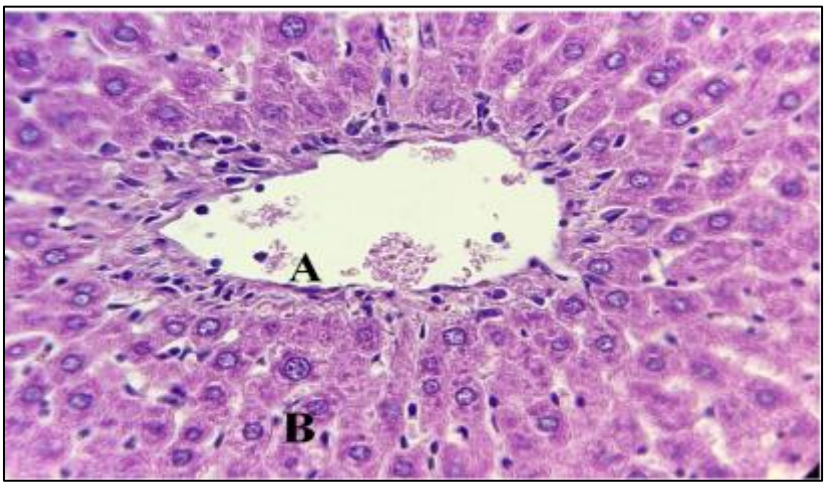

Figure 19 Group I, aggregated fibroblast and inflammatory cells around central vein (A). Inflammatory cells in sinusoids (B). H&E X40

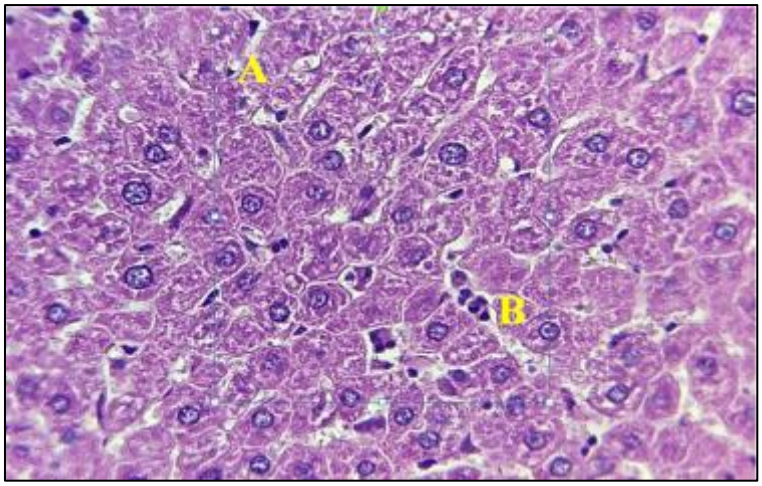

Figure 20 Group I, vacuolation (A). Inflammatory cells in sinusoids (B). H&E X40

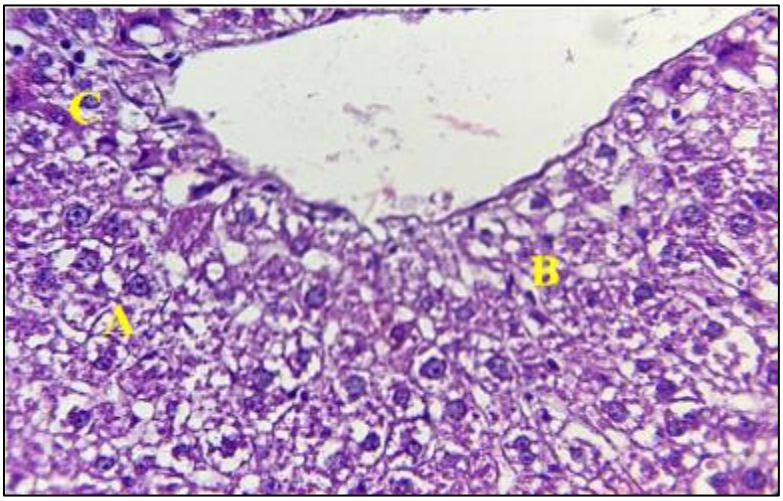

Figure 21 Group I, degeneration of hepatocytes (A). vacuolation (B). Inflammatory cells in sinusoids (C). H&E X40

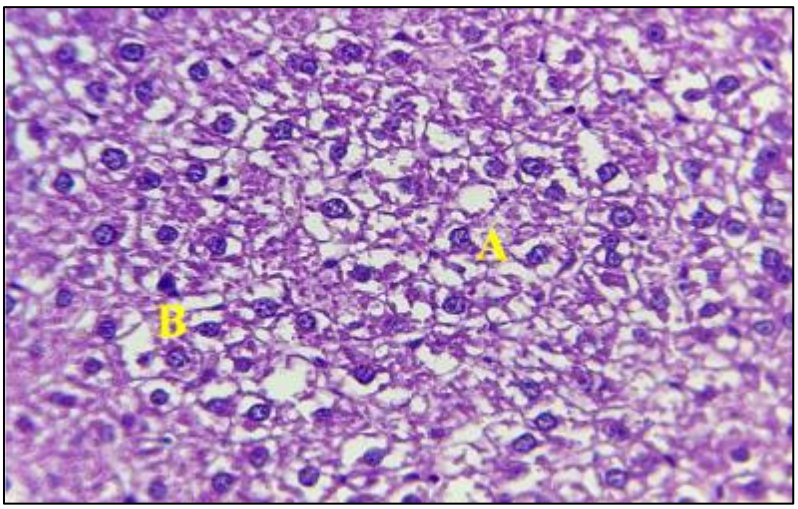

Figure 22 Group I, vacuolation (A). pyknosis of degeneration of hepatocytes (B). H&E X40

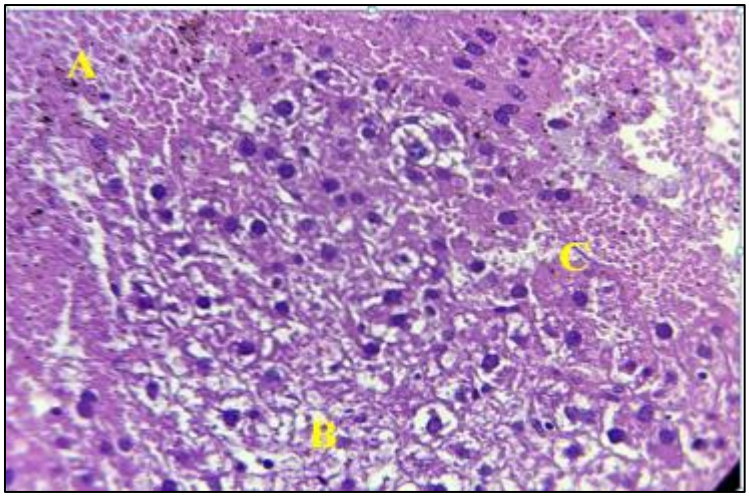

Figure 23 Group I, Hemosiderin deposition between degeneration of hepatocytes (A). Pyknosis of degeneration of hepatocytes (B). Necrosis in some area (C). H&E X40

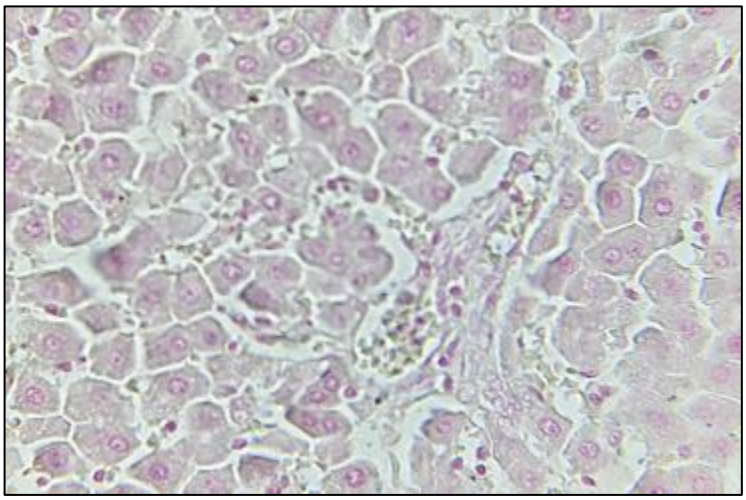

Figure 24 Group I, normal architecture of hepatocytes P. blue, 40X

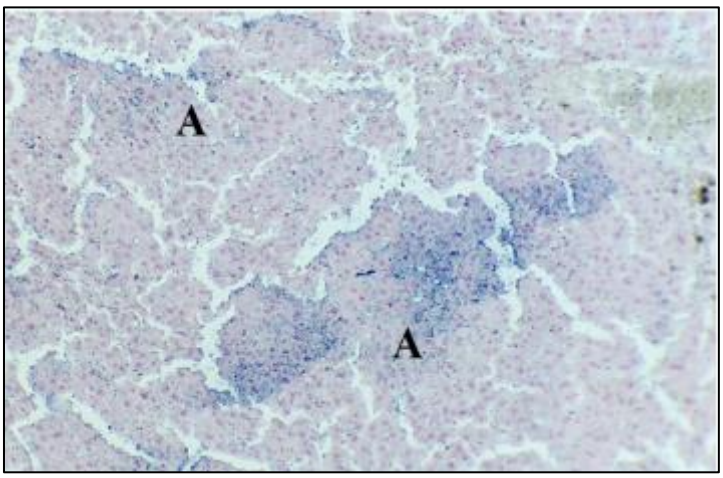

Figure 25 Group I, Iron deposition in between hipatocytes (A). P. blue, 40X

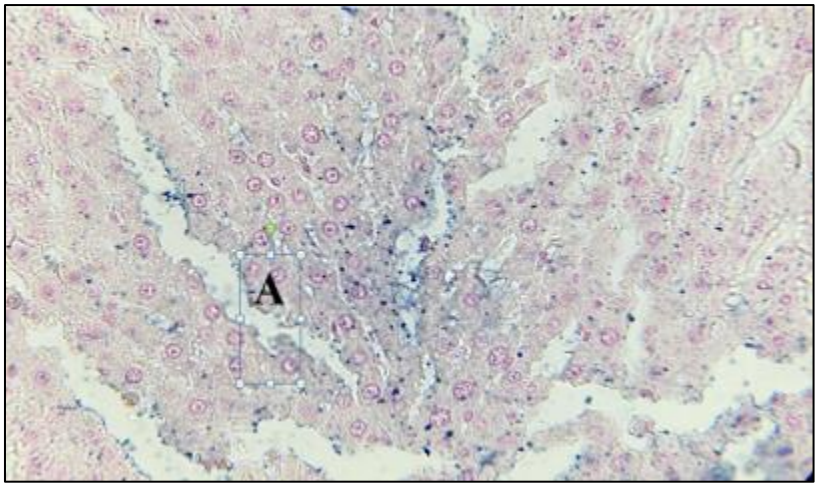

Figure 26 Group I, Iron deposition in between hepatocytes (A). P. blue, 40X

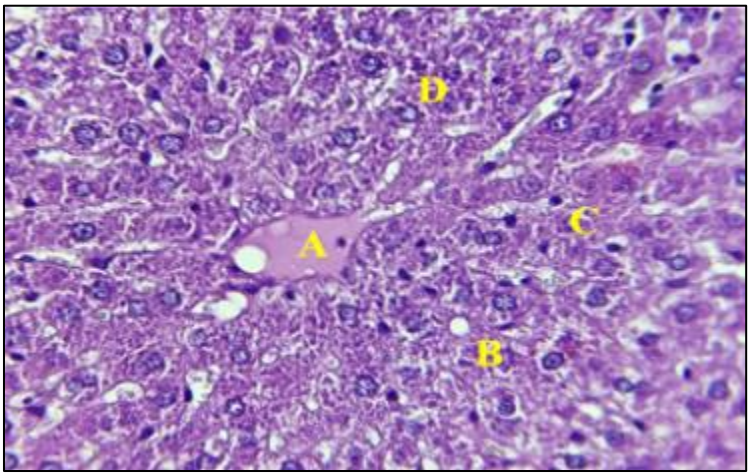

Figure 27 Group II, Haemolysis (A). Vacuolation of Degenerative hepatocytes (B). Infiltration of mononuclear cells (C). Degeneration of hepatocytes (D). H&E X40

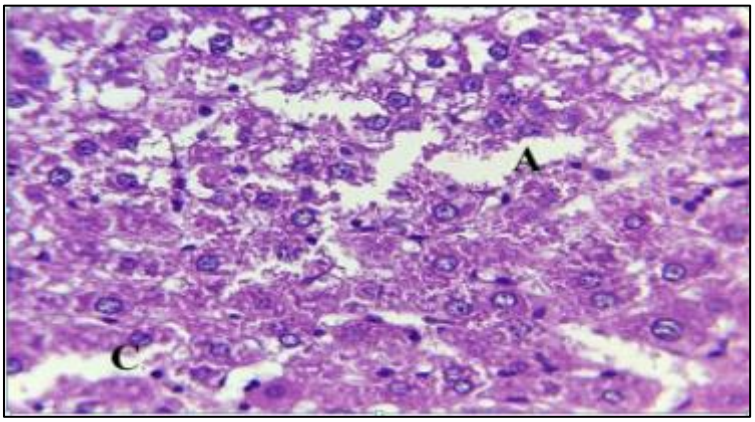

Figure 28 Group II, Necrosis of hepatocytes (A). Infiltration of mononuclear cells (B). (D). H&E X40

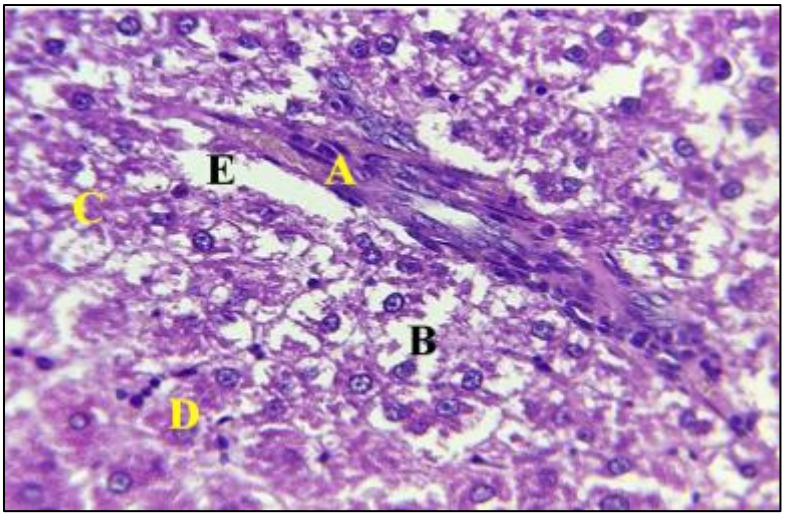

Figure 29 Group II, Infiltration of inflammatory cells around bile ducts (A). Necrosis of hepatocytes (B). Vacuolation of hepatocytes (C). Infiltration of mononuclear cells (D). congestion of blood vessel (E). H&E X40

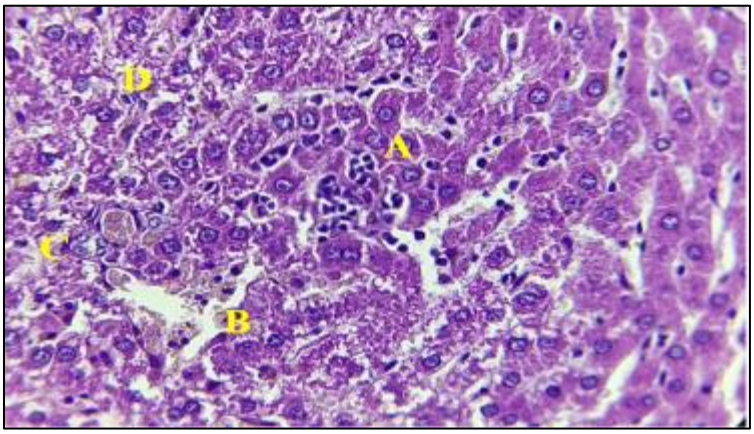

Figure 30 Group II, Infiltration of mononuclear cells (A). Haemolysis of RBCs (B). Pyknosis of hepatocytes (C). Degeneration of hepatocytes (D). H&E X40

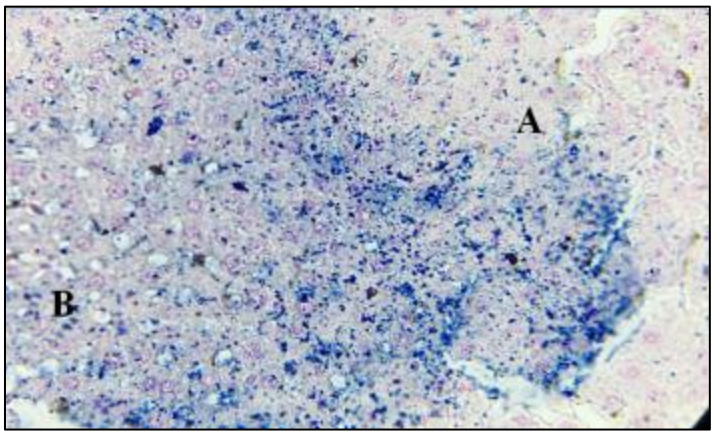

Figure 31 Group II, Iron deposition in between hepatocytes (A). Vacuolation in hepatocytes P. blue, 40X

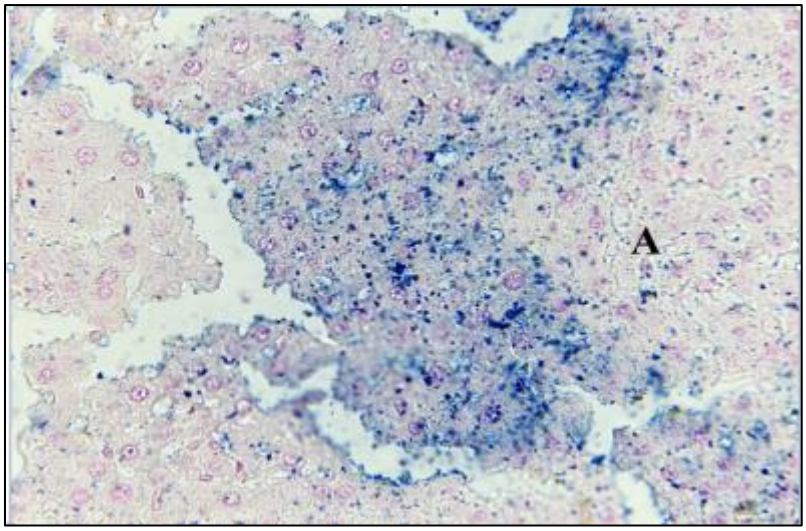

Figure 32 Group II, Iron deposition in between hepatocytes (A). P. blue, 40X

The results of the present study revealed significant increasing of MDA and Adropin serum level otherwise there is a significant decreased SOD and GSH when compared with control group on level P≤ 0.05 as shown in table (1) .

Table 1 Statistical value of M DA, SOD, GSH and Adropin (different letters represent significant difference on level P ≤ 0.05

Parameters / Groups	MDA(µmol/l)	SOD (IU/ml)	GSH(µmol/l)	Adropin
Control	158.60 ± 9.48 c	18.80 ± 2.86 a	250.80 ± 8.93 a	25.20 ± 2.86 c
GI	215.00 ± 10.56 b	8.60 ± 1.52 b	171.20 ± 8.67 c	34.60 ± 2.70 b
GII	243.60 ± 10.01a	3.80 ± 7.40 b	123.40 ± 7.40 c	46.00 ± 2.92 a

4. Discussion

This study designed to assessment the role of Nandrolone Decanoate, on histological architecture of brain, liver and Adropin level. Nandrolone Decanoate used in wide board by bodybuilders and athletes. Histological examination of brains revealed numerous histological alteration, congested of meningeal and cortical blood vessels and foamy appearance in whole section, degeneration of pyramidal cells, liquefaction degeneration hemolyzed, pyramidal cells atrophy, meningeal membrane are infiltrated with inflammatory cells, which reflect the toxic effect of drug on brain tissue, this finding was in agreed with Zelleroth *et al* (2019) they cleared, Nandrolone Decanoate induce cortical cells necrosis, in rat embryos these artifacts was increased with gavin dosage. Nandrolone Decanoate reduces the vital phase of cells (Ma *et al*, 2015; Busardò et al, 2015). Megahed et al 2024 declare the Nandrolone induced The pyramidal cells show shrunken pyknotic nuclei. Cellular vacuolation are also present. Glial cells with dark nuclei and wide pericellular area. Nandrolone Decanoate induced muscle fibers degeneration and karyolysis (Hassan *et al*., 2023; Abdelhafez, 2014). Mohamad et al., 2021) announced that steroid drugs induced hypertrophy of skeletal muscle fibers and congestion blood vessels. Nandrolone Decanoate increases the secretion of testosterone, was affect on brain function and nerve activity as well as effects on neurotransmitters release (Clark *et al*, 1995). Damião 2020 revealing significant morphological changes in the cerebral cortex of animals treated with doses of anabolic steroids.

The results of liver sections showed numerous alterations due to toxic effect of Nandrolone Decanoate administration such as cytoplasmic vacuolation, pyknosis and necrosis which increased with given dose. Stephan et al showed in them paper significant increases fr ee radicals in rats liver due to administration of Nandrolone Decanoate (Frankenfeld et al 2014). Patanè declare that the ND induced a significantly increased in collagen content deposition in the liver parenchyma of rats. (Patanè et al 2020). Giannitrapani et al. (2006) also revealed both androgens and estrogens have been involved in induced hepatocyte proliferation and may act as liver tumor promoters. Thus the changing in androgenic hepatocytes receptor may explain the liver structure alterations.

In presents study showed increased iron deposition in between liver cells. This form of iron, Fe3+ and storage of hemosiderin was contribute in the generation of free radicals ROS by the Fenton reaction, which induced severe cellular and tissue damage, thereby causes to fibrosis of the liver. This finding agreed with our results fibrosis adjacent central vein and aggregate fibroblast in around the portal bile duct. (Mehta et al 2019), (Akatsu et al 2020). Hemosiderin deposition induced macrophage aggregation in sinusoids due to hepatocytes injury (Ahmed et al 2020). The results of the present study revealed significant increasing of MDA serum level otherwise there is a significant decreased SOD and GSH when compared with control group. ROS molecules had high affinity to react with cellular component. Thus, an increasing in ROS molecules generation or a decrease in cellular ability for detoxification leads to increase of ROS level that can induced cellular alteration and oxidative modifications of DNA, proteins, and lipids synthesis. (Zhang et al 2020).

The present study showed significantly increasing increased of adropin level, are reflected negatively with the histological and cellular defects. High levels of adropin associated with insulin resistance (Tina *et al*, 2020),

The high level of adropin act as anti-inflammatory factors play a major roles anti the hyperlipidemia (Li et al 2024). The decreased level of Adropin is related with obesity, metabolic syndrome, and cardiovascular disease (Na, *et al* 2021), Adropin contribute and improve lipid metabolism, and inhibit inflammation of hepatocyte (Chen et al, 2024), therefore, Adropin has a therapeutic activities, and may serve as hyperlipidemia improvement (Bozic *et al*, 2021). Increasing levels of adropin were related with autoimmune disease Sjögren's syndrome, Behcet's disease and systemic sclerosis syndrome (Danolić,*et al*, 2021 ; Yolbas,*et al*,2016) on the other low level of adropin with osteoporosis and osteoarthritis patients (Gundogdu and Gundogdu, 2018). (Simac *et al*, 2022) rheumatoid arthritis Rheumatoid Arthritis.

5. Conclusion

The results of the present study conclude the toxic effect of androgenic anabolic steroids (Nandrolone Decanoate) administration induced a numerous histologic alteration in brain such as pia membrane discontinuous, congested blood vessels neuron degeneration, neuron shrinkage and atrophy. In liver hepatocyte degeneration necrosis, and blood vessel congestion, iron depositions, Malondialdehyde increased, superoxide dismutase, Glutathione decreased and adropin increased in related with histological texture as a point to increase of ROS in brain and liver.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was done

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