Effect of Pitavastatinon Non-Alcoholic Fatty Liver Disease (NAFLD) in Rats Fed on High Fat High Fructose Diet: Possible Underlying Mechanism

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Abstract

Background: non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases and is highly associated with several components of metabolic syndrome, particularly obesity, increased plasma lipid levels, glucose intolerance, and type 2 diabetes mellitus (T2DM) with insulin resistance (IR) and may progress to NASH and liver cirrhosis. **Objective:** investigating the effect and possible underlying mechanisms of Pitavastatin on the progression of NAFLD in rats fed on high fat high fructose diet. **Material and Methods:** forty male albino rats weighing (100-120) grams of local strain were used. Then, induction of NAFLD occurs by maintaining rats on high fat high fructose diet for 2 months followed by administration of pitavastatin with different doses. Then serial laboratory investigations including lipid profile, liver enzymes, oxidative stress and anti-oxidant markers were measured at the end of the experiment. Then, histopathological study of the liver were done **Results:** pitavastatin significantly ameliorate increases in serum SGOT, SGPT, lipid profile , hepatic steatosis, oxidative stress, inflammation , expression of cytokines through significant decrease in TNF- alpha, CRP, MDA, visceral fat index and also, significant increases in adiponectin and hepatic GPx.**Conclusion:**Pitavastatin is a potent novel synthetic inhibitor of HMG-CoA reductase, which can ameliorate NAFLD and prevent liver steatosis, fibrosis and possess lowering effects on plasma total cholesterol and TG through an inhibition of the assembly secretion of VLDL and enhanced cycling of hepatic LDL receptors. Also, have potent anti-oxidative, anti-inflammatory and anti-fibrotic effect.

Keywords: Pitavastatin, NAFLD, malnutrition, high fat high fructose.

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INTRODUCTION

Non-alcoholic fatty liver disease has beencategorized by hepatic fat accumulation without any other known reasons, including alcohol consumption, viral & autoimmune hepatitis, alpha-1antitrypsin deficiency, drugs as corticosteroids & oestrogens, & other disorders. **(1)**

Spectrum of hepatic diseases, including simple steatosis, non-alcoholic steatohepatitis, cirrhosis, & end-stage liver disease, are included in non-alcoholic fatty liver disease. **(2)**

Obesity, elevated plasma lipid levels, glucose intolerance and T2DM with insulin resistance are strongly linked to non-alcoholic fatty liver disease. **(3)**

Prevention of obesity, insulin resistance, steatosis, & oxidative stress have been essential stages in preventing NASH. **(4)** Anti-oxidant called vitamin E, when given to NASH studied cases, greatly improved their hepatic histology, according to recent clinical experiment. **(5)**

Consequently, active medication is thought to be required for care of studied cases with NASH,

particularly those who have metabolic syndrome& lifestyle adjustment to lower body weight.**(6)**

For both primary & secondary prevention of cardiovascular illness, statins are regarded as 1st-line lipid-lowering therapies. By lowering cholesterol synthesis, statins, which are 3-hydroxy-methylglutaryl coenzyme reductase inhibitors, prevent HMG-CoAfrom being converted to mevalonate. **(7)**

Short-term studies indicate that pitavastatin, moderately potent, modestly lipophilic statin, could have neutral or advantageous impacts on glucose metabolism. **(8)**

Many investigations have demonstrated that statins could also enhance hepatic insulin sensitization in both animal models & people.**(9)**

Current research aimed tostudy impacts of Pitavastatin on progression of NAFLD in rats fed on high fat high fructose diet by assessing its impact on serum lipids cholesterol & triglycerides, liver enzymes aspartate aminotransferase& alanine aminotransferase and histopathologicalvariations in induced NAFLD.

MATERIAL AND METHODS

The Faculty of Medicine's Animal Care & Use Committee approved procedures & policies that were followed in this research.

Chemicals and animal groups design: Pitavastatin tablets (**2** mg tab. achieved from local market, Egypt), Pitavastatin tablets (**4** mg tab. acquired from local market, Egypt) and Normalsaline (five hundredmlNaCl 0.9percent).

Kits: Kits for estimation of serum lipids, liver enzymes, random blood sugar, & oxidative stress enzymes.

Stains: Hematoxylin & eosin stain: It had been used for histopathological examination using electric light microscope & purchased from Sigma-AldrichChemical Company, St. Louis, MO, USA.

Animal design: local strain of forty male albino rats' weighing (100–120) grams was employed. The Nile Pharmaceutical Company was where the animals came from. They had been housed at ambient temperature in appropriate cages with natural light-dark cycle. They had been fed a typical diet of commercial rat food & unrestricted tap water. When the experiment began, they had been held for ten days to let them get used to new habitat.

Rats were divided into four equal groups:

Group 1 (control group): which were fed on routine meal and received one ml of normal saline each rat every day during trial via gastric tube.

Group 2 (NAFLD group):which were fed on high fat high fructose diet (HFHFr) comprisesthirty five percent lipids (one percent soybean oil +8.5percent lard +seventeen percent palm oil +8.5percent cocoa butter) &twenty five percent fructose for eight weeks to induce NAFLD. **(8)**

Group 3 (treated NAFLD group):whichwere fed HFHFr with Pitavastatintablets.

(**2** mg) suspension, at daily dose of0.18 mg/kg by gastric tube for seven weeks.

Group 4 (treated NAFLD group):whichwere fed HFHFr with Pitavastatintablets.

(**4** mg) suspension at daily dose of0.18 mg/kg by gastric tube for sevenweeks.

Oral administration of preparations: pre-measured medication dosages had been made & kept in fridge. To make administering & calculating doses easier, drugs had been dissolved in distilled water at concentration of ten milligrams per milliliter. Using smooth stainless-steel tube called gastric gavage that was attached to three ml syringe; all preparations had been given orally. To reduce risk of esophageal perforation, tube has broad bore & smooth beveled tip. To facilitate proper medication delivery & prevent regurgitation, it had been placed into esophagus throughout administration.

Obtaining blood samples: Blood samples had been collected from epicanthus of 14-hour-fasted rats at conclusion of research & in morning using hypodermic needles & centrifugation tubes. Tubes were centrifuged at 2000 rpm for ten minutes after being placed in refrigerator for clotting for hour. Pasteur pipettes had been used to transfer serum into Ependorph tubes, which had been then maintained at -twenty°C until analysis within week**(10)**. Serumhad been collected for estimation of lipid profile, liver enzymes, and oxidative stress markers. Random blood sugar was also estimated.

Preparation Liver homogenate: Following animal sacrifice, the livers had been promptly removed, separated from the blood in ice-cold saline, and dried with filter sheets. For histological analysis, small piece of each right liver lobe had been fixed in ten percent phosphate-buffered formalin. To create the ten percent (w/v) whole liver homogenate, about 0.5 gm of each liver had been homogenised using an ultrasonic homogenizer in five ml of ice-cold phosphate buffered saline. Homogenate had been centrifuged for fifteen min at 15000 rpm, & supernatant had been kept at -twenty°C until it had been utilised to measure malondialdehyde **(11)**.

Histopathological examination: Preparation: Rats had been fasted overnight, killed by cervical decapitation, & their livers had been promptly removed. Livers had been then fixed in four percent buffered isotonic formalin solution for twenty-four hours before being embedded in paraffin.

tissue samples had been then converted into paraffin blocks, from which various slices had been prepared. Five-mm-thick sections had been cut, stained with Mayer's hematoxylin & eosin, & seen under light microscope. Morphological alterations had been photographed using computer system assisted by digital camera**(12)**.

Microscopic study: At Al-Azhar University' faculty of Medicine's Pathology Department, Damietta. every slide was examined using computerised light microscope. For necrosis, hepatic cord disarray, & fatty alterations in the liver cells, liver slices had been examined.

STATISTICAL ANALYSIS:

With aid ofIBM SPSS software package version20.0, data had been fed into computer &assessed. IBM Inc., Armonk, NewYork Number & percentage had been used to indicate qualitative data. Normality of distribution had been examined usingKolmogorov-Smirnov test. range, mean, standard deviation, median, & interquartile range had been used to define quantitative data. At five percent level, significance of outcomes had been determined.**Used tests had beenF-test (ANOVA):** To compare more than2 groups for quantitative variables with generally distributed.

RESULTS

Our study is case control study which include examination of 40 case divided into 4 groups. Control group about 10 cases study, Group 2 NAFL about 10 cases study, Group 3 NAFL treated group with pitavastatin 2mg about 10 cases and Group 4 treated with pitavastatin 4mg about 10 cases.

Table 1:showed comparing among the studied groups as regard weight. In current research we found that there had been high variation among studied groups as regard final weight and weight gained. Initial weight is the same in all examined group, while the final body weight and weight gain initially increased, then decreased, and then stabilized over duration of research.

Table 2:showed studied groups as regard lipid profile. Group 4 treated with pitavastatin 4mg showed the lowest TC, LDL and the highest value of HDL followed by Group 3 NAFL treated group with pitavastatin 2mg then control group. The Group 2 NAFL showed the highest TC, LDL and the lowest value of HDL.

Table 3:showed comparing among studied groups as regard lab investigations. Group 4 treated with pitavastatin 4mg showed the lowest CRP , TNF and the highest value of adiponectin with a hepato-protective effect according to ALT and AST that were investigated. Followed by Group 3 NAFL treated group with pitavastatin 2mg then control group. The Group 2 NAFL showed the highest CRP, TNF and the lowest value of adiponectin.

Table 4:showed comparing studied groups as regard indices including liver index (%), visceral fat index (%), Hepatic GPxand MDAControl group showed the lowest liver index value, visceral fat index, MDA and highest glutathione peroxidase followed by Group 4 treated with pitavastatin 4mg then Group 3 NAFL treated group with pitavastatin 2mg. The Group 2 NAFL showed the highest liver index value, visceral fat index, MDA and lowest glutathione peroxidase.

Table 1: Comparing among the studied groups as regard weight**.**

	Group1 control (n=ten)	**Group2 NAFL (n=ten)**	**Group3** Pitavastatin **2mg (n=ten)**	**Group4** Pitavastatin **4mg (n=ten)**	**F**	**p**
Initial weight						
Range	125.5 – 131.1	125.6 – 131.1	128.4 – 131.1	124.8 – 131.1	2.296	0.094
Mean ± SD	128.2 ± 2.16	127.73 ± 2.01	129.74 ± 0.89	128.76 ± 1.88		
Final weight						
Range	248.9 – 287	473.6 – 508.5	402.1 – 434.8	367 – 394.6	554.325	<0.001*
Mean ± SD	268.92 ± 13.69	489.67 ± 12.75	417.69 ± 11.76	381.4 ± 11.11		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Weight gained						
Range	120.9 – 161.2	344.9 – 377.6	273.7 – 306.4	236.7 – 267.1	558.693	<0.001*
Mean ± SD	140.72 ± 14.3	361.94 ± 11.54	287.95 ± 11.93	252.64 ± 11.29		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p5<0.001*					

F: one-way ANOVA t-test

p: p value to compare among different categories.

p1: p value to compare among **Group1**&**Group2**

p2: p value to compare among **Group1**&**Group3**

p3: p value to compare among **Group1**&**Group4**

p4: p value to compare among **Group2**&**Group3**
p5: p value to compare among **Group2**&**Group4**
p6: p value to compare among **Group3**&**Group4**
*: significant at p≤0.05

Table 2: Comparing studied groups as regard lipid profile.

	Group1 (n=ten)	Group2 (n=ten)	Group3 (n=ten)	Group4 (n=ten)	F	p
Serum TC						
Range	79 – 91	139 – 151	65 – 85	50 – 72	364.073	<0.001*
Mean ± SD	84.8 ± 4.37	144.4 ± 4.35	74.1 ± 7.72	60.6 ± 7.24		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Serum LDL						
Range	28 – 39	60 – 81	22 – 36	20 – 30	170.160	<0.001*
Mean ± SD	33.7 ± 3.95	69.9 ± 6.82	27.9 ± 5.13	25.5 ± 3.54		
Post-hoc	p1<0.001*, p2=0.014*, p3<0.001*, p4<0.001*, p5<0.001*, p6=0.292					
Serum HDL						
Range	27 – 33	34 – 40	34 – 40	35 – 41	37.027	<0.001*
Mean ± SD	29.6 ± 1.71	37.4 ± 2.12	38.1 ± 1.97	38 ± 2.67		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4=0.470, p5=0.536, p5=0.918					

F: 1-wayANOVA t-test
p: p value to compare among different categories.
p1: p value to compare among **Group1**&**Group2**
p2: p value to compare among **Group1**&**Group3**
p3: p value to compare among **Group 1**&**Group4**
p4: p value to compare among **Group2**&**Group3**
p5: p value to compare among **Group2**&**Group4**
p6: p value to compare among **Group3**&**Group4**
*: significant at p≤0.05

Table 3: Comparing among studied groups as regard lab investigations.

	Group1 (n=ten)	Group2 (n=ten)	Group3 (n=ten)	Group4 (n=ten)	F	p
CRP						
Range	3.6 – 9.5	138.7 – 197.9	50.8 – 93.4	41.2 – 85.7	186.962	<0.001*
Mean ± SD	6.4 ± 2.3	163.94 ± 21.07	73.38 ± 12.7	63.67 ± 17.26		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
TNF-α						
Range	0.08 – 0.16	2.16 – 2.46	0.79 – 1.07	0.6 – 0.91	947.445	<0.001*
Mean ± SD	0.12 ± 0.03	2.33 ± 0.12	0.93 ± 0.1	0.75 ± 0.11		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Adiponectin						
Range	34.1 – 42.7	1.9 – 5.6	11.5 – 17.4	20 – 25.9	486.473	<0.001*
Mean ± SD	37.99 ± 2.82	3.73 ± 1.04	14.28 ± 1.88	22.36 ± 2.13		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Serum ALT						
Range	3.9 – 8	46.5 – 59.3	21.2 – 29.6	15.4 – 24.3	493.508	<0.001*
Mean ± SD	5.5 ± 1.18	53.97 ± 4.18	25.48 ± 2.64	20.24 ± 2.75		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Serum AST						
Range	4.1 – 8.4	35 – 54.7	21 – 28.9	13.4 – 25.3	188.644	<0.001*
Mean ± SD	5.61 ± 1.21	46.85 ± 6.3	23.8 ± 2.76	19.01 ± 3.72		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6=0.010*					

F: 1-wayANOVA t-test
p: p value to compare among different categories
p1: p value to compare among **Group1**&**Group2**
p2: p value to compare among **Group1**&**Group3**
p3: p value to compare among **Group1**&**Group4**
p4: p value to compare among **Group2**&**Group3**
p5: p value to compare among **Group2**&**Group4**

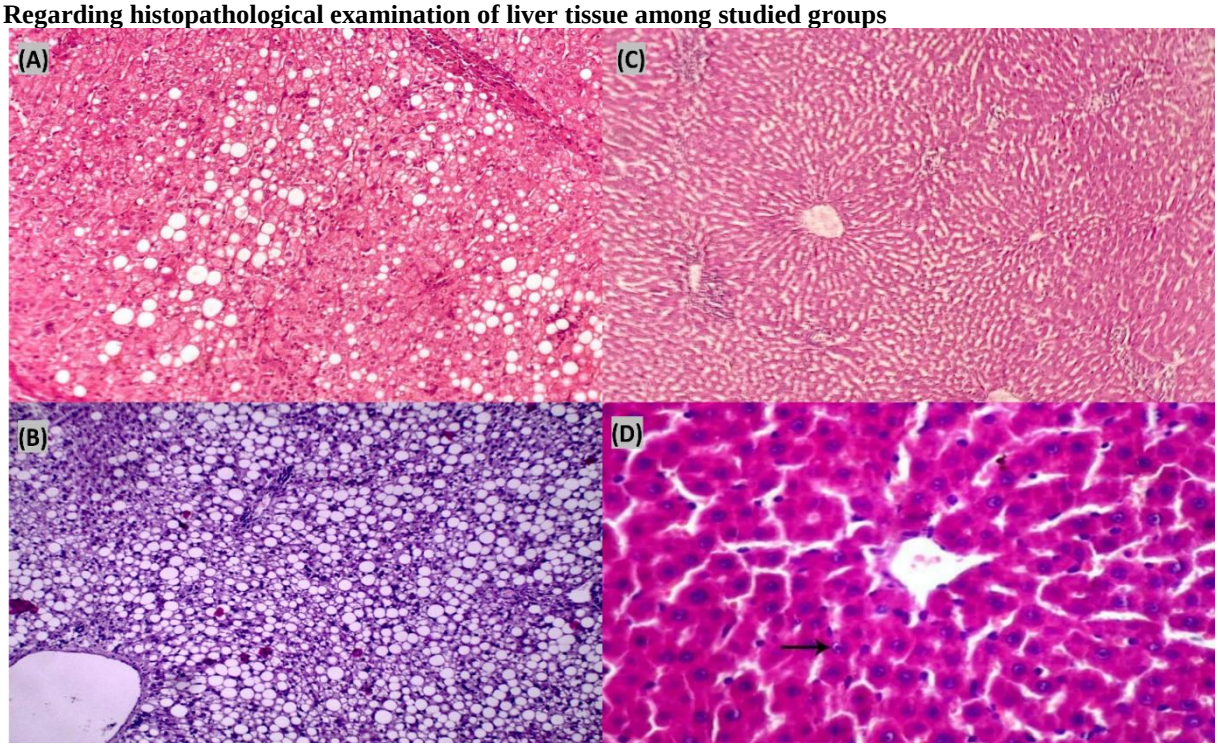
p6: p value to compare among **Group3**&**Group4**
*: significant at p≤0.05

Table 4: Comparing studied groups as regard indices

	Group1 (n=ten)	Group2 (n=ten)	Group3 (n=ten)	Group4 (n=ten)	F	p
Liver index (%)						
Range	1.75 – 1.97	3.03 – 3.24	2.45 – 2.63	2.15 – 2.3	661.619	<0.001*
Mean ± SD	1.86 ± 0.08	3.09 ± 0.06	2.53 ± 0.06	2.2 ± 0.06		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Visceral fat index (%)						
Range	1.22 – 1.6	5.33 – 5.45	3.31 – 4.15	2.71 – 3.65	616.688	<0.001*
Mean ± SD	1.4 ± 0.12	5.38 ± 0.04	3.74 ± 0.27	3.11 ± 0.29		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6<0.001*					
Hepatic GPx						
Range	25 – 32	4 – 7	14 – 21	16 – 23	229.242	<0.001*
Mean ± SD	27.7 ± 2.31	4.8 ± 0.92	18.9 ± 2.02	20.7 ± 2.41		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6=0.052					
MDA						
Range	1 – 5	23 – 31	13 – 19	9 – 18	125.815	<0.001*
Mean ± SD	3.4 ± 1.71	26 ± 3.4	16 ± 1.94	13.4 ± 3.03		
Post-hoc	p1<0.001*, p2<0.001*, p3<0.001*, p4<0.001*, p5<0.001*, p6=0.033*					

F: one-wayANOVA t-test
p: p value to compare among different categories
p1: p value to compare among **Group1**&**Group2**
p2: p value to compare among **Group1**&**Group3**
p3: p value to compare among **Group1**&**Group4**
p4: p value to compare among **Group2**&**Group3**
p5: p value to compare among **Group2**&**Group4**
p6: p value to compare among **Group3**&**Group4**
*: significant at p≤0.05

Regarding histopathological examination of liver tissue among studied groups



A photomicrograph of the liver of the different studied groups stained with H&E staining showed thatA (group III treated with pitavastatin 2 m): showed some fatty infiltrative changes although treatment with low dose of pitavastatin while, **B** (group II on HFHF diet): showed diffuse fatty infiltrative changes with loss of normal architecture of hepatocytes and congested blood sinusoids while, **C** (group I control): showed normal structure of hepatocytes with normal architecture of hepatocytes with no fatty infiltration while, **D** (group IV treated with pitavastatin 4m): showed significant attenuation in NAFLD

DISCUSSION

Most prevalent chronic liver disease in West is non-alcoholic fatty liver disease, which has strong link to dyslipidemia. It is significant public health issue since it affects more than thirty percent of general adult population & has possible to proceed from simple steatosis to irreversible & fatal non-alcoholic steatohepatitis **(13).**

Succession of parallel events, including as inflammation & oxidative stress, contribute to the disease's progression by damaging the hepatocytes & generating permanent fibrosis, which eventually results in cirrhosis & liver failure. Changes in composition of foods are thought to be crucial to development of illness, despite fact that aetiology of NAFLD is not yet fully understood **(14).**

Due to increasing epidemics of obesity & type2 diabetes, non-alcoholic fatty liver disease has emerged like public health concern. Simple steatosis, liver fibrosis, cirrhosis, & ultimately hepatocellular cancer are all on NAFLD spectrum **(15).**

Almost ninety percent of NAFLD studied cases have at least 1 of symptoms of metabolic syndrome, which includes central obesity, hypertension, & low high-density lipoprotein cholesterol. As severity and number of metabolic syndrome characteristics rise, NAFLD prevalence rises **(16)**

In last twenty years, prevalence of NAFLD has increased at faster rate than rates of obesity & overweight in general population. NAFLD had been found in Dionysus investigation in ninety four percent of studied cases who were obese (body mass index higher than & equal to thirty kg/m2), sixty seven percent of studied cases who were overweight (BMI higher than & equal to twenty-five kg/m2), & twenty five percent of studied cases who were normal weight.20 It is demonstrated that severe obesity is correlated with severe NAFLD **(17).**

Aspartate aminotransferase & alanine aminotransferase, random blood sugar, oxidative stress malondialdehyde and histopathological variations in induced NAFLD were evaluated in this research to determine impacts of pitavastatin on progression of NAFLD in rats fed high fat high fructose diet.

In current research we found that there had been high variation among studied groups as regard final weight & weight gained.

In agreement with our research, **Tveden-Nyborg et al. (18)** revealed that at beginning of trial, there had been no variations in BW across groups. After sixteen weeks, high-fat diet groups (HF, HFHS, & HF v HS) had greater BW than control & v HS groups ($p < 0.01$).

These outcomes had been compatible with, **Hassel holt et al. (19)** noted that only the differences in BW among control & HF ($p < 0.05$) & among HS & HFD ($p < 0.001$) persisted after twenty five weeks. Average energy consumption in all groups initially increased, then decreased, and then stabilised over duration of research (Fig. 1b). After sixteen weeks, cumulative weekly calorie intake had been greater in v HS group compared to HF v HS group ($p < 0.01$), but equivalent in all other groups (Fig. 1c). At twenty-five weeks, the cumulative energy intake had been higher in the v HS, HFHS, & HF v HS groups compared to control group, & it improved in v HS, HF (High Fat) v HS, & HF (High Sucrose) groups compared to the HF (High Fat) group.

In alignment with our research, **Birck et al. (20)** illustrated that During Sixteen & twenty-five weeks of high-fat feeding, liver weight in relation to body weight raised ($p < 0.0001$)as compared to control & v HS. Comparable outcomes for absolute liver weights had been seen, demonstrating that higher relative liver weights have not been brought on by reduced BW in the HFD groups.

Our current findings clearly revealed that there had been high variation among studied groups as regard lipid profile TC, LDL, HDL.

These results were compatible with **Veena et al. (21)** showed that Plasma TC and TG did not differ among groups at baseline. Plasma TC had been higher in HF, HFHS, & HF v HS at sixteen & twenty-five weeks matched to control & v HS ($p < 0.0001$). On the other hand, in control & v HS compared to HFD, plasma TG had been increased after sixteen weeks ($p < 0.0001$) & twenty-five weeks($p < 0.01$). FFA was always the same for all groups. VLDL-C ($p < 0.05$) & LDL-C ($p < 0.0001$) concentrations had been higher inHFD groups than in control & v HS groups after sixteen weeks on diets (Table 2). After twenty-five weeks, dyslipidemia persisted, with higher VLDL-C & LDL-C in HFD groups than in control & v HS groups ($p < 0.001$ & $p < 0.0001$).

In agreement with our research, **Ebersbach et al. (22)** stated that At Sixteen or twenty-five weeks, the rise in HDL-C following high-fat diet had not

been statistically significant when compared to control & v HS. At sixteen weeks, SAA concentrations had been lowering in allHFD groups as compared to v HS ($p < 0.01$), HF ($p < 0.01$), & HF v HS ($p < 0.001$). Only HF v HS showed reduced SAA than v HS at twenty five weeks ($p < 0.01$).

Tobar et al. (23) illustrated that Large-scale primary & secondary preventive studies for coronary heart disease have proven therapeutic advantages of cholesterol decrease by HMG-CoA reductase inhibitors (statins). Development of coronary events is influenced by other atherogenic lipoproteins, like TG-rich lipoproteins, as evidenced by successful lowering of LDL cholesterol. As result, statins with TG-Lowering characteristics are recently created.

In the present research we showed that there had been high difference among studied groups as regard lab investigations, CRP, TNF-α, Adiponectin, Serum ALT. Serum AST.

In alignment with our study, **Gaggini et al. (24)** stated that Plasma ALT ($p < 0.001$) & AST ($p < 0.0001$) elevated in all HFD groups at sixteen weeks & remained raised after twenty five weeks as compared to controls & v HS (ALT $p < 0.01$, AST $p < 0.0001$).

Instead, **Deaciuc et al. (25)** stated that there was no difference in Plasma ALP across groups at any time point ($p > 0.05$). Amount of DNA strand breaks & telomere length, two measures of genomic damage, do not vary across groups ($p > 0.05$).

Our current findings clearly revealed that there had been high variation among studied groups as regard liver indices, visceral fat index (%), Hepatic GPx, MDA.

Okada et al. (26) illustrated that impact on Malondialdehyde level, in comparison to the NAFLD control group, all treatment groups displayed significant drop, while the normal control group displayed considerable rise.

In alignment with our study, **Targher et al. (27)** stated that there was no association among serum MDA levels & histopathologic findings in NASH studied cases, despite fact that serum MDA levels had been markedly elevated in individuals with NASH, showing enhanced oxidative stress. It could be due to fact that none of NASH studied cases had significant liver liver fibrosis or inflammation, & majority of them had mild or no liver fibrosis at all.

In conclusion,Pitavastatin is a potent novel synthetic inhibitor of HMG-CoA reductase, which can ameliorate NAFLD and prevent liver steatosis, fibrosis and possess lowering effects on plasma total cholesterol and TG through an inhibition of the assembly secretion of VLDL and enhanced cycling of hepatic LDL receptors. Also, have potent anti-oxidative, anti-inflammatory and anti-fibrotic effect.

Declarations and statements

Ethics approval and consent to participate:

Approval of the study was obtained from the Institutional Review Board (IRB), Damietta Faculty of Medicine, Al-Azhar University and the research is acceptable according to the guidelines and declaration of Helsinki and our committee standard operating procedure guidelines

Consent for publication:

Not applicable.

Availability of data and materials:

All data and materials are fully presented in the manuscript.

Competing interests:

The authors declare that they have no competing interests.

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Author contributions

The study plan, experiments design and manuscript were done by **Walid mostafa said**.

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