e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(11); 191-196

Original Research Article

Incidence of Hepatic Steatosis and Other Adverse Outcomes in Patients using Atorvastatin

Balram Sai Prasanna

Postgraduate, Department of Pharmacology, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana.

Received: 21-09-2023 / Revised: 20-10-2023 / Accepted: 24-11-2023
Corresponding Author: Balram Sai Prasanna
Conflict of interest: Nil

Abstract

Background: Statins, widely prescribed for various chronic conditions such as cardiovascular diseases, cerebrovascular diseases, peripheral vascular diseases, and diabetes mellitus, have raised concerns regarding potential side effects with prolonged usage, including hepatic steatosis. We in the current study tried to analyze the incidence of hepatic steatosis in patients taking statins for long duration.

Methods: Patients on prolonged statin therapy were selected. Lab investigations (ALT), (AST), and (ALP), and Lipid Profile: serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides to monitor lipid levels. Fasting Blood Sugar (FBS) Fasting blood glucose levels to identify patients with diabetes or impaired glucose metabolism. Abdominal ultrasound was done to detect fatty changes in the liver.

Results: Overall, 34.33% of cases taking Atorvastatin tablets had fatty liver, while 65.67% did not. For diabetics, the prevalence of fatty liver was 36.84%, while for non-diabetics, it was 31.03%. The p-value for diabetics is 0.065, suggesting a possible association between diabetes and fatty liver change. The prevalence of fatty liver is slightly higher among diabetics than non-diabetics. The most common ADRs reported were fatigue (24 cases), myalgia (muscle pain) (16 cases), joint pain (12 cases), dysphagia (difficulty swallowing) (12 cases), and insomnia (11 cases) all were mild and self-limiting.

Conclusion: This study concludes that prolonged statin use induces fatty acid synthesis, leading to the accumulation of excess fatty acids in visceral organs, particularly the liver, and consequently resulting in fatty liver. To minimize the overall occurrence of adverse effects associated with statin use and enhance patient quality of life, it is crucial to exercise caution when employing these medications and avoid prolonged administration.

Keywords: Atorvastatin, Hepatic Steatosis, Lipid profile, Liver function tests.

Introduction

Statins, widely prescribed globally for chronic conditions such as cardiovascular diseases, cerebrovascular diseases, peripheral vascular diseases, and diabetes mellitus, are among the most commonly used drugs. [1, 2] Despite their popularity and perceived safety profile, it is crucial to underscore potential adverse effects and raise awareness of both risks and benefits, especially considering their widespread use, where uncommon adverse effects can have significant public health implications. The mechanism of action of statins involves inhibiting the HMG Co-A reductase enzyme, consequently impeding the conversion of HMG Co-A to mevalonate, a precursor for cholesterol, thereby reducing cholesterol production. [3] While about half of the body's cholesterol needs come from the diet, the remaining half is synthesized internally. [4] Various tissues, including the liver, intestine, ovaries, testes, adrenal cortex, nervous tissue, and skin, contribute significantly to the body's cholesterol pool. [5] Cholesterol, a crucial component of cell membranes and the myelin sheath of nerve cells serves as the precursor for various essential substances such as steroid hormones, glucocorticoids, mineralocorticoids, and vitamins. Statins, by inhibiting cholesterol synthesis, may impact the normal function of plasma cell membranes, potentially leading to a range of adverse effects, including chronic muscle pain, fatigue, joint pain, numbness, memory problems, mood disorders, depression, sleep disturbances, impaired immune function, and impotence. Moreover, statins' inhibition of Coenzyme-Q production, an important component of the mitochondrial electron transport chain, may result in adverse effects such as myalgia, chronic fatigue syndrome, hypertension, and cardiomyopathy. [6] Since both cholesterol and Coenzyme-Q production are affected by statins, various adverse effects may manifest. [1] Another notable concern is the

association between statin use and fatty liver changes, characterized by an abnormal accumulation of fat in liver cells. [7] Statins, through their impact on cholesterol synthesis, may contribute to fatty liver changes. [8] This study aims to investigate the prevalence of fatty liver in patients taking Atorvastatin tablets. Understanding this association could help guide the appropriate use of statins, particularly in individuals with liver conditions, and contribute to the recognition of fatty liver as part of the statin adverse drug profile. With this background, the present study was conducted to determine the frequency of fatty liver alterations in individuals using Atorvastatin tablets and to examine the presence of symptoms related to various adverse effects associated with Atorvastatin.

Material and Methods

This cross-sectional observational study was conducted at Kakatiya Medical College and MGM Hospital, Warangal, involving the Department of General Medicine and the Department of Pharmacology. Institutional ethical approval was secured for the study, and written consent was obtained from all participants after providing detailed explanations about the study in the local language. Inclusion in the study was limited to those who voluntarily expressed their willingness to participate.

Inclusion Criteria

1. The age group of 20 years and above
2. Males and females
3. Patients who were taking tablets. Atorvastatin for more than two years.
4. Patients who are willing to participate in this study.

Exclusion Criteria

1. Patients who have chronic liver diseases
2. Patients with chronic alcoholism
3. Patients taking other hepatotoxic drugs
4. Patients who are not willing to participate and give consent

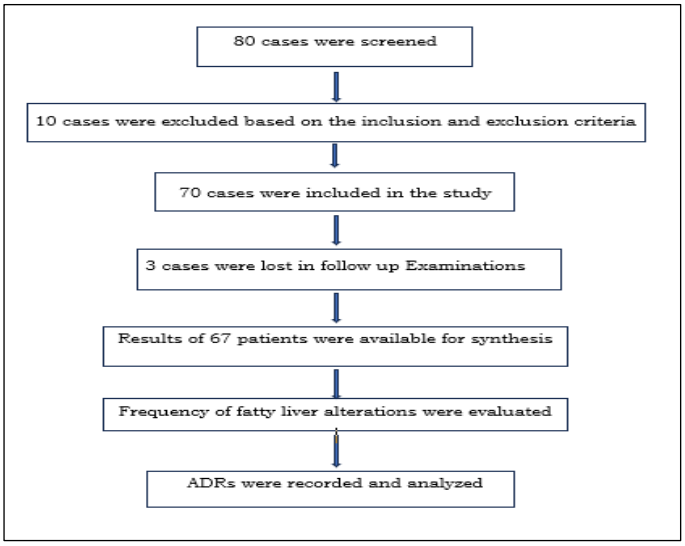

Figure 1: illustrates the study's schematic overview.

The demographic details of the patients which include age, gender, socioeconomic status, family history, and usage of other drugs were collected and noted in detail. A comprehensive medical history, including pre-existing conditions such as diabetes, obesity (BMI), dyslipidemia, and any liver-related disorders were recorded. The patients were subjected to a general physical examination and a thorough abdominal examination to assess for signs of hepatomegaly and tenderness in the liver areas. Skin examination was done for signs of xanthomas and lipid deposits. A basic neurological examination is to identify any signs of neuropathy or cognitive impairment, as some adverse effects may have neurological manifestations.

Laboratory Investigations: Included assessments of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin to evaluate hepatic function. Lipid Profile: included the measure of serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides to monitor lipid levels. Fasting Blood Sugar (FBS) Fasting blood glucose levels to identify patients with diabetes or impaired glucose metabolism. Abdominal ultrasound was done to detect fatty changes in the liver.

Statistical analysis: The data collected during the study were input into a Microsoft Excel spreadsheet

and subsequently analyzed. Continuous variables for the amitriptyline and sodium valproate groups were presented as mean standard deviation, percentages, and frequencies. Categorical variables were evaluated using the chi-square test and p-values of (<0.05) were considered as significant.

Results

Out of the 67 available results for analysis, there were 30/67(44.78%) males and 37/67(55.22%) females. Out of the total cases 38/67(56.71%) were diabetics and 29/67(43.28%) were non-diabetics. Table 1 shows the distribution of cases taking Atorvastatin tablets by age group and gender. The majority of cases are in the 51-60 age group (37.31%). The next most common age groups are the 61-70 age group (31.34%) and the 41-50 age group (19.40%). There are a small number of cases in the 31-40 age group (4.47%) and the 71-80 age group (7.46%). There are no cases in the 20-30 age group.

Table 1: Age group-wise distribution of cases taking Atorvastatin tablets included in this study

Age group years	Male	Female	Total	Percentage
20 - 30	0	0	0	0.00
31 - 40	1	2	3	4.47
41 - 50	6	7	13	19.40
51 - 60	11	14	25	37.31
61 - 70	10	11	21	31.34
71 - 80	2	3	5	7.46
Total	30	37	67	100

Table 2 shows the distribution of fatty liver change among cases taking Atorvastatin tablets, categorized by diabetic status. Overall, 34.33% of cases taking Atorvastatin tablets had fatty liver, while 65.67% did not. For diabetics, the prevalence of fatty liver was 36.84%, while for non-diabetics, it was 31.03%. The p-value for diabetics is 0.065, suggesting a possible association between diabetes and fatty liver change. The prevalence of fatty liver is slightly higher among diabetics than non-diabetics.

Table 2: Fatty liver change distribution of cases taking Atorvastatin tablets

Cases	Frequency	Fatty Liver positive	Fatty liver negative	P value
Diabetics	38	14(36.84%)	24(63.16%)	0.065
Non-Diabetics	29	9(31.03%)	20(68.96%)	
Total	67	23(34.33%)	44(65.67%)	

Figure 1 shows the percentage of cases with fatty liver increases with the duration of Atorvastatin usage. This suggests that Atorvastatin may increase the risk of fatty liver. Among cases taking Atorvastatin for 2-3 years, 25.93% had fatty liver, while 74.07% did not. For those taking Atorvastatin for 3-4 years, 37.50% had fatty liver, while 62.50% did not. For those taking Atorvastatin for 4-5 years, 45.45% had fatty liver, while 54.55% did not. For those taking Atorvastatin for more than 5 years, 40.00% had fatty liver, while 60.00% did not.

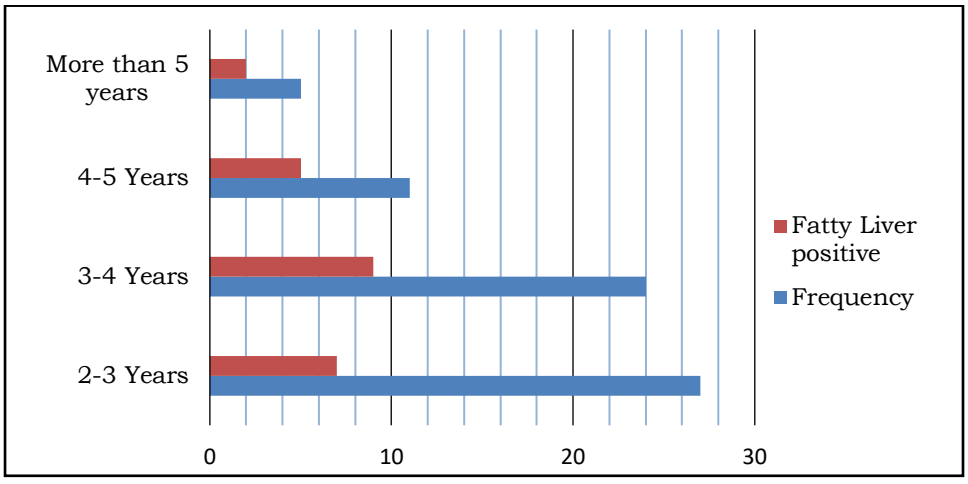

Figure 1: Distribution of cases based on the duration of Atorvastatin usage and appearance of fatty liver changes

Total Cholesterol: The average total cholesterol level was significantly higher in diabetic patients (210.3 mg/dL) compared to non-diabetic patients (182.17 mg/dL) with a p-value of 0.002. This suggests that diabetic patients have an increased risk of developing atherosclerosis. *Triglyceride:* The average triglyceride level was significantly higher in diabetic patients (195.0 mg/dL) compared to nondiabetic patients (169.20 mg/dL) with a p-value of 0.001 which is significant. *HDL (High-Density Lipoprotein):* The average HDL level was not significantly different between diabetic patients (33.5 mg/dL) and non-diabetic patients (34.8 mg/dL) with a p-value of 0.215. This suggests that HDL levels may not be a major factor contributing to the increased risk of cardiovascular disease in diabetic patients. *LDL (Low-Density Lipoprotein):* The average LDL level was significantly higher in diabetic patients (114.4 mg/dL) compared to non-diabetic patients (97.52 mg/dL) with a p-value of 0.013. This suggests that diabetic patients have an increased risk of developing LDL-mediated atherosclerosis (Table 3).

Table 3: Comparing the Lipid Profile Value Between Diabetic and Non-Diabetic Patients

Lipid Profile Values	Diabetic Patients	Non-Diabetic Patients	P Value
Total Cholesterol	210.3 ± 52.6	182.17 ± 28.30	0.002
Triglyceride	195.0 ± 48.2	169.20 ± 25.0	0.001
HDL	33.5 ± 8.5	34.8 ± 9.8	0.215
LDL	114.4 ± 30.22	97.52 ± 29.33	0.013

Table 4 illustrates the levels of AST (Aspartate Aminotransferase): The mean AST level exhibited a significant elevation in cases positive for fatty liver (54.05 U/L) in contrast to cases negative for fatty liver (30.34 U/L) with a p-value of 0.011. ALT (Alanine Aminotransferase): The average ALT level demonstrated a significant increase in cases positive for fatty liver (55.32 U/L) compared to cases negative for fatty liver (35.19 U/L) with a p-value of 0.0154. ALP (Alkaline Phosphatase): The mean ALP level did not exhibit a significant difference between cases positive for fatty liver (75.19 U/L) and cases negative for fatty liver (70.97 U/L) with a p-value of 0.450. In summary, these findings indicate that AST and ALT levels are notably higher in individuals with fatty liver disease as opposed to those without fatty liver disease.

Table 4: Comparing the LFT Values Between fatty liver positive and fatty liver negative cases.

Liver Function Test	Fatty Liver Positive	Fatty Liver Negative	P Value
AST U/L	54.05 ± 21.04	30.34 ± 12.33	0.011
ALT U/L	55.32 ± 21.22	35.19 ± 14.82	0.0154
ALP U/L	75.19 ± 16.54	70.97 ± 18.75	0.450

Figure 2 shows the most common symptom reported by patients with fatty liver disease is fatigue (23%). Myalgia (muscle pain) and joint pain are also common symptoms, reported by 19% and 13% of patients, respectively. Dysphagia (difficulty swallowing) and nausea were reported less frequently, by 13% and 1% of patients, respectively. Other symptoms reported include insomnia (11%), memory disturbances (1%), headache (7%), numbness (5%), and skin dryness (3%). Overall, this table suggests that fatty liver disease can present with a variety of symptoms, both common and rare. Fatigue, myalgia, and joint pain are the most common symptoms, while others such as dysphagia, nausea, insomnia, memory disturbances, headache, numbness, and skin dryness are less common but still reported by some patients.

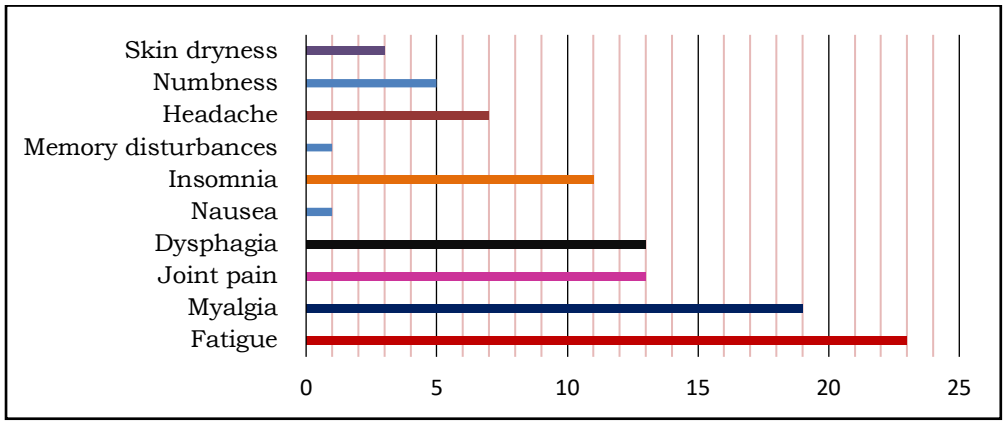

Figure 2: Showing the frequency of symptoms of cases taking atorvastatin

The most common ADRs reported were fatigue (24 cases), myalgia (muscle pain) (16 cases), joint pain (12 cases), dysphagia (difficulty swallowing) (12 cases), and insomnia (11 cases). All reported ADRs were mild or moderate in severity. No severe ADRs were reported. These findings suggest that Atorvastatin tablets are generally well-tolerated, with mild to moderate ADRs being the most common adverse effects (Table 5)

Table 5: Severity Assessment of Adverse Drug Reactions by Modified Hartwig Siegel Scale

ADR	Mild	Moderate	Severe
Fatigue	24	0	0
Myalgia	16	4	0
Joint pain	12	2	0
Dysphagia	12	2	0
Nausea	1	1	0
Insomnia	11	2	0
Memory disturbances	4	0	0
Headache	5	2	0
Numbness	5	0	0
Skin dryness	3	0	0

Discussion

Statins are widely prescribed for extended periods to address various conditions such as Dyslipidemia, Cardiovascular diseases, stroke, peripheral vascular diseases, Atherosclerosis, and Hypertension. [9] They have also been suggested for potential roles in conditions like Parkinson's disease, Alzheimer's disease, Multiple sclerosis, Inflammatory bowel disease, breast cancer, rheumatoid arthritis, and COPD. [10] Given their broad usage and prolonged duration, statins may lead to various adverse effects, some of which may not be thoroughly documented in the literature. Fatty liver changes, a potential consequence of long-term statin use, pose a concern as their adverse effects, including cirrhosis, decompensated liver disease, and even liver failure, may not be extensively covered in the existing literature. [11, 12] This study aimed to analyze the prevalence of fatty liver changes and alterations in lipid profiles among 67 patients taking Atorvastatin for over two years, spanning ages 20 to 80. The age distribution indicated a higher number of patients above 50 years, with a slightly greater proportion of female patients compared to male patients. A liver ultrasound was conducted for all 67 patients, revealing that 34.33% of patients exhibited fatty liver changes. The findings indicated a higher percentage of patients with fatty liver among those who had been taking statins for more than 4 years, with an increase observed as the treatment duration extended.

Among the 67 patients, 38 were diabetic, and 29 were non-diabetic. Fatty liver was observed in 36.84% of diabetic patients and 31.03% of non-diabetic patients. The statistical analysis (P value 0.065) suggested that the difference between diabetic and non-diabetic patients was not significant, implying that fatty liver changes were attributed to statins rather than diabetes mellitus. The mean values of lipid profile parameters (Total cholesterol, LDL, HDL, Triglycerides) for all 67 patients indicated an overall increase beyond the normal range. A comparison of mean values between diabetic and non-diabetic patients revealed a statistically significant increase in serum total cholesterol, LDL, and TG levels among diabetic patients. Acetyl CoA, derived from glucose metabolism, serves as the precursor for both cholesterol and fatty acid synthesis. Statin-induced inhibition of cholesterol synthesis enhances fatty acid production in the liver. Excessive fatty acid production leads to an increase in triglycerides, which enter the systemic circulation. The surplus triglycerides accumulate as ectopic fat, particularly in the liver, resulting in the development of fatty liver.

Analysis of liver enzymes (AST, ALT, and ALP) in individuals with and without fatty liver revealed a significant elevation in AST and ALT levels among those with fatty liver. These differences demonstrated statistical significance, with a P-value of 0.01, indicating an association between fatty liver changes, liver injury, and elevated liver enzymes. The study identified that 34.33% of patients exhibited fatty liver changes, accompanied by an overall increase in triglyceride levels. This supports the hypothesis that statins indirectly stimulate fatty acid synthesis in the liver by inhibiting cholesterol synthesis. The long-term effects of fatty liver and elevated triglyceride levels may lead to severe complications such as cirrhosis, central obesity, and vascular diseases. [13] The findings from this study underscore that fatty liver changes are commonly observed in patients undergoing chronic statin therapy. Consequently, fatty liver should be included in the adverse effect profile of statins. [14] The majority of drug-induced liver injury and fatty liver typically revert to normal upon discontinuation of the causative drug. Therefore, limiting the use of statins and avoiding

prolonged durations in various indications can mitigate drug-induced fatty liver in patients and prevent long-term complications associated with statins and fatty liver. Statins, through the inhibition of cholesterol and coenzyme Q synthesis, may induce various adverse effects, including chronic muscle pain, fatigue, joint pain, numbness, memory problems, mood disorders, sleep disturbances, impaired immune function, impotence, chronic fatigue syndrome, hypertension, and cardiomyopathy, with some of these effects not being documented in the literature. [15]

In this study, a questionnaire was administered to all participants to assess symptoms related to the adverse effect profile of Atorvastatin. Out of 67 patients, nearly all reported experiencing at least one adverse effect symptom. Fatigue was the most commonly reported adverse effect (21 patients), followed by myalgia (16). Joint pain, dysphagia, and sleep disturbances were also prevalent among many patients. Adverse effects were analyzed using the WHO causality assessment scale, with most adverse drug reactions falling under the "possible" category, and some categorized as "probable." According to the modified Hartwig-Siegel scale, the majority of adverse effects were classified as mild. [16] The adverse effects mentioned above, such as fatigue, myalgia, joint pain, dysphagia, and sleep disturbances, can significantly impact the quality of life for patients. These effects are particularly prevalent among individuals taking statins for extended periods.

Conclusion

This study concludes that prolonged statin use induces fatty acid synthesis, leading to the accumulation of excess fatty acids in visceral organs, particularly the liver, and consequently resulting in fatty liver. To minimize the overall occurrence of adverse effects associated with statin use and enhance patient quality of life, it is crucial to exercise caution when employing these medications and avoid prolonged administration. Therefore, it is advisable to restrict statin use to appropriate indications and for shorter durations.

References

1. Cham S, Evans MA, Denenberg JO, Golomb BA. Statin-Associated Muscle Related Adverse Effects: A Case Series of 354 Patients. Pharmacotherapy. 2010 Jun;30(6):541–53.
2. Walley T, Folino-Gallo P, Stephens P, Van Ganse E, Euro-Med Stat group. Trends in prescribing and utilization of statins and other lipid-lowering drugs across Europe 1997-2003. British Journal of Clinical Pharmacology. 2005 Nov;60(5):543–51.
3. Tripathi KD. Essentials of Medical Pharmacology. Seventh edition. New Delhi: Jaypee Brothers Medical Publishers (P), Ltd; 2013; p. 636
4. Murray RK, Harper HA, editors. Harper's illustrated biochemistry. 29th Ed. New York, NY: McGraw-Hill Medical; 2012; p. 122–123
5. Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil PA. Harper's illustrated biochemistry. Thirtieth edition. New York Chicago San Francisco Athens London Madrid Mexico City Milan New Delhi Singapore Sydney Toronto: McGraw-Hill Education; 2015; p. 267.
6. Murray RK, Harper HA, Editors. Harper's illustrated Biochemistry. 29th ed. New York, NY: McGraw-Hill Medical publishers 2012; p. 122–123.
7. Kumar V, Abbas AK, Aster JC, editors. Robbins and Cotran pathologic basis of disease. Ninth edition. Philadelphia, PA: Elsevier/Saunders; 2015; p. 845– 847.
8. Murray RK, Harper HA, Editors. Harper's illustrated Biochemistry. 29th ed. New York, NY: McGraw-Hill Medical; 2012; p. 218-281.
9. Zhou Q, Liao JK. Statins and cardiovascular diseases: from cholesterol-lowering to pleiotropy. Curr Pharm Des. 2009;15(5):467-78.
10. Davies JT, Delfino SF, Feinberg CE, Johnson MF, Nappi VL, Olinger JT, Schwab AP, Swanson HI. Current and Emerging Uses of Statins in Clinical Therapeutics: A Review. Lipid Insights. 2016 Nov 14; 9:13-29.
11. Vargas JI, Arrese M, Shah VH, Arab JP. Use of Statins in Patients with Chronic Liver Disease and Cirrhosis: Current Views and Prospects. Curr Gastroenterol Rep. 2017 Sep; 19(9):43.
12. Bays H, Cohen DE, Chalasani N, Harrison SA. The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl): S47–57.
13. Kothari S, Dhami-Shah H, Shah SR. Antidiabetic Drugs and Statins in Nonalcoholic Fatty Liver Disease. J Clin Exp Hepatol. 2019 Nov-Dec;9(6):723-730.
14. Natalie C. Ward, Gerald F. Watts, and Robert H. Eckel. Statin Toxicity. Mechanistic Insights and Clinical Implications. Circulation Research 2019; 124(2): 328-350.
15. Bełtowski J, Wójcicka G, Jamroz-Wiśniewska A. Adverse effects of statins - mechanisms and consequences. Curr Drug Saf. 2009 Sep; 4(3): 209-28.
16. Petrova G, Stoimenova A, Dimitrova M, Kamusheva M, Petrova D, Georgiev O. Assessment of the expectancy, seriousness, and severity of adverse drug reactions reported for chronic obstructive pulmonary disease therapy. SAGE Open Med. 2017 Jan 31; 5:20503121 17690404.