Mesopotamia Environmental Journal
ISSN 2410-2598
Journal homepage http//:www.bumej.com

DOI: http://dx.doi.org/10.31759/mej.2019.5.1.0022

Atorvastatin with sAST

EnammS.abdullah

Department of Science, College of Basic Education, University of al-Mustanseriah , Iraq.

Corresponding author:abodireem200810@gmail.com

To cite this article:

Abdullah ,E.S. Atorvastatin with sAST. *Mesop. environ. j*., 2019, Vol. 5, No.1, pp. 10-22 .

Received date: 25/5/2019 accepted date: 21/7/2019 published date:15/9/2019

Abstract:

The study discussed the indirect effect of Atorvastatin as one of statin group (lipid lowering agent) on sAST (sGOT the old name of enzyme), by study the direct and indirect effect of Atorvastatin on the samples of serum taken from 27 patients known case of hyperlipidemia, and started treatment protocol with Atorvastatin, after 3 months of treatment, incidence of presented elevation of sAST is 0.5% in the atorvastatin treated population, some of those within 12 hours of low dose atorvastatin consumption liver functions were fully recovered to the baseline level 11 days after discontinuation of atorvastatin treatment.

Keywords: aspartate transaminase, alanine transaminase and Rx (treatment)

Introduction

Fat metabolism and hyperlipidemia:

Cholesterol:

Is a chemical compound that the body requires as a building block for cell membranes and for hormones like estrogen and testosterone, the liver produces about 80% of the body's cholesterol and the rest comes from dietary sources like meat, poultry, eggs, fish, and dairy products. Foods derived from plants contain no cholesterol.[14]

Cholesterol does not travel freely through the bloodstream. Instead, it is attached or carried by lipoproteins (lipo = fat) in the blood. There are three types of lipoproteins that are categorized based upon how much protein there is in relation to the amount of cholesterol:-

1- Low-density lipoproteins (LDL) contain a higher ratio of cholesterol to protein and are thought of as the “bad” cholesterol. Elevated levels of LDL lipoprotein increase the risk of heart disease, stroke, and peripheral artery disease, by helping form cholesterol plaque along the inside of artery walls. The artery narrows (atherosclerosis) and blood flow decreases. If the plaque ruptures, it can cause a blood clot to form that prevents any blood flow. This clot is the cause of a heart attack or myocardial infarction if the clot occurs in one of the coronary arteries in the heart.

2- High-density lipoproteins (HDL) are made up of a higher level of protein and a lower level of cholesterol. These tend to be thought of as “good” cholesterol. The higher the HDL to LDL ratio, the better it is for the individual because such ratios can potentially be protective against heart disease, stroke, and peripheral artery disease.

3- Very low-density lipoproteins (VLDL) contain even less protein than LDL. VLDL like LDL has been associated with plaque deposits.[14,15]

Table 1 normal value of serum cholesterol

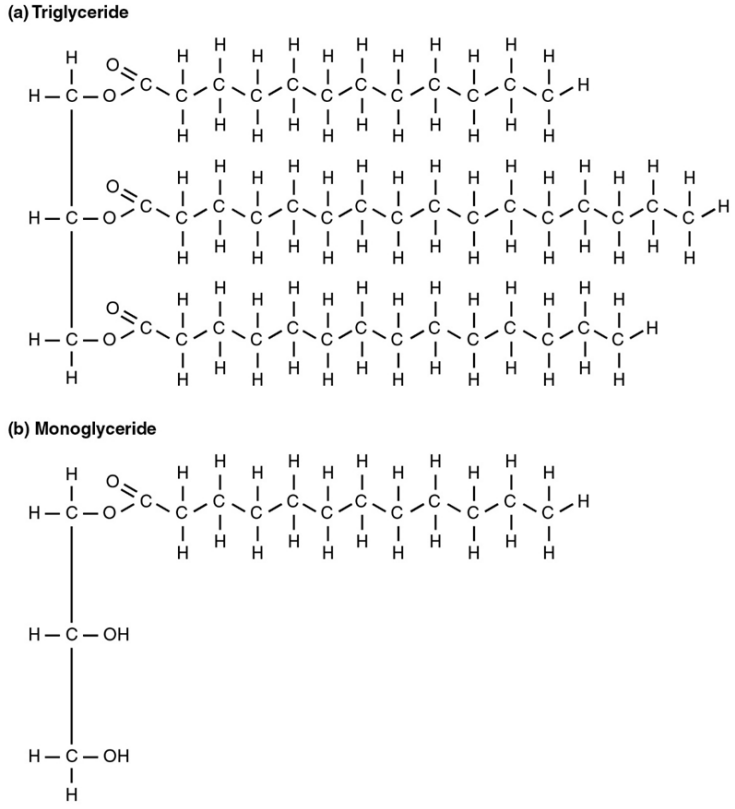
Total serum cholesterol	• <200 mg/dL = desired values • 200–239 mg/dL = borderline to high risk • 240 mg/dL and above = high risk
HDL Cholesterol	• With HDL cholesterol the higher the better • <40 mg/dL for men and <50 mg/dL for women = higher risk • 40-50 mg/dL for men and 50-60 mg/dL for women = normal values • >60 mg/dL is associated with some level of protection against heart disease

LDL Cholesterol	• With LDL cholesterol the lower the better • <100 mg/dL = optimal values • 100 mg/dL-129 mg/dL = optimal to near optimal • 130 mg/dL-159 mg/dL = borderline high risk • 160 mg/dL-189 mg/dL = high risk • 190 mg/dL and higher = very high risk

Triglycerides:

Type of fats that ingested as food or synthesized by adipocytes or hepatocytes from carbohydrate precursors.

Metabolism entails the oxidation of fatty acids to either generate energy or synthesize new lipids from smaller constituent molecules. Lipid metabolism is associated with carbohydrate metabolism, as products of glucose (such as acetyl CoA) can be converted into lipids.[14]

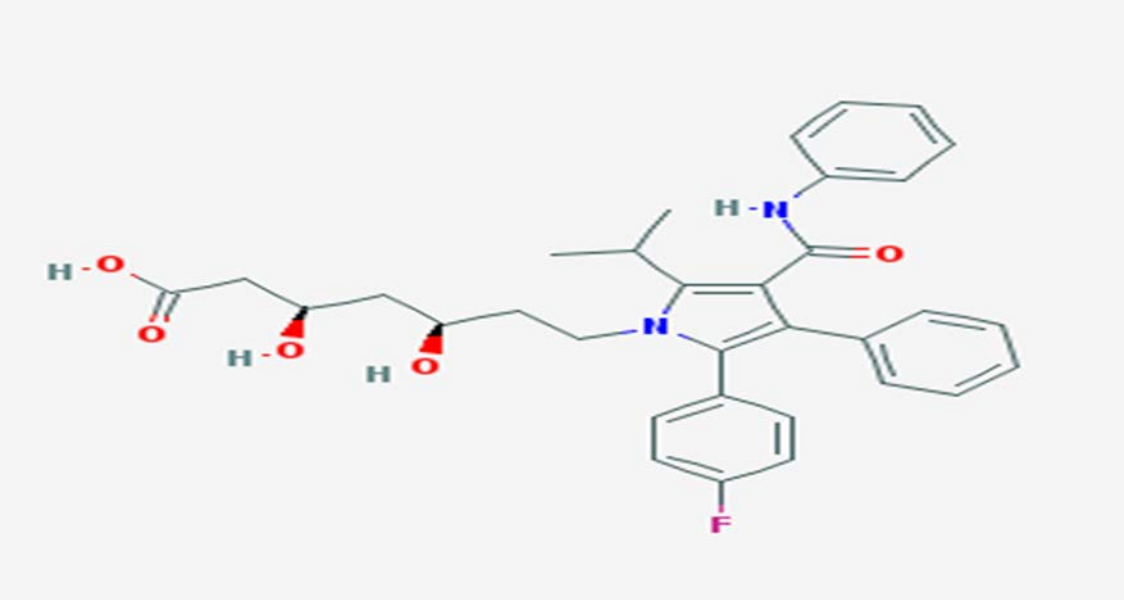


After a meal, triglycerides in the diet is absorbed from the small intestine in the form of chyme, a digestive hormone called cholecystokinin (CCK) is released by intestinal cells in the intestinal mucosa. CCK stimulates the release of pancreatic lipase from the pancreas and stimulates the contraction of the gallbladder to release stored bile salts into the intestine.[15]
Together, the pancreatic lipases and bile salts break down triglycerides into monoglycerides and free fatty acids.Themonoglycerides& free fatty acid used to obtain the energy for body by oxidation to release the ATP (adenosine tri-phosphate) the energy unit of the body, or store in liver.[15]Many factors that lead to increase the serum cholesterol & triglycerides levels.Hereditary factors and high lipid dietary intake, lack of daily exercise and some behavioral habit like smoking and alcohol consumption may role the effects.

The patients they have a hyperlipidemia treated by habitual changes e.g (exercise, low dietary food, lack or give up smoking and alcohol consumption), with medications like statin groups.[14,15]

Atorvastatin:

Is a pyrrole and hepatic acid derivative {C33H35FN2O5} hydroxymethylglutaryl-COA reductaseinhibitor (statin), and anticholesteremicagent that is used to reduce serum levels of LDL-cholesterol; apdipoproteinandtriglycerides to increase serum levels of HDL-cholesterol in the treatment of hyperlipidemias and prevention of cardiovascular diseases in patients with multiple risk factors.Atorvastatin is a member of the drug class known as statins.Dosage: - 10mg, 20mg, 40mg, 80mg.
It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels.[1,2]



Atorvastatin structure ... $C_{33}H_{35}FN_2O_5$

Side effect of Atorvastatin:

General:-

In general, atorvastatin has been well tolerated. Less than 2% of patients in premarketing clinical studies discontinued treatment due to adverse effects.

Gastrointestinal:-

Gastrointestinal side effects have been the most commonly reported. These have been reported in less than 4% of patients and have included constipation, flatulence, dyspepsia, and abdominal pain. Diarrhea has been reported in up to 5.3% of patients

and may be dose-related. Other gastrointestinal side effects observed with HMG-CoA reductase inhibitors have included pancreatitis, anorexia, and vomiting. Most effects tended to be mild and transient.[3]

Hepatic:-

Hepatic side effects including altered liver function have been observed with all HMG-CoA reductase inhibitors. In premarketing clinical trials, up to 0.7% of patients experienced persistent, elevated AST and/or ALT values greater than three times the upper normal limits on two or more occasions. Elevations of liver enzymes may be dose-related. Other hepatic side effects of the HMG-CoA class have included hepatitis, cholestatic jaundice, fatty changes in the liver, cirrhosis, fulminant hepatic necrosis, and liver failure.[3]

In clinical trials, liver enzyme elevations returned to pretreatment levels upon discontinuation or dose reduction of atorvastatin. Nawrocki and colleagues reported elevated bilirubin levels in 2/30 patients and elevated AST and ALT levels in 1/30 patients.[4]

Musculoskeletal:-HMG-CoA reductase inhibitors (statins) have been associated with rare cases of severe myopathy and rhabdomyolysis.[5]

Hematologic:-

Hematologic side effects including hemolytic anemia, thrombocytopenia, and leukopenia have occurred with HMG-CoA reductase inhibitors. These effects may be manifestations of a hypersensitivity reaction.[5]

Nervous system:-

Nervous system side effects of headache and weakness, dizziness, drowsiness, fatigue, cranial nerve dysfunction, tremor, vertigo, memory loss, decline in cognitive function, paresthesia's, peripheral neuropathy, and peripheral nerve palsy.[6]

Renal:-Renal side effects including acute renal failure secondary to rhabdomyolysis have been reported with HMG-CoA reductase inhibitors.[6,7]

Endocrine:-Endocrine side effects associated with the use of other HMG-CoA reductase inhibitors have included hypospermia, gynecomastia, and thyroid dysfunction.[8]

Hypersensitivity:-Hypersensitivity reactions have been observed rarely with HMG-CoA reductase inhibitors.[8]

Psychiatric

Psychiatric side effects of HMG-CoA reductase inhibitors have included decreases in libido, anxiety, depression, and insomnia.[5,7]

Genitourinary:-

Genitourinary adverse effects associated with other HMG-CoA reductase inhibitors have included erectile dysfunction, impotence, and testicular pain.[3,5]

Dermatologic:-
Dermatologic reactions have occurred rarely. In premarketing trials, up to 3.8% of patients complained of a rash. Phototoxicity has been associated with atorvastatin.[4]
Cardiovascular:-
Analysis of study data has shown an increased risk of hemorrhagic stroke in patients treated with atorvastatin who had a stroke or TIA within 6 months preceding treatment compared to placebo.[1,2]
Cardiovascular side effects occurring since market introduction have included angioneurotic edema, peripheral edema, and chest pain. Atorvastatin may also increase the incidence of hemorrhagic stroke in patients with a history of recent stroke or TIA.[7]
Respiratory:-Respiratory symptoms reported since market introduction have included bronchitis, rhinitis, pharyngitis, and sinusitis.[5]
Ocular:-Ocular side effects including a case of reversible ophthalmoplegia as well as a case of ocular myasthenia have been reported.[6]
Immunologic:- Immunologic side effects including a possible case of atorvastatin-induced reversible positive antinuclear antibodies have been reported.[4]

Other

Other side effects reported during clinical trials (in more than 2% of patients) have included infection, accidental injury, flu syndrome, abdominal pain, and back pain. Other side effects reported post marketing have included anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiform, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, fatal and nonfatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.[6,7,8]

Aspartate aminotransferase (AST)

Is found in high concentrations in liver, heart, skeletal muscle and kidney. AST is present in both cytoplasm and mitochondria of cells. In cases involving mild tissue injury, the predominant form of AST is that from the cytoplasm. Severe tissue damage results in more of the mitochondrial enzyme being released. High levels of AST can be found in cases such as myocardial infarction, acute liver cell damage, viral hepatitis and carbon tetrachloride poisoning. Slight to moderate elevation of AST is seen in muscular dystrophy, dermatomyositis, acute pancreatitis and crushed muscle injuries.[9,10]

Normal Values:-

Males:- 0-11 months: not established 1-13 years: 8-60 U/L > or =14 years: 8-48 U/L

Females:- 0-11 months: not established 1-13 years: 8-50 U/L > or =14 years: 8-43 U/L

Elevated aspartate aminotransferase (AST) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as one hundred times the upper reference limit, although twenty to fifty-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions.[11,12]

More common causes of elevated liver enzymes include:

- Certain prescription medications, including statin drugs used to control cholesterol.
- Drinking alcohol
- Heart failure
- Hepatitis viral A,B,C & Autoimmune hepatitis
- Nonalcoholic fatty liver disease
- Obesity
- Over-the-counter pain medications, particularly acetaminophen (Tylenol, others)
- Celiac disease (small intestine damage caused by gluten)
- Cirrhosis (early stages of liver scarring)
- Cytomegalovirus (CMV) infection
- Dermatomyositis (inflammatory disease that causes muscle weakness and skin rash)
- Epstein-Barr virus
- Gallbladder inflammation (cholecystitis)
- Heart attack
- Hemochromatosis (too much iron stored in your body)
- Hypothyroidism
- Liver cancer
- Mononucleosis
- Pancreatitis (pancreas inflammation)
- Polymyositis (inflammatory disease that causes muscle weakness)
- Wilson's disease (too much copper stored in your body

Material and Methods

AST & ALT kit (RANDOX).

Blood from hyperlipidemic patients.

Laboratory instrument & company provider:-

1- Centrifuge 122593, German, Hettich
2- Water bath 790792, German, MeMert
3- Spectronic – 203300166456, American

Enzymes source:-

Sample of blood from 27 hyperlipidemic patients in different age & sex.

The blood on nonheparinized test tube, then serum separated by centrifuge on 3000 C/M for 15 minutes.

Enzyme assay:-

The principle of measured activity of AST depend on colorimetric method.

AST

α – oxoglutarate + L-Aspartate → L-glutamate+oxaloacetate

AST is measured by monitoring the concentration of oxaloacetate formed with 2, 4-dinitrophenyl-hydrazine.

Solutions:-

Table 2. Determination of activity enzyme used the following solution

Solution	Concentration mmol/L
R1=AST Buffer Phosphate Buffer L-Aspartate α-oxoglutarate	 100 mmol/L 100 mmol/L 2 mmol/L
R2=2,4-dinitrophenyl hydrazine	2 mmol/L
R3=sodium hydroxide Pyruvate standard Pyruvate	 2mmol/L

Experimental Design

1-Determine the enzyme activity (AST) on serum by kit procedure

A-Sample

add (0.5ml) from R1 (AST buffer) on test tube, then add (0.1ml) from sample (serum) to the same test tube, then the test tube put in water bath for 30 minutes on 37 C◦ then add 0.5 ml of the R2 (2, 4-dinitrophenyl hydrazine) without water bath for 20 minutes for 20-25 C◦ then add 5 ml from R3 (NaOH) after 5 minutes calculate the absorption of sample.

B-Reagent Blank

add 0.5ml from R1 on test tube, then add 0.5ml from R2 with 0.1ml from distill water without water bath for 20minutes on 20-25 C◦ then add 5ml from R3 by concentration after dilution (0.4 N) after 5minutes calculate the absorption of reagent blank.

2-Read the absorption to each sample on wave length 545, then calculate the result to define the enzyme activity by use the following equation:-

(IU/L) AST activity = Test – control

T = serum absorption, C= spectronic absorption

3-Compare the result of the samples with the normal value of AST.[13]

4-Diluted 2.5 mg/ml of Atorvastatin as active material by the following procedure:-

A-Diluent: dimethylsulfoxide (D.M.S.O)

B-Standard solution (0.125mg/ml) of propylene glycol in diluent

C-Sample solution (2.5mg/ml) of Atorvastatin (as propylene glycol solvate) in diluent

Results and Discussion

The study discuss the direct & indirect effect of Atorvastatin on sAST,

incidence of presented elevation of sAST is 0.5% in the atorvastatin treated population , some of those within 12 hours of low dose atorvastatin consumption liver functions were fully recovered to the baseline level 11 days after discontinuation of atorvastatin treatment.[16] By examine a sample of serum from 27 known cases of hyperlipidemic patients, whom prepare to treat with Atorvastatin as lipid lowering agent, within 4 months from started treatment with follow up, and have chronic heart diseases (CHD) ,Diabetes mellitus DM,.

The study upon in AL-Kindy general hospital in east of capital Baghdad, on 8-9-10-11-12 /2015.

The group of patients was in different age, sex, and sAST result before Atorvastatin as a direct effect (by adding atorvastatin solution on serum samples directly) & indirect effect by consumption of atorvastatin pills after a period of treatment. Depending on a dose 20mg/day.

Table 3. The result of sAST to the patients before treatment

Patient No.	Age	Gender	Coexisting diseases	Combined drugs	Date	sAST U/L
No 1	54	♂	CHD	Clopidogrel	3/8/2015	18
No 2	41	♂	--------	----------	3/8/2015	23
No 3	39	♂	DM	Metformin	3/8/2015	28
No 4	52	♀	DM	Mixed insulin	3/8/2015	41
No 5	46	♀	HTN	Captopril	3/8/2015	36
No 6	61	♂	HTN	Metoprolol	5/8/2015	39
No 7	63	♀	CHD	Isosorbide	5/8/2015	53
No 8	58	♀	---------	----------	5/8/2015	24
N0 9	42	♂	----------	----------	6/8/2015	35
No 10	38	♀	----------	----------	9/8/2015	25
No 11	40	♂	---------	----------	9/8/2015	33
No 12	51	♂	DM	Soluble insulin	9/8/2015	29
No 13	49	♀	----------	----------	9/8/2015	19

No 14	37	♀	----------	----------	9/8/2015	37
No 15	53	♂	HTN	Telmisartan	10/8/2015	17
No 16	48	♂	----------	----------	12/8/2015	45
No 17	44	♀	HTN	Losartan	12/8/2015	22
No 18	59	♂	CHD	Clopidogrel	12/8/2015	63
No 19	62	♂	CHD	Aspirin , isosorbid	12/8/2015	27
No 20	42	♀	----------	--------	13/8/2015	20
No 21	44	♂	----------	----------	16/8/2015	29
No 22	56	♀	DM	Glibenclamide	16/8/2015	41
No 23	38	♀	----------	----------	16/8/2015	39
No 24	40	♀	----------	----------	18/8/2015	31
No 25	37	♂	----------	----------	18/8/2015	28
No 26	47	♂	----------	----------	19/8/2015	45
No 27	55	♀	HTN	Atenolol	19/8/2015	19

As above in table (1-1) we saw the following point:

1-Normal result are 21 patients.

2-Border line 4 patients (patients No 4, 16, 22, 26).

3-Neglected patients 2 (patients No 7, 18) cause they already have high AST result.

Table 4. The result of sAST after addition Atorvastatin solution on the same patients serum

Patient No.	Age	Gender	Date	sAST U/L	sAST U/L after addition Atorvastatin solution
No 1	54	♂	3/8/2015	18	18
No 2	41	♂	3/8/2015	23	22
No 3	39	♂	3/8/2015	28	25
No 4	52	♀	3/8/2015	41	44
No 5	46	♀	3/8/2015	36	35

No 6	61	♂	5/8/2015	39	34
No 7	63	♀	5/8/2015	53	51
No 8	58	♀	5/8/2015	24	26
N0 9	42	♂	6/8/2015	35	33
No 10	38	♀	9/8/2015	25	21
No 11	40	♂	9/8/2015	33	32
No 12	51	♂	9/8/2015	29	32
No 13	49	♀	9/8/2015	19	24
No 14	37	♀	9/8/2015	37	33
No 15	53	♂	10/8/2015	17	17
No 16	48	♂	12/8/2015	45	44
No 17	44	♀	12/8/2015	22	23
No 18	59	♂	12/8/2015	63	61
No 19	62	♂	12/8/2015	27	25
No 20	42	♀	13/8/2015	20	22
No 21	44	♂	16/8/2015	29	31
No 22	56	♀	16/8/2015	41	37
No 23	38	♀	16/8/2015	39	33
No 24	40	♀	18/8/2015	31	31
No 25	37	♂	18/8/2015	28	24
No 26	47	♂	19/8/2015	45	43
No 27	55	♀	19/8/2015	19	26

The results show: - there is no change in the serum AST above the normal value except the neglected patients (No 7, 18) as mention in table 4

Table 5. The results of sAST after started Atorvastatin pills consumption (20mg/day)

Patient No.	Age	Gender	Date	sAST U/L 1st study	sAST U/L after treatment with atorvastatin
No 1	54	♂	14/11/2015	18	18
No 2	41	♂	6/9/2015	23	22
No 3	39	♂	9/12/2015	28	25
No 4	52	♀	22/9/2015	41	44
No 5	46	♀	26/9/2015	36	35
No 6	61	♂	15/9/2015	39	34
No 7	63	♀	21/11/2015	53	51
No 8	58	♀	8/10/2015	24	26
N0 9	42	♂	16/11/2015	35	33
No 10	38	♀	19/11/2015	25	21
No 11	40	♂	12/10/2015	33	32
No 12	51	♂	14/12/2015	29	32
No 13	49	♀	7/9/2015	19	24
No 14	37	♀	8/11/2015	37	33
No 15	53	♂	17/12/2015	17	17
No 16	48	♂	11/9/2015	45	49 *****
No 17	44	♀	3/11/2015	22	23
No 18	59	♂	16/10/2015	63	61
No 19	62	♂	15/11/2015	27	54 *****
No 20	42	♀	1/12/2015	20	22
No 21	44	♂	4/10/2015	29	31
No 22	56	♀	12/12/2015	41	37
No 23	38	♀	21/12/2015	39	33
No 24	40	♀	3/10/2015	31	64 ******
No 25	37	♂	14/9/2015	28	24

No 26	47	♂	21/10/2015	45	43
No 27	55	♀	2/12/2015	19	26

The results show:-

1- Normal value in 19 patients.
2- Border line 3 patients (No 4, 22, 26).
3- Elevated 3 patients (No 16, 19, 24).
4- Neglected 2 patients (No 7, 18).

As we see in table 3 after adding Atorvastatin solution directly to the serum, there is no markedly different from the study of table 2 before adding, and if there is some different in result that may related to technical error or chemical reaction.
So, there is no direct effect of Atorvastatin on serum AST.

In table 4, after the same patients started with Atorvastatin pills treatment, by a different periods within month to 4 months.
There is a different on samples studies for 3 patients (No 16, 19, 24) as indirect effect of Atorvastatin on serum AST.
3/27 = 11%. So there is NO direct effect of Atorvastatin on sAST.
But can effect as elevated liver AST after cell damage when the patients use the drug as hyperlpidemic lowering agent, after a period of using drug and the study mention the AST result of the same patients after 3months of uses treatment, the Atorvastatin can cause hepatic cells damage, so can effect of sAST and elevated it.
If the sAST elevated more than the normal value after 3 months of Atorvastatin treatment, so doctors must stopped the treatment and changed the management protocol. We depend the period of 3months interval between the comparison of sAST study before & after Atorvastatin treatment from the BNF (British National Formulary) approved.
By the compare this study with a study of Atorvastatin induced acute elevation of hepatic enzymes & the absence of cross-toxicity of pravastatin Y. Liu, Z. cheng and G.-P .Shi at 2011. The author result change of sAST equal to 0.5% [16]
And our study show the change equal to 11%. The p value = 0.0001 significant.

References

[1]Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. "Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial". Journal of the American Medical Association 295 (13): 1556–65. doi:10.1001/jama.295.13.jpc60002. PMID 16533939, April 2006.

[2]McCrindle BW, Ose L, Marais AD. "Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial". J. Pediatr. 143 (1): 74–80. doi:10.1016/S0022-3476(03)00186-0. PMID 12915827, July 2003.

[3] Ozaki K, Kubo T, Imaki R, Shinagawa H, Fukaya H, Ohtaki K, Ozaki S, Izumi T, Aizawa Y. "The anti-atherosclerotic effects of lipid lowering with atorvastatin in patients with hypercholesterolemia". J. Atheroscler. Thromb. 13 (4): 216–9. doi:10.5551/jat.13.216. PMID 16908955, August 2006.

[4] Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacsohn JL, Weiss SR, Keilson LM, Brown WV, Miller VT, Shurzinske LJ, Black DM (January 1996). "Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia". Journal of the American Medical Association 275 (2): 128–33. doi:10.1001/jama.03530260042029. PMID 8531308,1996.

[5] Backman JT, Luurila H, Neuvonen M, Neuvonen PJ. "Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites". Clin. Pharmacol. Ther. 78 (2): 154–67. doi:10.1016/j.clpt.2005.04.007. PMID 16084850, August 2005.

[6] Medical Product Reviews. "Atorvastatin Calcium (Lipitor Tablets) - Uses, Dosage and Side Effects". Retrieved 3 May 2012.

[7] Heart Protection Study Collaborative Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 360:7–22,2002.

[8] Cannon, CP, Braunwald, E, McCabe, CH et al, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 350:1495–1504,2004.

[9] Berg, JM; Tymoczko, JL; Stryer, L .Biochemistry. W.H. Freeman. pp. 656–660. ISBN 978-0-7167-8724-2,2006.

[10]Hirotsu K, Goto M, Okamoto A, Miyahara I ."Dual substrate recognition of aminotransferases". Chem Rec 5 (3): 160–172. doi:10.1002/tcr.20042. PMID 15889412,2005.

[11]Okamoto A, Kato R, Masui R, Yamagishi A, Oshima T, Kuramitsu S "An aspartate aminotransferase from an extremely thermophilic bacterium, Thermusthermophilus HB8". J Biochem 119 (1): 135–44. doi:10.1093/oxfordjournals.jbchem.a021198. PMID 8907187,1996.

[12]GPnotebook> reference range (AST) Retrieved on Dec 7, 2009.

[13] Reitman,S.,and Frankel,S.,Amer.J.Clin.Path.,1957;28:56.

[14]Uto Y (2016) Recent progress in the discovery and development of stearoyl CoA desaturase inhibitors. Chemistry and physics of lipids 197: 3-12.

[15] Li X, Chen Y-T, Hu P, Huang W-C (2014) Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling. Molecular cancer therapeutics 13: 855-866.

[16] Newman CB,Palmer G, Silbershatz H, etal. Safety of atorvastatin derived from analysis of 44 completed trails in 9,416 patients. Am J Cardiol.2003;92:670-676. [PubMed] [Google Scholar]