Role of Ezetimibe in Combination with Statins(Simvastatin and Atorvastatin) in Controlling Dyslipidemia

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Abstract

Cardiovascular risk is independently increased by plasma lipids abnormalities (low- density and high density lipoprotein -cholesterol and triglycerides). Most patients have more than one lipid abnormality. Combination therapy with lipid-modifying agents could offer an important therapeutic option for improving the overall lipid profile. Combinations have demonstrated to provide additive efficacy and significant reductions in coronary events . This study was designed to evaluate the effect of ezetimibe, when used in combination with other hypolipidaemic agents (statins) on lipid profile as well as on liver function ,renal function, oxidative stress, and platelets function when given to dyslipidaemic patients . Forty four patients (24 males and 20 females) with age ranged between 40-70 years (54 ±14.6) with dyslipidaemia on statins therapy for at least 6 month were involved in this clinical trials. They were randomized into two groups treated with either a combination of 20 mg/day simvastatin or a combination of 20mg/day atorvastatin and 10mg/day of ezetimibe.The study also included 22 apparently healthy subjects with age ranged (40-70years) and sex(11males and 11 females) matching that of the patients group. Serum lipid profile (total cholesterol -TC, triglycerides -TG, low density lipoprotein-cholesterol –LDL-C, very low density lipoprotein-cholesterol-VLDL-C, and high density lipoprotein-cholesterol –HDL-C), oxidative stress marker (Malondialdehyde-MDA), liver functions indices (Alanin aminotransferase -ALT,Aspartate aminotransferase- AST, total bilirubin), renal function parameters (urea, creatinine, and microalbuminuria) and platelets function test (bleeding time)were evaluated before and after 4 and 6 weeks of starting ezetimibe treatment . Treatment with ezetimibe plus simvastatin or atrovostatin resulted in significant lowering in TC, TG, LDL-C levels with elevation in HDL-C also the LDL/HDL ratio lowered significantly (by 38.16%). This effect was associated with significant changes in liver function , and oxidative stress without changes in platelets function nor in renal function. The results presented in this study indicated that ezetimibe can be used in clinical practice for the treatment of dyslipidaemia, when combined with other hypolipidaemic agents like simvastatin and atorvastatin to improve the therapeutic profile with ameliorating some of their adverse effects.

Keywords : Ezetimibe , Statins , Dyslipidemia

الخلاصة

ان خطر أمراض الأوعية القلبية يمكن إن يزداد بصورة غير معتمدة عند الاختلال في الدهون الثلاثية والدهون البروتينية عالية الكثافة وواطئة الكثافة. وجد ان معظم المرضى لهم أكثر من خلل واحد في الدهون. ان العلاج المركب من المواد المعدلة للدهون يوفر فائدة علاجية مهمة لتحسين كل مستويات الشحوم في الدم . و العلاج المركب يمكن ان يكون له فعالية إضافية مسبباً هبوطاً مغوياً في التأثيرات على الشرايين التاجية. أجريت هذه الدراسة وصممت لتقييم فعالية الايزتايمب مع مواد خافضة للدهون مثل الستاتينات على معايير الكيمياء الحياتية والمتمثلة بمستويات ايض الدهون و فرط الأكسدة ووظائف الكبد والكلى ، إضافة إلى تأثيره على وظائف الصفيحات الدموية (زمن النزف) ومقارنة هذه التأثيرات مع أدوية تقليدية خافضة للدهون (سمفاستاتين و اتورفستاتين) كنظام مختلط مع الازيتياميب عند مرضى الشحام .اشتملت هذه الدراسة على (44) مريضا (24 ذكور، 20 اناث) بعمر يتراوح بين (40-70) سنة وبمعدل 54± 14.6 مريضاً بداء الشحام مستمرين على العلاج بادوية الستاتين. تم تقسيم المرضى عشوائياً الى مجموعتين كالأتي:
المجموعة الأولى: هي مجموعة المرضى الذين استخدموا نظام مختلط بين السمفاستاتين والايزيتيميب 20+10 ملغم يومياً والمجموعة الثانية على نظام مختلط بين الاتورفاستاتين والايزيتايميب 20+10 ملغم يومياً. استمرت فترة المتابعة ستة أسابيع متتالية. كذلك ضمن الدراسة مجموعة مقارنة من الأصحاء بأعمار مقاربة وبنفس توزيع الجنس لمجاميع المرضى بالشحام وبعدد (22). تم قياس مستويات الشحوم في الدم (TC,TG,HDL,LDL) ومعايير فرط الاكسدة المالوندالديهايد ووظائف الكبد (AST,ALT T.Bil.) ووظائف الكلى (S.Urea,creatinine,MAU) ووظائف الصفيحات الدموية (Bleeding Time) قبل اعطاء العلاج وبعد مرور 4 اسابيع من اعطاء الازيتاميب. اظهرت تحاليل البيانات فروقا مغوية واضحة للازيتاميب مع السمفاستاتين او الاتروفاستاتين على مستوى شحوم الدم حيث لوحظ حصول انخفاض معنوي في تراكيز (TC,TG&LDL) وارتفاع مستوى HDL وانخفاض ملحوظ في نسبة

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LDL/HDL ترافق مع تغير معنوي في وظائف الكبد .ALT,AST,T.Bil . كذلك ظهر تحسن معنوي في معايير فرط الاكسدة متمثلة بانخفاض مستوى MD A و لم يتم ملاحظة أي تأثيرات ظاهرة او سلبية ذات دليل معنوي لوظائف الكلى والكبد والصفيحات الدموية.في ضوء النتائج التي افرزتها هذه الدراسة يمكن استنتاج مايلي :ان الازيتاميب يمكن ان يستخدم كعلاج اضافي بكفاءة لعلاج مرض الشحام وعندما يؤخذ مع ادوية خافضة للكوليسترول كالسمفاستاتين والاتروفاستاتين يمكن ان يحسن الفائدة العلاجية ومنع التأثيرات الجانبية المتوقعة.

Introduction

Dyslipidemia can be the result of a genetic predisposition, secondary causes or a combination of both.[1] The major lipid components of serum, Cholesterol and triglycerides can produce three forms of dyslipidemia: Hypercholesterolemia, hypertriglyceridemia and a combination of both. In each case, the dyslipidemia is the result of an elevation in either the number or composition of specific lipoproteins , which is an important determinant for selecting the appropriate drug therapy.[2,3] The NCEP guidelines for diagnosis of dyslipidemia, however, are based on clinical cut point that indicates relative risk for coronary disease. Including the general recommendation that total cholesterol and HDL levels to be measured every five years beginning at age 20 in persons who do have a family history of coronary heart or other atherosclerotic disease.[4] . LDL is considered as the primary atherogenic lipoprotein, and the smaller the size of the LDL particle, the more it is able to penetrate into subendothelial tissue, thereby contributes to the development of atherosclerosis.[5] For people with CHD, several large trials have demonstrated that aggressive lipid lowering is beneficial in people with CHD with considering the following points:-

A target LDL. Cholesterol level below 70-80 mg/dl is recommended for people who have CHD and have multiple major risk factors (e.g patients with diabetes or who smoke). Patients who experience myocardial infraction (MI) should be started on the cholesterol lowering medication while in the hospital and are advised to make life style changes , regardless of their LDL-cholesterol level.A target LDL-cholesterol level less than 100mg/dl is recommended for people who have CHD but do not have many additional risk factors.Life style changes as well as medications may be recommended when LDL levels are greater than 100mg/dlWhilest for people without a history of CHD also appear to benefit from lipid lowering therapy although the treatments are not as aggressive as in patients with CHD [6] . Five major classes of drugs are available now for the treatment of dyslipidemia , each with different effects on the various lipids and lipoprotein profile (Table-1) [7,8]. Statins are the most potent drugs available now for reducing LDL-C, they bring about moderately lower triglyceride level and modestly increase HDL-C levels [9] .

Table (1) : Major classes of drug used in treating dyslipidemia [2]

Drug class	LDL-cholesterol	HDL-cholesterol	Triglycerid
Statins	↓ 18%-55%	↑ 5%-15%	↓ 7%-30%
Bile acid sequestrates	↓ 15%-30%	↑ 3%-5%	No change or increase
Niacin	5%-25%	15%-35%	↓ 20%-50%
Fabric acid	↓ 5%-20% May be increased in patients with high triglyceride level	↑ 10%-20%	↓ 20%-50%
Cholesterol absorption inhibitors	↓ 17%-19%	↑ 1%-4%	↓ 0%-6%

Statins are considered the first line treatment of hypercholesterolemia in patient who have failed to adequately respond to dietary therapy.[10,11] Currently available products include Simvastatin, Atorvostatin, Lovastatin , Pravastatin, Fluvastatin Rosuvastatin [12]. oral agent that competitively inhibits HMG-CoA reductase, the catalytic enzyme in the conversion of HMG-CoA to mevalonic acid in the rate limiting step of cholesterol biosynthesis . [13]Recently, a potential mechanism for poor response to statin therapy was described by Patel et al(2001), [14] where the poor responders had a low basal rate of cholesterol synthesis that may be secondary to a genetically determined increase in cholesterol absorption possibly mediated by a polipoprotein E4 or by polymorphism in the HMG-CoA reductase gene.[15,16] Generally statins are contra-indicated in active liver disease (or persistently abnormal liver function tests) and in pregnancy (adequate contraception required during treatment and for 1 month afterwards) and breast-feeding. [17]The side effects of statins are reversible myositis which is a rare but a significant side-effect of the statins. Simvastatin and atorvastatin also cause headache; altered liver-function tests (rarely, hepatitis) and gastro-intestinal effects including abdominal pain, flatulence, diarrhea, nausea and vomiting. Rash and hypersensitivity reactions (including angioedema and anaphylaxis) have been reported rarely. [17] The new class of lipid modifying agents, cholesterol absorption inhibitors, acts to lower LDL-C concentrations by almost 20% regardless of concurrent therapy, and have a modest effect on HDL-C and triglycerides[18].Ezetimibe (Zetia, Merck/ Schering-plough pharmaceuticals) is the first agent approved in this class, might be a good option for patients who do not tolerate or respond to statin therapy .However, this product is contraindicated in patients with active liver disease. Ezetimibe acts through selective inhibition of intestinal cholesterol absorption . [19] Experimental studies suggest that ezetimibe prevents dietary and biliary cholesterol uptake that transport across the intestinal wall. [20,21] Ezetimibe -glucuronide, the primary metabolite, is transported from the liver back to the intestine in bile, and is a more potent inhibitor of cholesterol absorption than ezetimibe itself .[22]Relatively high level of fecal ezetimibe (69% of the administered dose) suggests limited absorption and possible hydrolysis of the glucuronide metabolite .[23] The dose of ezetimibe 10mg once daily.[17] The present study was designed to evaluate the possible effects of adding 10 mg daily dose of Ezetimbe (for 4 and 6 weeks) to hyperlipidemic patients ongoing with statins therapy (simvastatin 20 mg or atorvastatin 20 mg/day) on different components of lipoproteins in plasma, some biochemical markers for assessing liver , kidney and platelets function ,as well as , serum MDA levels.

Materials and Methods

This study was carried out in Al-Basrah General Hospital by selecting 44 patients (24 males and 20 females) with age ranged between 40-70 years (54 ± 14.6) presented with hyperlipidaemia (serum total cholesterol >200mg/dL) for more than 6 months on statins ,not having any CVD, from December 2006 to march 2007 . Twenty two apparently healthy subjects with comparable age and weight were also involved in this study as a control .Fasting blood specimens were utilized for assessing lipid profile (total serum cholesterol [24], triglyceride[25], and high density lipoprotein-cholesterol (26), low density lipoprotein-cholesterol [27] Liver function tests(Alanine minotransferase-ALT (Aspartate aminotransferase -AST [28] total bilirubin [29] , renal function tests (urea[30], creatinine[31] and microalbominurea -MAU [32], platelets function tests (Bleeding time IVY method) [33] and oxidative stress (serum malondialdehyde –MDA[34]. Subjects were randomized into five groups:

Group 1: which include 22 apparently healthy subjects (11 male, 11 female) that not received any therapy during the study.

Group 2: which include 11 (6 male and 5 female) dyslipidaemic patients treated with Simvastatin 20 mg orally given as single daily dose at bed time for 6 weeks interval.

Group 3: which include 11 (6 male and 5 female) dyslipidaemic patients treated with Atorvastatin 20 mg orally given as single daily dose at bed time for 6 weeks interval.

Group 4: which include 11 (6 male and 5 female) dyslipidaemic patients treated with Simvastatin 20 mg + Ezetimibe 10 mg orally taken at bed time for 6 weeks interval.

Group 5: which include 11 (6male and 5 female) dyslipidaemic patients treated with Atrovastatin 20 mg + ezetimibe 10 mg orally taken at bed time for 6 weeks interval .

All values were expressed as means ± standard error of mean. Data were analyzed by in dependent T-test to assess the difference between two groups. P value less than 0.05 was considered significant).[35]

Results

Both simvastatin and atorvastatin treated groups (figure-1), showed no significant change in serum total cholesterol after 4 weeks of ezetimibe therapy ,but after 6 weeks of the addition of ezetimibe to simvastatin, there was a significant lowering in serum total cholesterol level as compared with both baseline . However , simvastatin treated group showed significant ($p<0.05$) reduction in serum TG levels after 4 weeks from the addition of ezetimibe (-28.6%)as compared with normal values , after 6 weeks from addition of ezetimibe it produced (-30.69%) reduction as compared with normal values (figure-2).While, 4 weeks of ezetimibe addition to atorvastatin produced a significant lowering ($p<0.05$) in serum TG level as compared to both normal and baseline values (-31.93%and -29.36%, respectively). After 6 weeks serum TG levels were lowered by(-19.6%,-17.4%) as compared with normal and baseline values respectively.However, the hyperlipidemic group treated with simvastatin exert non significantly elevated levels of serum HDL-C after 4 weeks from the addition of ezetimibe (figure-3) .

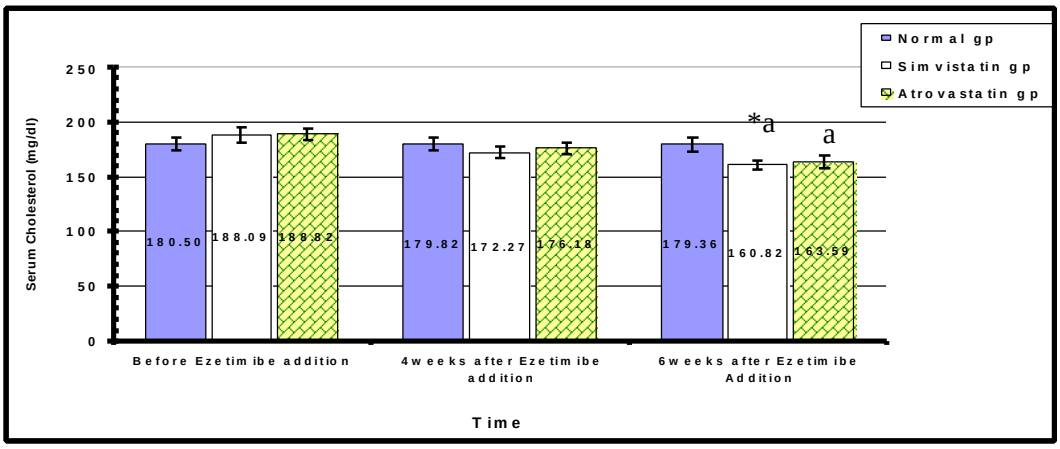

Figure (1) : A histogram showing serum total cholesterol, for Simvastain and Atrovastatin groups that received Ezitimibe; as compared with control

* = significant at $p<0.05$ as compare with normal values in same column.
a = significant at $p<0.05$ as compared with baseline values.

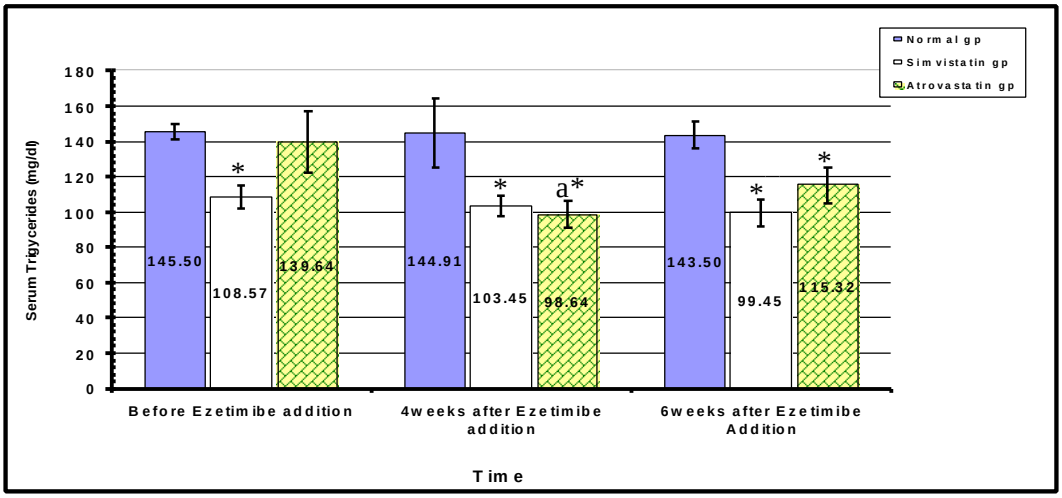

Figure (2): A histogram showing serum triglyceride, for Simvastain and Atrovastatin groups that received Ezitimibe; as compared with control group

* = significant at $p<0.05$ as compare with normal values in same column.
a = significant at $p<0.05$ as compared with baseline values.

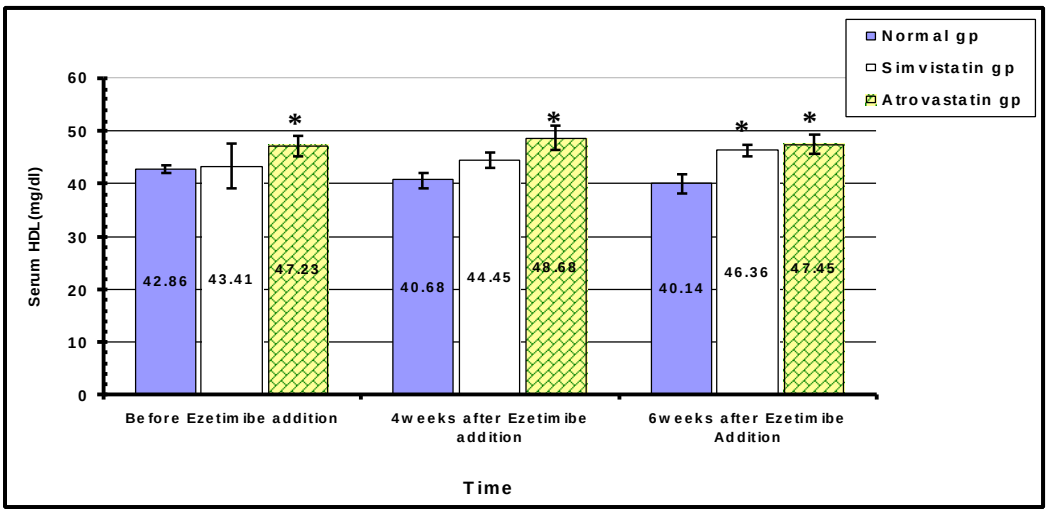

Figure (3): A histogram showing serum HDL-cholesterol, for Simvastain and Atrovastatin groups that received Ezitimibe; as compared with control group.

* = significant at $p<0.05$ as compare with normal values in same column.

But after 6 weeks there were significant ($p<0.05$) elevations in serum HDL-C level (15.4%,6.79%) as compared with normal and baseline values respectively .Atorvastatin group, showed significantly ($p<0.05$) higher serum HDL-C level before, after 4 weeks, and after 6 weeks from addition of ezetimibe. (10.19%, 19.66% & 18.21% respectively) as compared with value of normal group. Plasma LDL-C level was non significantly lowered after 4 weeks from addition of ezetimibe to simvastatin treated group (figure-4) but after 6 weeks there were a significant ($p<0.05$) lowering in serum LDL-C levels (-20.95%,-21%) as compared with baseline and normal values respectively. While, atorvastatin group, showed no significant alteration in serum LDL-C level both after 4 and 6 weeks from addition of ezetimibe. However, simvastatin group showed no significant changes in LDL/HDL ratio after 4 weeks of ezetimbe therapy as compared to those values before adding ezetimbe and that of control (table .2) .

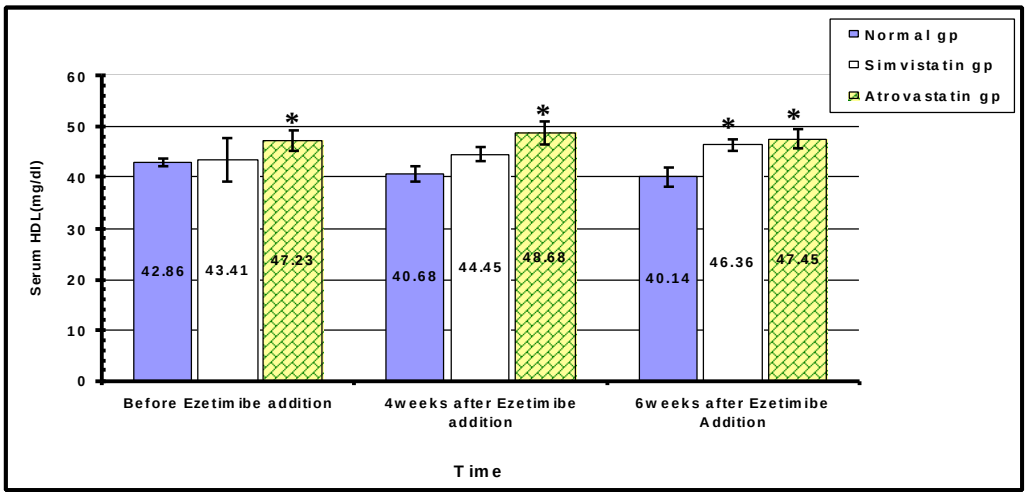

Figure (4) : A histogram showing serum LDL-cholesterol, for Simvastain and Atrovastatin groups that received Ezitimibe; as compared with control group.

* = significant at $p<0.05$ as compare with normal values in same column.

Table (2): Effect of Ezitimibe Addition on LDL/HDL ratio in patients treated with HMG-CoA reductase inhibitors (Atrovastatin & Simvastatin); in comparison with normal individuals (values expressed as mean ± standard error of mean , N= Number of subjects)

Groups	Duration of treatment	LDL/HDL ratio			
Normal N=22	Base line values	2.79	±	0.20	
	After 4 weeks	3.13	±	0.34	
	After 6 weeks	3.23	±	0.30	
Patient treated with Simvastatin & Ezitimibe N=22	Base line values	3.38	±	0.43	
	After 4 weeks	2.51	+	0.23	
	After 6 weeks	2.09	±	0.15	*a
Patient treated with Atrovastatin & Ezitimibe N=22	Base line values	2.68	±	0.22	
	After 4 weeks	2.35	±	0.24	
	After 6 weeks	2.34	±	0.19	*

* = significant at $p<0.05$ as compare with normal values in same column.
a = significant at $p<0.05$ as compared with baseline values.

But 6 weeks values were significantly ($p<0.05$) lowered (-38.16%,-35.29%) as compared with both baseline and control values respectively, a comparable results were obtained with atorvastatin treated group in LDL/HDL ratio (-27.5%,-12.68%)) as compared with normal and baseline values, respectively.In table -3, the studied groups exert a significant changes in serum ALT activity after 6weeks from addition ezetimibe (18.77%,5.66%)as compared to both baseline and control values respectively.While, the atorvastatine group exert no significant alterations in ALT activity in serum through the study. Simvastatin treated group of patients showed non significant elevation in serum AST activity after 4 weeks from addition ezetimibe(8.39%,11.7%) as compared with baseline and normal values ,respectively ,but after 6 weeks a significant ($p<0.05$) elevation in serum AST activity was noticed (13.6%)as compared to pretreatment value. Meanwhile, atoravastatin treated group was presented with a significant ($p<0.05$) lowering in serum AST activity (-7.12%,-14.4%)as compared with both baseline and normal values respectively. In simvastatin treated patients there was a significant ($p<0.05$)lowering in serum total bilirubin level(-15.5%,-17.09%) after4&6 weeks as compared to the control values, respectively (table-3). In atorvastatin treated group, ezetimibe showed a significant ($p<0.05$)lowering in serum total bilirubin (-8.18%, -13.6%) respectively as compared with baseline and normal values respectively.

Table (3) : Effect of Ezetimibe addition on serum ALT , AST and Total bilirubin in patients treated with Simvastatin and Atrovostatin in comparison with normal Subjects (values are expressed as mean ±SEM , N= Number of subjects)

Groups		Duration of treatment	Serum ALT (IU/L)				Serum AST IU/L	Serum total Bilirubin
Normal N=22		Base line values	13.82	±	0.72		14.8±0.66	1.26±0.03
		After 4 weeks	13.77	±	0.55		13.86±0.58	1.16±0.5
		After 6 weeks	13.59	±	0.47		14.50±0.65	1.17±0.04
Patient treated with Simvastatin & Ezitimibe N=22		Base line values	12.09	±	0.81		11.32±0.32*	1.03±0.04*
		After 4 weeks	14.18	±	0.66		12.27±0.48*	0.98±0.03*
		After 6 weeks	14.36	±	0.56	a	12.86±0.43a*	0.97±0.04*
Patient treated with Atrovastatin & Ezitimibe N=22		Base line values	12.91	±	0.60		12.77±0.56*	1.10±0.05*
		After 4 weeks	13.45	±	0.50		11.86±0.54*	1.03±0.05
		After 6 weeks	13.45	±	0.36		11.45±0.46*	1.01±0.03*

* = significant at $p<0.05$ as compare with normal values in same column.
a = significant at $p<0.05$ as compared with baseline values.

(Table- 4) showed no significant alteration in serum urea level before and after 4 and 6 weeks from addition of ezetimibe to all studied groups, nor in serum creatinine levels ,nor in microalbuminuria values. Serum MDA levels simvastatin treated groups were presented with a significant ($p<0.05$) lowering in serum MDA (-42%) as compared with baseline values (figure-5) .After 4 and 6 weeks of utilizing ezetimibe in atrovastatin treated group serum MDA significantly ($p<0.05$) lowered (19.8%,26.7%) as compared with baseline values.The simvastatin and atorvastatin treated patients showed no significant alterations in bleeding time values by the addition of ezetimibe to their therapy (table- 5).

Table (4) : Effect of Ezetimibe addition on serum urea,creatinine and microalbuminuria in patients treated with Simvastatin and Atrovostatin in comparison with normal Subjects (values are expressed as mean±SEM , N= Number of subjects)

Groups	Duration of treatment	Serum Urea(mg/dl)				Serum Creatinine (mg/dl)	Microalbuminuria (mg/day)
Normal N=22	Base line values	39.00	±	1.61		1.19±0.04	203.23±8.36
	After 4 weeks	39.73	±	2.03		1.16±0.05	207.09±11.3
	After 6 weeks	37.91	±	1.01		1.24±0.10	202.09±8.66
Patient treated with Simvastatin & Ezitimibe N=22	Base line values	39.43	±	1.98		1.28±0.14	201.73±8.59
	After 4 weeks	40.00	±	2.09		1.31±0.15	204.09±14.80
	After 6 weeks	39.27	±	1.78		1.29±0.14	206.09±18.70
Patient treated with Atrovastatin & Ezitimibe N=22	Base line values	36.68	±	2.08		1.13±0.04	211.55±10.40
	After 4 weeks	35.23	±	1.72		1.03±0.05	208.55±11.30
	After 6 weeks	36.23	±	0.97		1.11±0.02	209.05±17.40

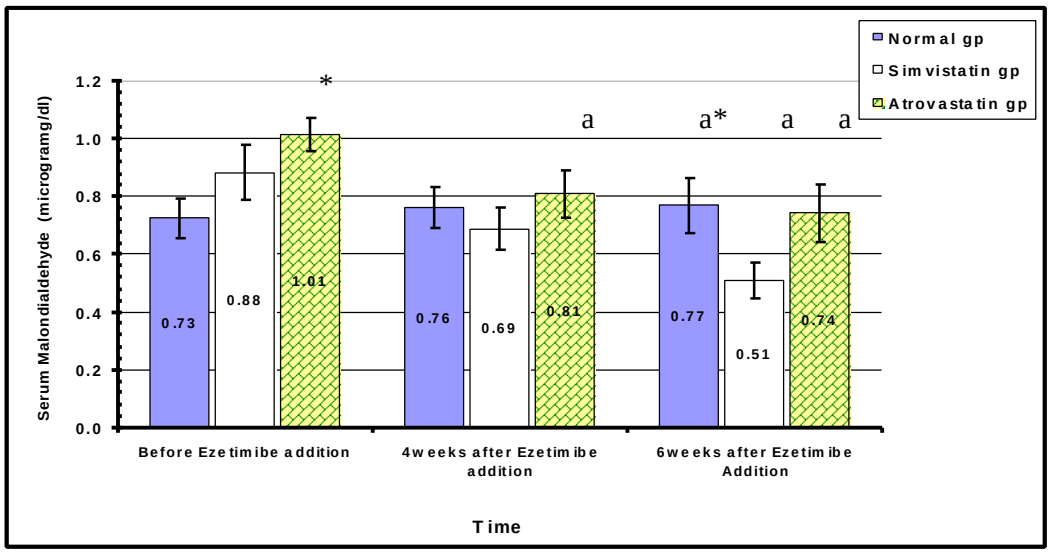

Figure (5): A histogram showing serum Malondialdehyde for Simvastatin and Atrovastatin groups that received Ezitimibe; as compared with control group

a = significant at $p<0.05$ as compared with baseline values.

* = significant at $p<0.05$ as compare with normal values in same column.

Table (5): Effect of Ezitimibe Addition on bleeding time, in patients treated with HMG-CoA reductase inhibitors (Atrovastatin & Simvastatin); in comparison with normal individuals (Values expressed as mean ± Standard error of mean , N= Number of subjects)

Groups	Duration of treatment	Bleeding time (minutes)			
Normal N=22	Base line values	2.54	+	0.18	
	After 4 weeks	2.48	±	0.17	
	After 6 weeks	2.45	±	0.13	
Patient treated with simvastatin & Ezitimibe N=22	Base line values	2.26	±	0.12	
	After 4 weeks	2.50	±	0.23	
	After 6 weeks	2.62	±	0.33	
Patient treated with atrovastatin & Ezitimibe N=22	Base line values	2.26	±	0.20	
	After 4 weeks	2.97	±	0.35	
	After 6 weeks	2.17	+	0.35	

Discussion

As previously presented in figures (-1), (-2), (-3) and (-4) treatment with ezetimibe plus statins successfully improves lipid profile markers in dyslipidaemic patients during 6 weeks of treatment .These results are consistent with results of other studies that included the administration of ezetimibe plus statins to patients with disordered lipids profiles could result in significant reduction in TC, LDL-C and TG levels, [36] with significant elevation in HDL-C levels , which could be attributed to mechanisms that are related to ezetimibe lowering effect on cholesterol which could be complement to the inhibitory action of statins on cholesterol biosynthesis representing an important new option for treatment in combination with statin [37]. Ezetimibe has an excellent safety and liability profile when administered with statins [38,39]. Also it has a low potential for drug interactions. [40] Many patients receiving statins therapy fail to reach their LDL- goal [41] , because its mechanism of action is complementary to that of statins, ezetimibe were studied for its potential additive lipid-lowering effects in patients already receiving statin therapy in double-blind as well as placebo-controlled trials [36,42]. Significant improvements were observed for other indicators of CHD risk (total cholesterol , non-HDL-C, apolipoprotein B, LDL-C: HDL-C ratio) in patients receiving ezetimibe-statin therapy.[36]When ezetimibe was combined with simvastatin or atorvastatin it caused a significant reduction in triglyceride level with time from baseline compared with statin monotherpy [43]. Combination therapy of simvastatin and ezetimibe was more effective than atorvastatin in reducing LDL-C in patients with primary hypercholesterolemia.[44] Preliminary studies have indicated that there were no significant effect of ezetimibe on absorption of fat-soluble vitamins[45] .Following absorption of ezetimibe where it is glucuronidated in the intestine wall the parent drug and its glucuronidated derivatives can undergo enterohepatic recircalation, that limits peripheral exposure [46] Ezetimibe is first in cholesterol absorption inhibitors, it 's action is consistent with the binding thereby blocking of sterol transporter on the brush border membrane of in intestinal epithelial cells [47]. Through inhibiting the intestinal cholesterol absorption ezetimibe can effectively reduce of biliary/dietary cholesterol delivered to the liver via chylomicron and chylomicron reminants, hence reduce cholesterol content of atherogenic particles chylamicrons / chylomicrors ruminants, VLDL, LDL).Meanwhile the reduced delivery of intestinal cholesterol to liver increase hepatic receptor activity and increase clearance of circulating LDL-C. [47]Ezetimibe, via inhibiting intestinal cholesterol and plant-sterol absorption, may modify the atherogenicity of chylomicron remnants and reduce systemic plant-sterol levels[48]. These effects are likely to reduce cardiovascular risk. It has been reported that there is a strong relationship between hepatic dysfunction and dyslipidaemic complications[49,50] However, the data presented in table- 3 representing a modulation in some liver markers in group treated with simvastatin plus ezetimibe after 6 weeks of treatment in case of ALTand AST. Such results could be due to relatively low doses of statins (20mg) wherase, other studies revealed a significant elevation in those enzymes.[13]The elevation in transaminases activities were primarily asymptomatic and not

associated with cholestasis. Serum transaminases returned to pretreatment level with discontinuation of combination therapy or with continued treatment [51]. Ezetimibe is being used with increasing frequency in many patients to augment the LDL-cholesterol lowering effects of statins [52] The recent Second United Kingdom Heart and Renal Protection (UK-HARP-II) study found in a randomized, controlled study that 10mg of ezetimibe added to 20mg of simvastatin in patients with (chronic kidney disease) CKD resulted in an incremental reduction of LDL-cholesterol level over simvastatin alone without an excess risk of abnormal liver or muscle markers or other advers events. [53] The purpose for the evaluation of renal function was to explor the safety of a combination of ezetimibe and statins in this respect .Statins at appropriately adapted doses have the same efficacy in chronic renal disease patients as in subjects with normal kidney function, and their tolerance is not a problem[54] In the present study the effect of ezetimibe plus statins (simvastatin or atorvastatin) have no significant effect on renal function , as in table-4 . Therefore, no dosage adjustment for ezetimibe is needed in patients with renal insufficiency. Efforts to improve lipid profiles now are targeted primarily for the treatment and prevention of cardiovascular disease, may also prevent the development of renal disease [55]. One important risk factor for atherosclerosis is an elevation in a particular type of plasma cholesterol specifically LDL -C. Oxidation of LDL -C is thought to render the lipoprotein to be athergenic ,because oxidized -LDL is more readily taken up by macrophages via scavenger receptors. [56]The data presented in figures (5) showed that serum MDA levels were significantly lowered by about (-33.7%) when ezetimibe was added to simvastatin treated group after 6 weeks .Meanwhile, level of MDA was significantly lowered after 4 weeks from addition ezetimibe to atorvastatin treating group by about (-19.8%) as compared with pretreatment values . However, MDA level after 6 weeks from addition ezetimibe to either groups lowered MDA level below those reported even for the normal group . Furthermore , the lowering effect on lipids pereoxidation produced by simvastatin/ezetimibe combination was better than that produced by ezetimibe/atorvastatin combination.[57] A recent study showed that despite the comparable modest reduction of serum cholesterol levels by ezetimibe, an intestinal inhibitor of cholesterol absorption, and statin, only the statin improved endothelial function[58] Thus, it is likely that the beneficial effects of statins on endothelial function extend beyond cholesterol reduction. Indeed, statins have been shown to reduce cardiovascular events in patients, irrespective of serum cholesterol levels [59] . In this study, the effects of adding ezetimibe to statins therapy (Simvastatin or Atorvastatin), in patients with dyslipidemia showed no significant changes in platelets function in both groups, this could indicate no adverse effect on platlets function as seen in table -5 .Although non of the studied groups of dyslipidaemic patients exert any deviation in bleeding time values from those reported from normal subjects ,before initiating ezetimibe therapy. This would support the administration ezetimibe plus simvastatin or atorvastatin without any adverse effect on platelets, so patients with platelets dysfunction could take ezetimibe with statin safely .However, there is no evidence or clinical trials about effect of ezetimibe with statins on platelets function and specifically on bleeding time.

conclusions:

1. Ezetimibe can be used in combination with simvastatin or atorvastatin to improve their lipid-lowering action both effectively and safely in the treatment of dyslipidemia.
2. Ezetimibe can be used safely in combination with statins in patients with renal disease.
3. Ezetimibe exerts no further modification to liver function that could be produced by statins when used in combination with statins.
4. Ezetimibe/simvastatin and Eztimibe / atorvastatin could exert asignificant antioxidant effect in patients with dyslipidemia.
5. Non of the tested drugs (ezetimibe nor simvastatin nor atorvastatin) produced significant modification of platelets activity.

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