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Efficacy of Ezetimibe as Monotherapy in Hypercholesterolemic Patients with and without Diabetes: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Hyperlipidemia, hypertension, and diabetes are common diseases in the elderly. They are the main factor of cardiovascular disease and thus increase the risk of mortality. Recently, the death rate caused by COVID-19 is not predictable but has been increased by many factors, including age, hyperlipidemia, diabetes mellitus, obesity, and cardiovascular disorders.

Objective: Since many patients with these conditions are under lipid-lowering therapy, we carried out this study to evaluate the effect of ezetimibe on hyperlipidemia in patients with type 2 diabetes mellitus, non-diabetic, and COVID-19.

Patients and methods: In this study, 13 hypercholesterolemic patients were categorized per disease suffering from (Diabetes, non-diabetic and COVID-19). All patients were administered 10 mg of ezetimibe each day for 90 days. Afterward, their lipid profile was measured at baseline and then after 30, 60, and 90 days. Plasma total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL) were measured.

Results: HDL increased in diabetic and hypertensive patients by 24% and 6.2 % but decreased in the COVID patients by 1.29 %, in response to ezetimibe. Total Cholesterol and LDL decreased by 39.64 %, 30.32 % & 58.58% and 38.4 %, 25.33%, & 54.93 %, respectively. Results showed a considerable increase in triglyceride concentration by 13.5% and 23 % at 30 and 90 days of treatment in COVID-19 patients.

Conclusion: These findings reveal that ezetimibe was an effective treatment of hyperlipidemia among diabetic patients. In addition Sars-CoV-2 might be a factor interacting with hyperlipidemia-reducing therapy and lower ezetimibe efficacy. However, larger cohort studies are required to confirm these findings.

Keywords: Ezetimibe, Covid-19, Hyperlipidemias, Diabetes Mellites.

INTRODUCTION

Hyperlipidemia is a medical disorder characterized by an elevation of any or all lipid profile and lipoproteins in the blood. It is also called hypercholesterolemia/hyperlipoproteinemia [(1)]. Hyperlipoproteinemia includes several metabolic disorders that involve elevations in the plasma lipoprotein levels, whereas hyperlipidemia represents the increased levels of plasma triglycerides [(2)]. Hyperlipoproteinemia has two main clinical consequences, including acute pancreatitis and atherosclerosis. The latter can also occur in patients with marked hyperlipidemia, which results in recurrent attacks of the life-threatening disease [(3)]. Hyperlipidemia is the presence of high levels of cholesterol in the blood. The normal range for total blood cholesterol in humans is between 140 to 200 mg per deciliter (mg/dL) of blood and above 240 mg/dl is classified as a high cholesterol level in blood[(4)]. Elevated plasma triglyceride level in association with hyperlipidemia is common and contributes to an increased risk of heart disease, high VLDL and LDL cholesterol levels, and decreased HDL cholesterol levels[(5)].

Ezetimibe is a cholesterol absorption inhibitor; it is an effective LDL-C lowering agent and is safe and well-tolerated [(5)]. Ezetimibe is absorbed rapidly and undergoes wide glucuronidation in the liver. Both ezetimibe and ezetimibe-glucuronide are transported through the enterohepatic circulation and are brought to the intestinal epithelial cell brush border which is the site of pharmacological action. As it is rapidly absorbed, ezetimibe reaches a peak serum concentration in 4 h to 12 hours, the serum half-life is approximately 22 hours, in addition to its high protein-bound affinity (99.7%)[(4)]. The drug is excreted in the bile back into the intestinal lumen, where it inhibits the Nieman Pick C1 like 1 protein (NPC1L1) protein again [(6)]. NPC1L1 protein is essential for intestinal cholesterol absorption and is the molecular target of ezetimibe [(7)], which is finally excreted in feces, with a minor 10% excretion in the urine [(6)].

Although ezetimibe was developed as an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, but it is proved that its target of action is the cholesterol transport protein NPC1L1 thus inhibiting cholesterol uptake from small intestine [(8, 9)]. In other words ezetimibe act as selective intestinal cholesterol absorption interacting with hepatic NPC1L1 to inhibit biliary cholesterol absorption and further reduce serum cholesterol levels [(5)].

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Severe acute respiratory syndrome produced by SARS-CoV-2 can be an exceptional challenge to global healthcare systems and governments [(10)]. It was responsible for the deaths of over 2 million in over 220 countries so far [(11)]. Metabolic disease along with cardiovascular disorders are common diseases among patients and may also increase the risk of mortality with COVID-19 infection [(12)]. Other factors including hyperlipidemia is responsible for increasing risks of clots, strokes, and they account for approximately seventeen million deaths each year [(13)].

In addition, Co-morbidity including diabetes, hypertension and cardiovascular diseases were reported as risk factors for severe COVID-19 in several countries including Italy, China, and the USA [(14-16)]. For example, 18% of COVID-19 hospitalized patients from Lombardy, Italy, were reported to have hypocholesteremia [(17)]. Moreover, 35% of patients were reported to suffer from atherosclerotic cardiovascular diseases with 50% mortality among them [(18)]. Since the control of hyperlipidemia can prevent recurrent attacks of the life-threatening disease [(3)].

Diabetic dyslipidemia is characterized by an increase in small dense low density lipoprotein particles and in triglyceride (TG)-rich lipoproteins, and a decrease in high density lipoprotein (HDL) cholesterol, with an increase in non-HDL cholesterol [(19)]. Lipid abnormalities in patients with type 2 diabetes also include an increase in oxidized very low-density lipoprotein (VLDL) and chylomicron remnants. Although not always detected by the lipid measures used in clinical practice, all of these abnormalities contribute to diabetic dyslipidemia, and this atherogenic dyslipidemia is one of the major cardiovascular risk factors in people with type 2 diabetes [(20)].

The aim of the present study was to evaluate the effect of ezetimibe on hyperlipidemia in patients with type 2 diabetes mellitus, non-diabetic, and COVID-19.

PATIENTS AND METHODS

In this study, 13 adult patients (7 females and 6 males) were selected from those admitted to Sauad Kaffafi Hospital outpatient clinic. The patients' age range was between 33 and 65 years. All were suffering from hyperlipidemia. Patients were selected after physical examination and they were meeting the inclusion criteria, which was triglyceride level more than 100 mg/dl, total cholesterol level more than 200 mg/100 ml.

Exclusion criteria:

Hypersensitivity to drugs, liver toxicity, patients suffering from renal dysfunction, inability to follow for 3 months due to patient leaving or discontinuing therapy and children up to 18 years.

Patients are grouped into 3 groups according to the type of disease suffering from; Diabetes mellites group, non-diabetic group and COVID-19 group.

Blood samples were collected after 14 fasting hours. Then samples were, centrifuged and left to settle. Blood analysis and PCR were performed at Laboratories using the "Cobas C111" device. Blood samples for lipid measurements were collected at baseline and after 30, 60 and 90 days, and lipid concentration was measured by centrifugation (beta-quantification). VLDL and other risk factors were calculated by the Friedewald equation.

Ezetimibe 10 mg was given as initiated therapy for hyperlipidemia, one tablet daily for three months.

Diabetic Patients were on sitagliptin 50 mg tablets twice/day. COVID 19 patients received paracetamol 500 mg every 6 hours.

Ethical consent:

An approval of the study was obtained from Misr University for Science and Technology Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) test was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Complete lipid profile analysis was carried out on all patients on day 0 (base line) and then on day 30, 60 and 90 respectively. The results showed the effect ezetimibe 10 mg on patients with hyperlipidemia and suffering from other diseases. The percent reduction from the baseline in LDL levels and total cholesterol, was significantly greater within all groups. Significant reductions of total cholesterol level was observed after treatment in patient's suffering from diabetes mellitus. HDL levels increased significantly but not in COVID-19 patient (Table 1).

Table (1): Patient demographic date in the three groups.

Age (years)	49.8 ± 10.6
No. of patients	13
Sex	7 (55 %) / 6 (45 %)
Base line Total cholesterol (mean ± S.D) (mg/dl)	267.4 ± 51.6
Base line Triglycerides (mean ± S.D) (mg/dl)	139.6 ± 6.4
Base line HDL (mean ± S.D) (mg/dl)	53.6 ± 12.8
Base line LDL (mean ± S.D) (mg/dl)	182.1 ± 8.9
Base line VLDL (mean ± S.D) (mg/dl)	27.6 ± 5.4
Base line RF (mean ± S.D)	5.14 ± 1.2
History of H.T (number)	4 (30 %)
History of D.M (number)	6 (50 %)
COVID-19 (number)	3 (10 %)

Effect of Ezetimibe on lipid profile:

Ezetimibe decreases absorption of cholesterol and thus decrease cholesterol by 60 % of TC and 49.9 % of TG reductions, 63.3% of LDL reduction and 16.4% increase on HDL observed after 90 days day of starting mono therapy (Table 2 and figure 1).

Table (2): Effect of Ezetimibe on lipid profile.

	Base	**90 days**	**% Change ± S. D**
Total C	267.4 ± 51.6	168.5 ± 54	-60.3 ± 5.4
Total TG (mg/dL)	139.6 ± 46.4	106.2 ± 31.8	-49.9 ± 7.9
HDL (mg/dL)	53.6 ± 12.8	58.7 ± 11.9	16.4 ± 4.6
LDL (mg/dL)	182.1 ± 38.9	117.1 ± 24.1	-63.4 ± 7.5
VLDL (mg/dL)	27.6 ± 9.1	21.2 ± 6.2	-52.5 ± 8.1
Risk	5.1 ± 1.2	2.9 ± 1	-73.2 ± 5.4

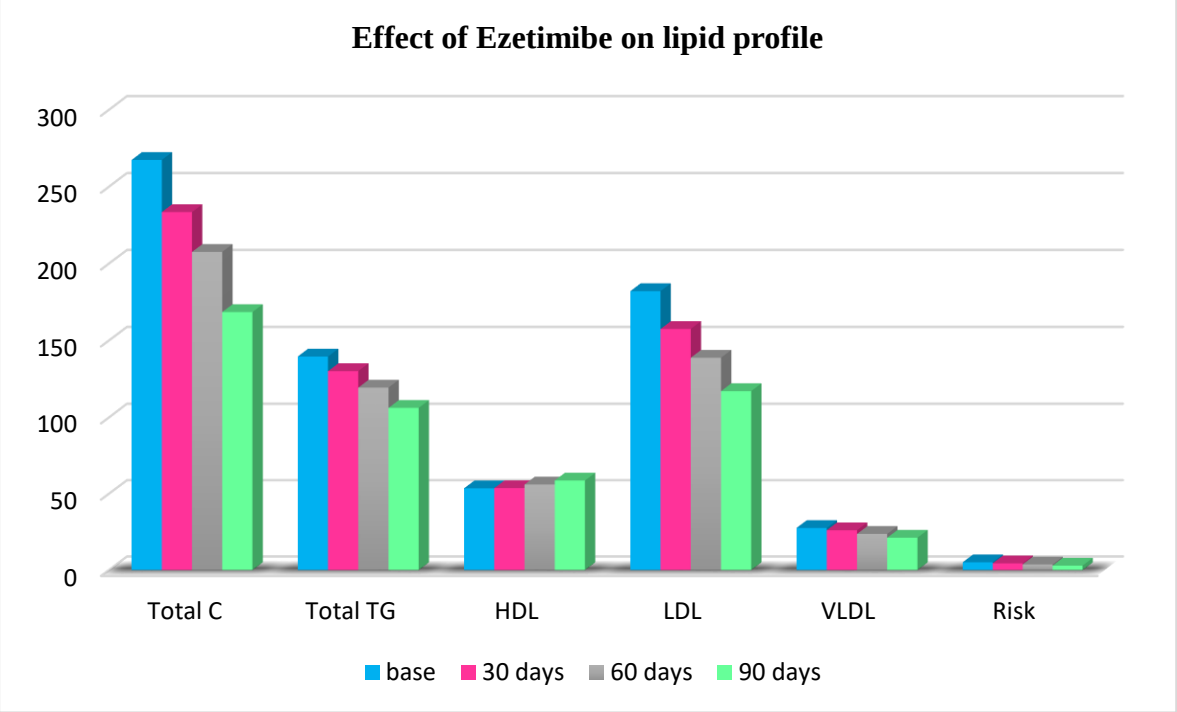

Figure (1): Effect of Ezetimibe on lipid profile.

Table (3) showed the effect of ezetimibe on lipid profile of diabetic and non-diabetic patients as there was no statistically significant difference except for a statistically significant decrease of cholesterol % and LDL% in diabetics (P values 0.029 and 0.005 respectively).

Table (3): % Change on lipid profile in different groups.

Groups	Serum Total Cholesterol % Change	Serum triglycerides % Change	HDL % Change	LDL % Change	VLDL % Change	HDL Risk Factor % Change
Diabetes	38.0165	34.7826	-37.5000	37.5000	34.7826	55.0000
	53.3333	25.2101	20.3390	46.8531	25.0000	42.1053
	50.0000	40.0000	-33.3333	50.0000	40.0000	63.2353
	22.7273	17.4157	-15.5556	25.3333	14.7059	33.3333
	34.1085	24.1071	-13.6364	32.2917	22.7273	41.3793
non-diabetic	50.0000	31.3725	-11.1111	27.3438	30.0000	58.0645
	20.6009	26.0000	-7.1429	28.1250	25.0000	30.9091
	20.3704	20.0000	-5.2632	20.5128	20.0000	25.5319
Covid-19	58.5890	-23.4568	-1.2987	54.9356	-25.0000	59.5238
P Value	0.029	0.46	0.517	0.005	0.481	0.166

Figures (2 & 3) showed the effect of ezetimibe on lipid profile of diabetic patients with a marked decrease in total cholesterol and LDL% change compared to non-diabetic patients expressed.

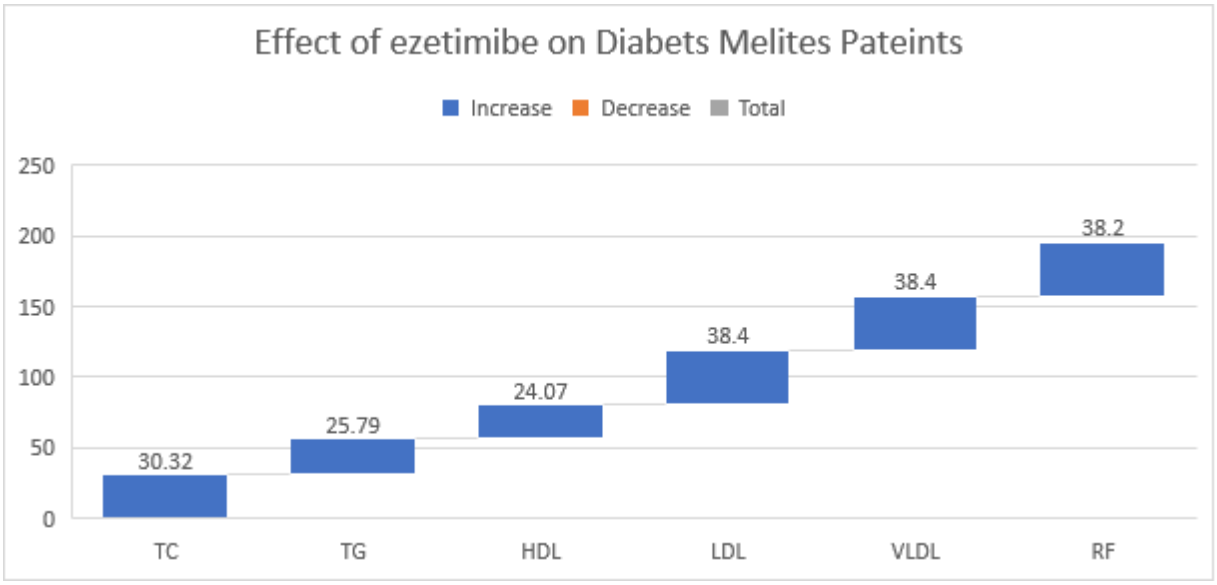

Figure (2): Effect of ezetimibe on diabetes mellitus patients.

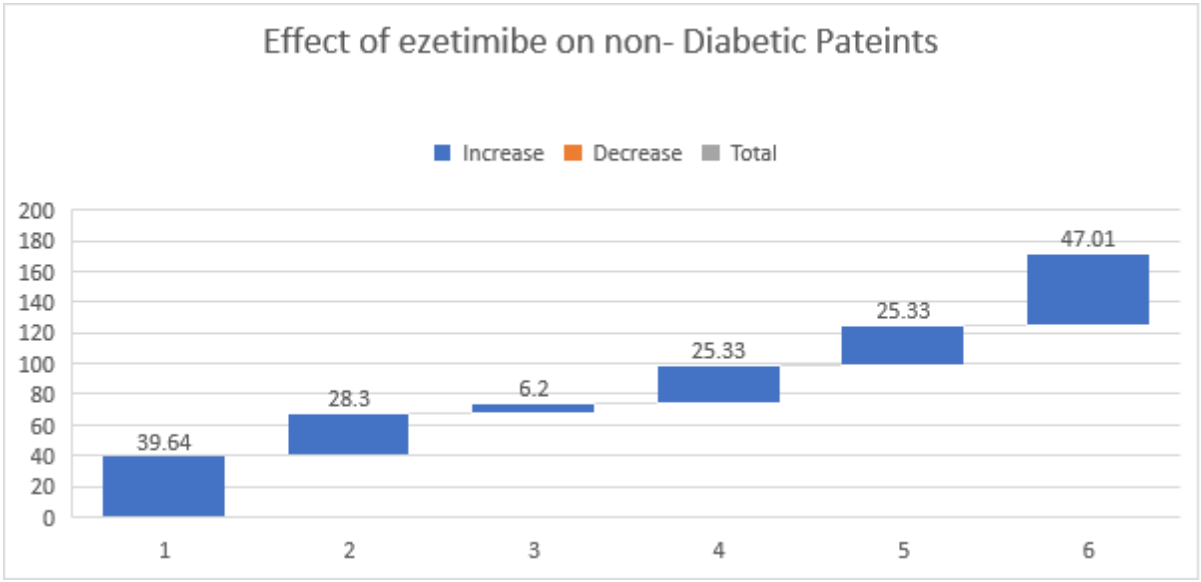

Figure (3): Effect of ezetimibe on non-diabetic patients

DISCUSSION

As ezetimibe is a potent inhibitor of cholesterol uptake, treatment with ezetimibe will decrease the formation of clots and thus decrease mortality, especially among COVID-19 patients [21]. Changes in lipid metabolism are an early step in atherogenesis and can cause vessel injury through coagulopathy and endothelial dysfunction. This emphasized the role of cholesterol in vasculopathy caused by COVID-19 infection [22].

In the current study, ezetimibe affected lipid profile of diabetic and non-diabetic patients. Regarding, hypertensive and COVID patient, there was no statistically significant difference except for statistically significant decrease of cholesterol % change in diabetic and hypertensive patients (p-value = 0.027, and 0.029 respectively) and decrease of LDL% in diabetic hypertensive patients (p-value = 0.020, and .005 respectively). **Bonaca *et al.* [23],** highlighted the relevant benefit of the use of ezetimibe in diabetic patients in his study. Another meta-analysis study also proved that the lipid lowering efficacy of ezetimibe is higher among diabetic patients, with significantly higher reductions of LDL-C, total cholesterol, and non-HDL-C in comparison with non-diabetic patient [24]. On the other hand, **Wu *et al.* [25]** reported that imbalanced lipid profile is not significantly associated with the 28-day all-cause mortality of COVID-19 patients, even in those accompanied with CVDs or diabetes. **Wohl *et al.* [26]** stated that ezetimibe monotherapy at 10 mg/day induced an about 5.3% reduction in LDL cholesterol, and decreased triglyceride (TG) by about 8% in HIV patients with primary dyslipidemias after 6-weeks study. These findings are consistent with the current research, as we reported that the same dose of ezetimibe caused a reduction of total cholesterol and LDL decreased by 39.64 %, 30.32 % & 58.58% and 38.4 %, 25.33% & 54.93 % respectively in the three groups.

There was slight decrease in high-density lipoprotein (HDL) cholesterol by about 10%, Also, ezetimibe caused reduction of LDL cholesterol by about 21%. Serum total cholesterol was decreased by 17%, HDL risk ratio was reduced by 6%. There was a slight decrease in high-density lipoprotein (HDL) cholesterol by about 10%. However, triglyceride (TG) and VLDL levels were increased by 13% and 12%, respectively in COVOD-19 patient. These findings disagree with those of **Atlee *et al.* [27],** who stated that ezetimibe has a rapid onset of action and caused decrease with 8.5% of LDL, 7.6% of TC and 9.1% of TG reductions and 0.2% increase on HDL that was observed in 25th day of initiating monotherapy. Also, **Geiss *et al.* [28]** found that patients with TG values >150 mg/dL had significantly greater reductions in the concentrations of small, dense LDL particles compared to those with normal TG levels (49% vs. 19%, respectively). These results indicate that ezetimibe considerably reduces LDL cholesterol by inhibiting the reabsorption of biliary cholesterol.

Hence, the elevated triglycerides (TG) level is believed to be a risk factor for acute pancreatitis [29]. This study showed an increase level of TG in the COVID-19, even with treatment with ezetimibe that increases the risk of cardiovascular complications, thrombosis and even pancreatitis [30]. This finding can explain the importance of cholesterol in the cell membrane when a virus enters the host cell, and the efficiency of viral infection is significantly reduced when cholesterol deficiency is induced in the cell membrane. After a viral infection has already occurred, increased LDL cholesterol levels can interact with macrophages in atherosclerotic plaques or engage in some activation and increase the secretion of proinflammatory cytokines [31, 32]. Furthermore, low HDL cholesterol can cause dysregulation in the innate immune response and increase risk of COVID-19 infection [33].

This study could alert that Sars-CoV-2 negatively affects the ezetimibe efficiency on triglycerides, but it can also show individual noncompliance with high dietary fat intake. Further clinical studies on a more significant sample number are required to confirm this conclusion.

CONCLUSION

This stu dy recommends ezetimibe as an effective treatment of hyperlipidemia among diabetic patients, and it supports that COVID-19 might affect the ezetimibe reduction efficacy on triglycerides level on 30 days administration period and increase the risk of mortality among hyperlipidemia, COVID-19, atherosclerosis, and pancreatitis patients. Therefore, better hyperlipidemia management and monitoring are required among acutely ill COVID-19 patients to improve the prognosis of the infection.

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Author contribution: Authors contributed equally in the study.

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