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EFFECT OF ZINC SUPPLEMENTATION AS AN ADJUNCT TO ATORVASTATIN ON LIPID PROFILE IN HYPERLIPIDEMIC PATIENTS: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background: 'Hyperlipidemia' is a significant contributor to cardiovascular disease risk, and while medications such as statins are widely used, optimal lipid parameters are not always reached. Zinc is proposed to help with lipid metabolism. **Objective:** This study aimed to find out how zinc supplementation affects cholesterol levels in patients with high lipid levels already being treated with atorvastatin. **Materials and Method:** This study was a randomized double-blind placebo-controlled clinical trial conducted at Bangladesh Medical University (BMU), Dhaka, in 92 hyperlipidemic patients aged between 18–75 years and excluding diabetic hyperlipidemiapatients to avoid confounding effect. Subjects were randomized to receive zinc supplementation (30 mg/day) or placebo with atorvastatin for 8 weeks. The lipid profiles i.e. total cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and triglycerides, were obtained at baseline and after 8 weeks .The data was analyzed using SPSS version 25 considering *p*as 0.05). **Results:** The initial demographic and lipid parameters were similar across the groups ($p > 0.05$). At the end of 8 weeks, total cholesterol and triglycerides values were significantly lower in the intervention group compared to controls (p 0.05). Lipids parameters were significantly lower in both groups (*p*for all parameters< 0.001) after the treatment when analyzed within-group. Importantly, this shows that the intervention group had a significantly greater decrease in triglyceride levels compared to the control group. **Conclusion:** Adding zinc to atorvastatin therapy significantly lowers triglycerides in people with high cholesterol. Additional long-term studies are required to validate clinical advantages.

Keywords: Hyperlipidemia; Zinc supplementation; Atorvastatin; Lipid profile; Triglycerides; Randomized controlled trial.

INTRODUCTION

Hyperlipidemia is defined by elevated circulating levels of lipids, most importantly total cholesterol, LDL cholesterol and triglycerides. This condition is pivotal to the progression of cardiovascular diseases, which remain a major contributor to global mortality[1,2]. In countries like Bangladesh, the prevalence of hyperlipidemia is especially high, affecting nearly half of the population[3].

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Among lipid measures, elevated triglycerides are particularly important because they strongly predict coronary artery disease, especially in people with metabolic issues[4]. The first-line treatment is statins like atorvastatin, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and thus decrease cholesterol synthesis[5]. However, not all patients achieve optimal lipid control, and prolonged high-dose therapy can have adverse effects[6]; therefore, other therapies must be considered.

Zinc is a crucial micronutrient involved in multiple physiological processes, including antioxidant protection, insulin regulation, and lipid metabolism[7,8]. Evidence suggests that zinc supplementation can positively influence lipid balance by lowering total cholesterol, LDL, and triglyceride levels, while potentially increasing HDL concentrations [9,10]. This effect may result from reduced fat breakdown, lower free fatty acid release, and changes in liver lipid production[11]. Based on this, our study aims to determine whether zinc supplementation can enhance the lipid-lowering effect of atorvastatin, especially in reducing triglyceride levels in hyperlipidemic patients.

MATERIALS AND METHOD

This study was conducted as a randomized, double-blind, placebo-controlled clinical trial at BMU, Dhaka; March 2020 to July 2022. The study was approved by the Ethical Review Committee of BMU. All subjects gave written informed consent before participating. The study protocol was also registered at ClinicalTrials. gov (NCT05395143), and a total of 142 subjects were screened at baseline according to NCEP ATP III criteria. Following exclusion of those with diabetes to lessen metabolic confounding, 92 subjects with hyperlipidemia, aged between 18 and 75 years were enrolled. Participants were randomized in a 1:1 fashion to receive zinc (30 mg/day) plus atorvastatin or placebo plus atorvastatin for 8 weeks. Statistical analysis was performed in SPSS version 25, and $p<0.05$). Figure 1 displays the methodology of the study (Figure 1).

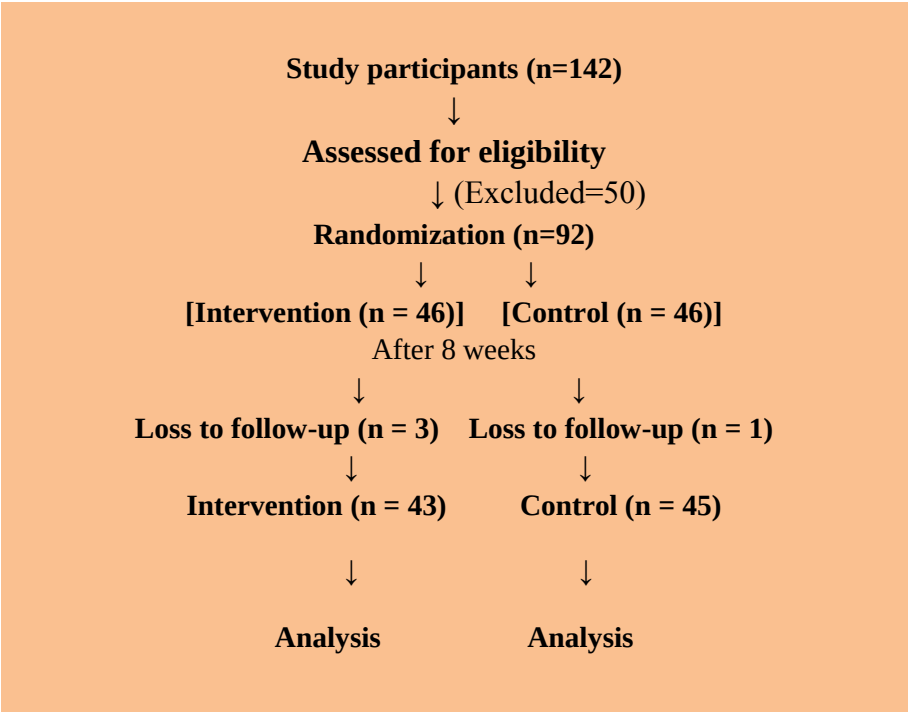

Figure 1: Methodology of the study.

RESULTS

The distribution of ages and sex was not significantly different between the intervention group and controls (p> 0.05), showing that both groups were comparable at baseline (Table 1).

Table 1: Comparison of demographic characteristics between two groups

Demographic	Intervention Group (n=46)	Control Group (n=46)	*p* value
Age (years)			
Mean ± SD	54.20 ± 11.27	54.61 ± 13.28	[u]0.115
Median (range)	53.5 (34-74)	54 (34-74)	
Sex			
Male	26 (56.5%)	27 (58.7%)	[c]0.833
Female	20 (43.5%)	19 (41.3%)	

[u= Mann Whitney U test; c= chi square test was done]; n=number of subjects in each group

Lipid parameters include total cholesterol, HDL, LDL and triglycerides at baseline in the intervention and control groups were comparable (p> 0.05), indicating successful randomization as summarized in Table 2. The differences were significant after 8 weeks of treatment. Greater total cholesterol reduction and HDL elevation in intervention than control (p<0.05) (Table 3).

Table 2: Comparison of baseline lipid profile between two groups

Parameter	Intervention Group (n=46)	Control Group (n=46)	p value
TC (mg/dl)			
Mean ± SD	258.43 ± 50.75	261.07 ± 34.43	[u]0.115
Median (range)	243 (190–414)	264 (186–338)	
HDL (mg/dl)			
Mean ± SD	30.37 ± 7.04	32.09 ± 6.21	[t]0.218
Median (range)	30 (19–49)	32 (20–45)	
LDL (mg/dl)			
Mean ± SD	158.72± 30.08	165.33± 29.67	[t]0.292
Median (range)	153.5 (110–221)	168.5(110–246)	
TG (mg/dl)			
Mean ± SD	256.80 ± 83.34	253.63 ± 74.22	[t]0.847
Median (range)	250.5 (109–458)	247 (106–390)	

[t= unpaired t test and u= Mann Whitney U test was done]; n=number of subjects in each group; TC=Total Cholesterol; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; TG=Triglyceride

Table 3: Comparison of lipid profile at 8 weeks between two groups

Parameter	Intervention Group (n=46)	Control Group (n=45)	*p* value
TC (mg/dl)			
Mean ± SD	158.50 ± 39.82	177.70 ± 37.75	[u]**0.015**
Median (range)	145.5 (100–270)	183 (106–245)	
HDL (mg/dl)			
Mean ± SD	39.48 ± 5.85	43.37 ± 7.99	[t]**0.011**
Median (range)	41 (28–50)	44 (28–65)	
LDL (mg/dl)			
Mean ± SD	96.86 ± 31.54	93.14 ± 32.93	[u]0.515
Median (range)	91.5 (46–197)	90 (43–180)	
TG (mg/dl)			
Mean ± SD	130.5 ± 44.86	190.84 ± 48.86	[t]**0.001**
Median (range)	127.0 (61–229)	177.0 (104–298)	

[t = unpaired t test andu= Mann Whitney U test was done.]; n=number of subjects in each group; TC=Total Cholesterol; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; TG=Triglyceride

Both groups showed significant improvement in their lipid profiles ($p < 0.001$), with the intervention group experiencing a greater reduction in triglyceride levels compared to the control group (Table 4).

Table 4: Within-group changes in lipid profile from baseline to 8 weeks

	Parameter	Mean difference ± SD	95% CI	p-value
Intervention Group	TC (mg/dl)	-101.31 ± 46.74	-115.53 to-87.10	**<[w]0.001**
	HDL (mg/dl)	8.75 ± 6.46	6.79 to 10.76	**<[w]0.001**
	LDL (mg/dl)	-62.93 ± 29.57	-71.92 to -53.94	**<[w]0.001**
	TG (mg/dl)	-125.45 ± 91.49	-153.27 to -97.63	**<[w]0.001**
Control Group	TC (mg/dl)	-85.09 ± 36.28	-96.25 to -73.92	**<[w]0.001**
	HDL (mg/dl)	11.02 ± 8.04	8.54 to 13.50	**<[w]0.001**
	LDL (mg/dl)	-69.18 ± 34.07	-79.67 to -58.70	**<[w]0.001**
	TG (mg/dl)	-65.58 ± 69.61	-87.00 to -44.15	**<[w]0.001**

[w= Wilcoxon signed rank test was done]; TC=Total Cholesterol; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; TG=Triglyceride

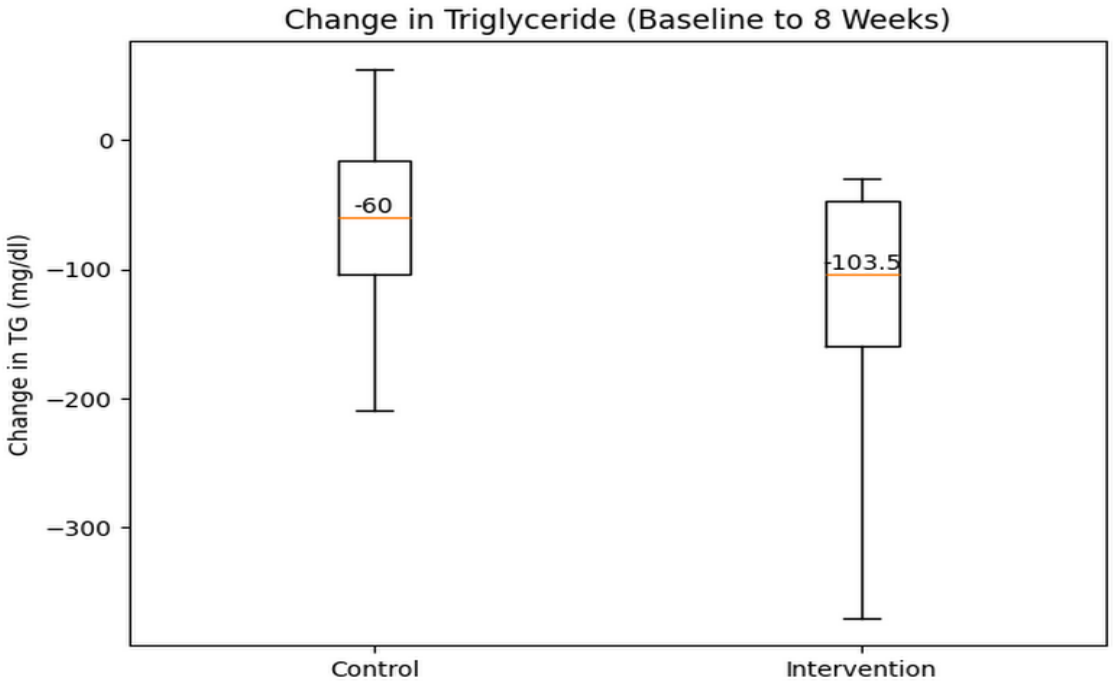

Figure 2: Boxplot showing change in triglyceride levels from baseline to 8 weeks in control and intervention groups.

The reduction in triglyceride levels was greater in the intervention group compared to the control group, as demonstrated by a lower median change and wider distribution (Figure 2).

DISCUSSION

The present randomized controlled trial demonstrated that baseline demographic characteristics and lipid parameters were comparable between the intervention and control groups (age: 54.20 ± 11.27 vs 54.61 ± 13.28 years; $p > 0.05$), indicating appropriate randomization and homogeneity of the study population. Similar baseline comparability has been reported in previous meta-analyses and clinical trials evaluating zinc supplementation[8] . After eight weeks of treatment, significant improvements in lipid parameters were observed. Total cholesterol levels were significantly lower in the intervention group compared to the control group (158.50 ± 39.82 vs 177.70 ± 37.75 mg/dl; $p = 0.015$), which is notably greater than the pooled reduction reported in meta-analyses (−10.92 mg/dl)[8] . This enhanced reduction may be attributed to the combined effect of zinc supplementation with atorvastatin, higher baseline lipid levels, and the inclusion of hyperlipidemic patients under controlled clinical conditions.

In contrast, HDL levels were significantly lower in the intervention group compared to the control group (39.48 ± 5.85 vs 43.37 ± 7.99 mg/dl; p = 0.011), differing from previous findings where zinc supplementation showed a modest increase in HDL (+2.12 mg/dl overall and +6.15 mg/dl in non-healthy individuals)"[8] . This discrepancy may be explained by variations in metabolic status, patient characteristics, and potential interaction with statin therapy. Regarding LDL cholesterol, no significant difference was observed between the groups (96.86 ± 31.54 vs 93.14 ± 32.93 mg/dl; p = 0.515), suggesting that zinc does not provide additional LDL-lowering benefit beyond statin therapy. Interestingly, this result differs from some earlier studies that reported only modest reductions in lipid parameters with zinc supplementation[8]. This variation may be due to differences in baseline lipid levels, patient characteristics, or study design.

Zinc supplementation effect on lipid profile

One of the most notable findings of this study was the greater reduction in triglyceride levels observed in the zinc-supplemented group. This suggests that zinc may enhance the triglyceride-lowering effect of atorvastatin. This magnitude of reduction is considerably higher than that reported in previous studies (−10.92 mg/dl)[8] , supporting a synergistic effect of zinc with atorvastatin.

The observed effects may be explained by several biological mechanisms. Zinc is known to reduce oxidative stress, influence lipid metabolism, and increase the activity of proteins such as metallothionein, all of which may contribute to improved lipid regulation [7,12]. Another possible explanation could be the underlying nutritional status of the participants. In populations where zinc deficiency is relatively common, supplementation may produce more noticeable metabolic benefits, particularly in individuals with high carbohydrate intake[13].

Overall, the findings of this study are in line with existing evidence supporting the role of zinc in improving lipid metabolism. However, the magnitude of improvement observed here appears to be greater than that reported in some previous studies.Despite these promising findings, several limitations should be considered. The relatively small sample size, short duration of the study, and lack of detailed dietary and lifestyle assessment may have influenced the results. Additionally, baseline zinc levels were not measured, which could have provided further insight into the response to supplementation.

CONCLUSION

In summary, adding zinc to standard atorvastatin therapy appears to provide additional benefits, particularly in reducing triglyceride levels in patients with hyperlipidemia. This combination may offer a simple and effective strategy for improving lipid control.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SOURCE OF FUNDING

Not applicable.

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