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EFFECT OF VOGLIBOSE ON LIPID PROFILE IN ALLOXAN-INDUCED DIABETIC RABBITS WITH TYPE-II DIABETES MELLITUS AND DYSLIPIDEMIA.

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ABSTRACT

Diabetes is an iceberg disease. There is an increase in the prevalence and incidence of Type-II DM globally. It is an incurable metabolic disorder. Diabetes mellitus always regarded primarily as a disturbance of carbohydrate metabolism. It is the last few decades that the disturbances in lipid metabolism has been described in association with Type II DM. Diabetes is a syndrome characterized by chronic hyperglycemia and disturbance of carbohydrate, lipid, and protein metabolism. There are several reports showing that hyperglycemia and hyperlipidemia are associated with increased cardiovascular risks.Alfaglucosidase inhibitors like acarbose,voglibose and miglitol inhibits the action of enzyme alfaglucosidase and reduces post prandial hyperglycemia on chronic use. As voglibose decreases post prandial hyperglycemia it spares beta cells of the pancrease and decreases the progress of the disease and also decreases insulin resistance.36 rabbits were induced diabetic by administering alloxan I.V. in the marginal ear vein of rabbits. Doses of alloxan required to induce diabetic according to kg body wt of the rabbits as reference table. Voglibose was found to be statistically significant than control group lipid profile at 8thweek of treatment (p<.01).Voglibose an alfaglucosidase inhibitor having beneficial effect on hyperlipidemia associated with hyperglycemia. Voglibose treatment tends to decrease the diabetes induce rise in lipid levels and decrease the risks of coronary heart diseases.These result suggests that,voglibose reduces progression of coronary heart disease along with impaired glucose tolerance stage and may be a candidate for an anti atherosclerotic drug for type II DM with dyslipidemia.

KEY WORDS: α-glucosidase inhibitors, voglibose, alloxan.

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INTRODUCTION

Diabetes is an iceberg disease. There is an increase in the prevalence and incidence of Type-IIDM globally. It is an incurable metabolic disorder. Diabetes mellitus always regarded primarily as a disturbance of carbohydrate metabolism. It is the last few decades that the disturbances in lipid metabolism have been described in association with Type II DM. Diabetes is a syndrome characterized by chronic hyperglycemia and disturbance of carbohydrate, lipid, and protein metabolism [1]. There are several reports showing that hyperglycemia and hyperlipidemia are associated with increased cardiovascular risks [2]. High levels of serum cholesterol, triglyceride, LDL, as well as low HDL are significantly associated with type II DM [3]. Lipid and Lipoprotein abnormalities are seen in an impaired glucose tolerance stage of DM. Fisher in 1903 emphasized about dyslipidemia in DM. Roben in 1935 concluded from his studies that lack of control of diabetes is an important factor for occurrence of hyperlipidemia. TG is the first lipid fraction to be effected in type-II DM and an independent risk factor for atherosclerosis. Normally, insulin inhibits lipoprotein lipase in adipose tissue. Insulin resistance causes unrestricted lipolysis leading to increased fatty acid flux in the liver and increase in higher triglyceride synthesis [4]. Effect on insulin on hepatic VLDL triglyceride synthesis depends on the duration of exposure. Short term exposure inhibits and long term (chronic) exposure increases VLDL triglyceride synthesis [4]. It is well known that insulin resistance and compensatory hyperinsulinemia are associated with increased TG and decreased HDL. Lipid profile are altered in early hyperglycemic stage of impaired glucose tolerance (IGT)[4]. HMG CoA reductase enzyme is the rate limiting enzyme in CH synthesis. Insulin increases its activity and thus regulates hepatic CH synthesis.

The main pharmacological intervention in IGT with dyslipidemia is oral hypoglycemia agents (OHA) or insulin with hypolipidemic drugs like statins, fibrates, bile acid sequestrants and niacin. The OHA with hypolipidemic action should be preferred in clinical practice. Alfa glucosidase inhibitors like acarbose, voglibose and miglitol inhibits the action of enzyme alfa glucosidase and reduces post prandial hyperglycemia on chronic use. As voglibose decreases post prandial hyperglycemia it spares beta cells of the pancreas and decreases the progress of the disease and also decreases insulin resistance. In animal models of TYPE-II DM alfa glucosidase inhibitors reduces TG in a dose dependent manner [5]. Alfa glucosidase inhibitors like acarbose and voglibose has shown to lower TG but its effect is inconsistent with most studies report a small but insignificant diminution [6][7].In some studies small reductions in the level of fasting TG and Total Cholesterol have been reported [8][9].Effects of alfa glucosidase on Total Cholesterol and HDL was controversial and appear to be minor or absent in dose range used in clinical practice[10][11]. Acarbose has been reported to lower LDL/HDL ratio by 26.7% [9].Alfa glucosidase inhibitors can also lower TG level [9].These favorable effects of alfa glucosidase inhibitors on lipid profile is due to glycemic control more than a direct action of the drug. This study was designed to compare the lipid profile of voglibose with diabetic control and with that of Metformin treated diabetic rabbits .

Objective

To evaluate the beneficial effect of voglibose (an alfa glucosidase inhibitor) on lipid profile in impaired glucose tolerance with dyslipidemia in alloxan induced diabetic rabbits.

MATERIALS AND METHODS

Thirty six healthy rabbits (New Zealand white) weighing between 1000 to 1800 gm were housed at the Central Animal House of IMS and Sum Hospital Bhubaneswar. The study protocol was duly approved by IAEC (SOA university, Bhubaneswar) July 2013.The animals were housed in stainless steel cages under standard laboratory condition (light period 8.00 am to 8.00pm,20-24^{0}C,relative

humidity 55%, green fodder and water available ad libitum). The animals received human care [13]. The rabbits were divided into three experimental groups (diabetic control, diabetic treated with Metformin 50mg/kg body wt and diabetic treated with voglibose 1mg/kg body wt) each containing 12 rabbits. All the 36 rabbits were induced diabetic by administering alloxan I.V. in the marginal ear vein of rabbits [14][17][20]. Doses of alloxan required to induce diabetic according to kg body wt of the rabbits as reference table .1.[14][19].Rabbits exhibiting fasting blood sugar more than 150 mg/dl after a stabilization period of seven days were considered as diabetic.[15].Rabbits were randomly divided in to three groups. Rabbits of group I was received 5 ml of normal saline as placebo daily and served as control. Rabbits of group II were treated with Metformin 50 mg/kg body wt and group III were treated with voglibose 1 mg/kg body wt. daily orally by gavage method for eight weeks. Blood samples were collected from marginal ear vein of all the rabbits every week throughout the eight weeks of experimental period[16][18].Plasma was obtained by centrifugation of samples[18].The plasma Total CH(TCH),Triglyceride(TG),High Density Lipoprotein(HDL) were evaluated by autoanalyzer (Cobas 400 plus),Central LAB,IMS and SUM Hospital, Bhubaneswar.The LDL levels was calculated by using Friedwald formula: LDL=Total Cholesterol-(HDL+TG/5).

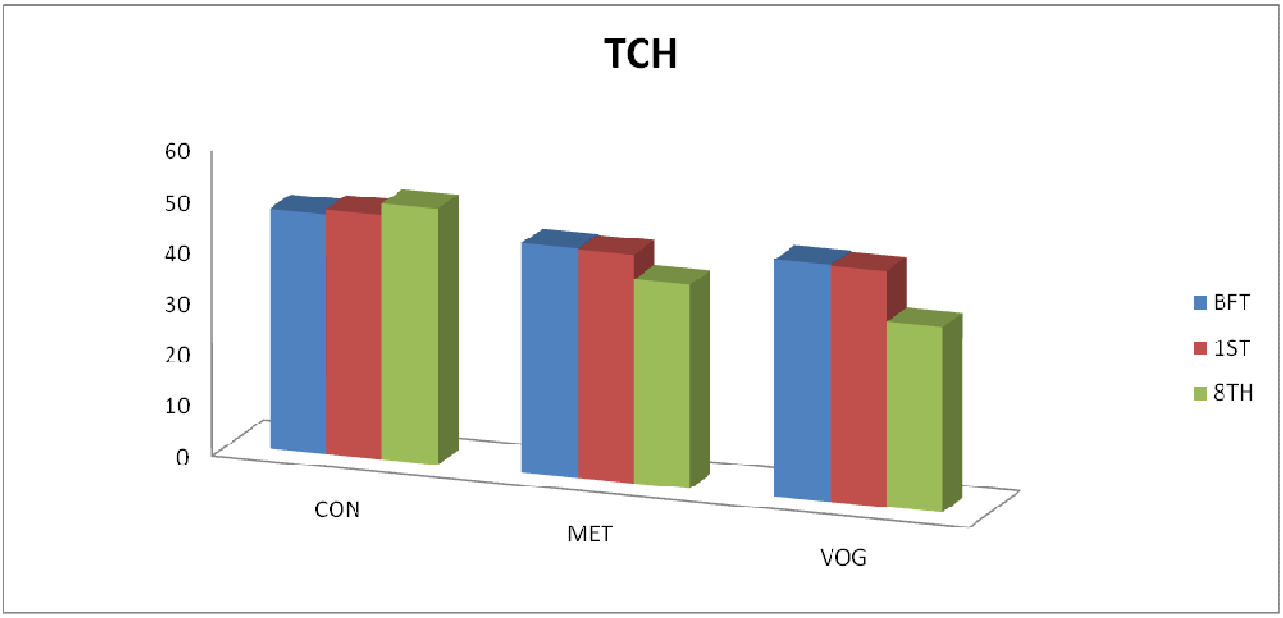
Statistical Analysis

Data pertaining to different parameters has been summarized, as mean± SD and analyzed using Analysis of Variance (ANOVA). Duncan multiple comparison test (DMRT) was used to test for differences among means for which ANOVA indicated a significant (p<.01) F ratio.

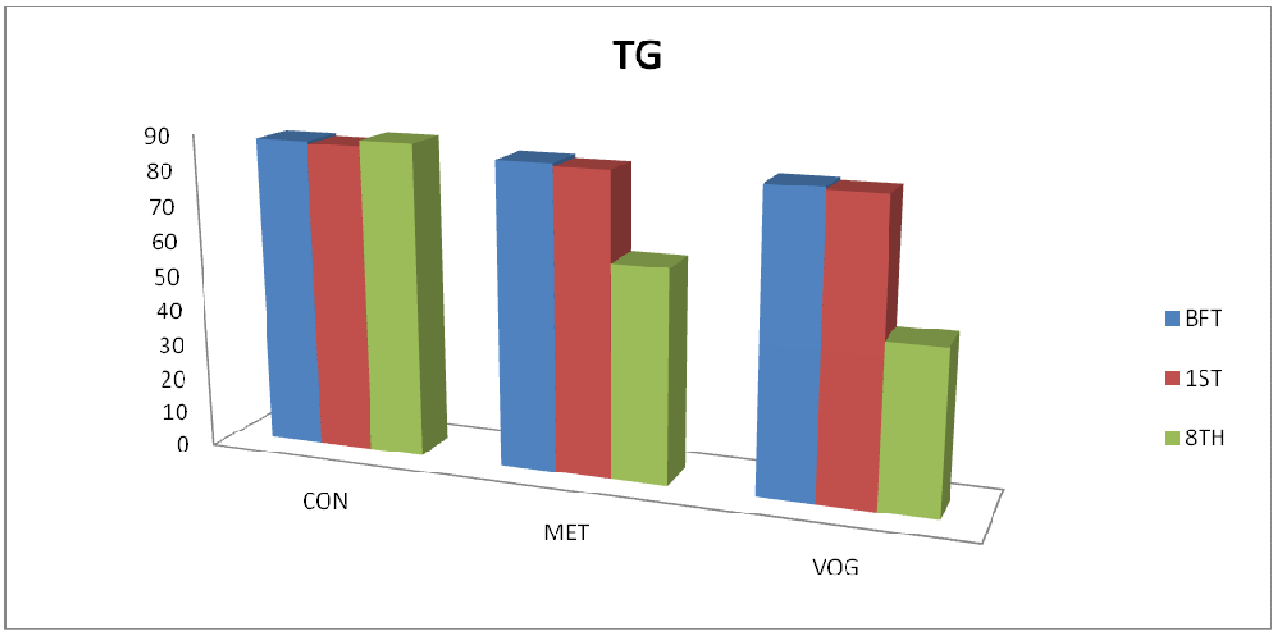
Table 1
DESCRIPTIVE STATISTICS OF VARIOUS CHARACTERS

TCH				TG			HDL			LDL		
Groups	**BFT**	**1ST**	**8TH**	**BFT**	**1ST**	**8TH**	**BFT**	**1ST**	**8TH**	**BFT**	**1ST**	**8TH**
Group-1	47.333^{a} ±0.67	48.167^{a} ±0.62	50.417^{a} ±0.78	88.000^{a} ±0.56	87.333^{a} ±1.06	89.083^{a} ±1.44	25.417^{a} ±0.88	24.333^{a} ±0.89	20.000^{b} ±0.40	4.250^{b} ±0.17	6.417^{b} ±0.51	12.583^{a} ±0.54
Group-2	45.167^{c} ±0.44	45.000^{b} ±1.01	40.083^{b} ±0.67	86.545^{a} ±2.17	85.000^{b} ±1.10	60.167^{b} ±0.79	23.000^{b} ±0.76	23.167^{b} ±0.58	24.750^{a} ±0.75	5.000^{b} ±0.21	4.750^{c} ±0.41	3.250^{b} ±0.37
Group-3	46.583^{b} ±0.48	46.417^{b} ±0.58	36.417^{c} ±0.67	84.000^{b} ±1.29	83.250^{b} ±1.19	45.750^{c} ±1.29	21.250^{b} ±0.72	21.417^{b} ±0.43	25.167^{a} ±0.84	8.500^{a} ±0.37	8.333^{a} ±0.30	2.083^{c} ±0.22

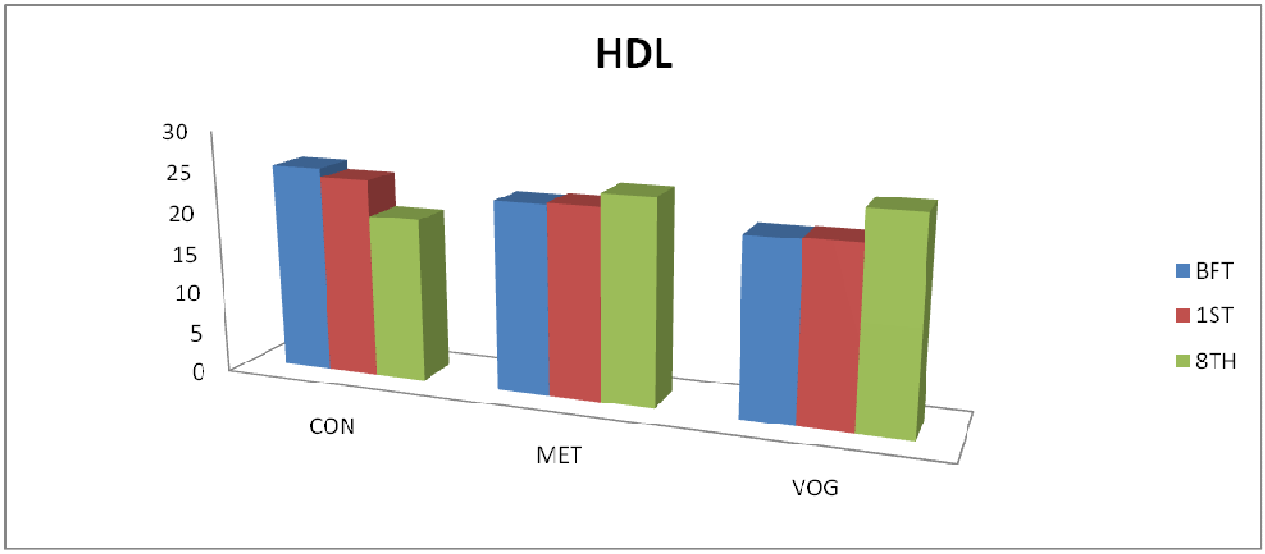
Mean with same superscripts within the column do not differ statistically



Graph 1
Effect of placebo, metformin and vog on TCH(mg/dl)before treatment,1st wk and on 8th

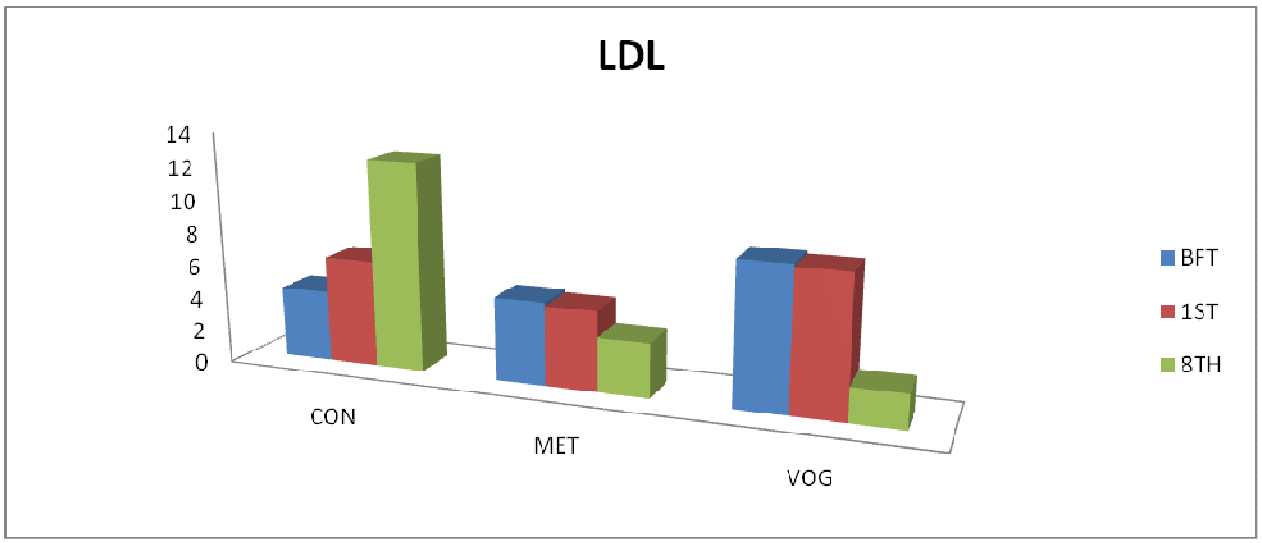


Graph2
Effect of placebo, Metformin and vog on TG (mg/dl)before treatment, 1st wk and on 8th wk.



Graph3

Effect of placebo, Metformin and vog on HDL (mg/dl))before treatment,1st wk and on 8th wk.



Graph4

Effect of placebo, Metformin and vog on LDL(mg/dl) on BFT,1st and 8th wk.

Table 2
ANOVA TABLE

ANOVA						
		Sum of Squares	**Df**	**Mean Square**	**F**	**Sig.**
TCHBFT	Between Groups	29.056	2	14.528	4.089	0.026
	Within Groups	117.250	33	3.553		
	Total	146.306	35			
TCH1ST	Between Groups	60.389	2	30.194	3.853	0.031
	Within Groups	258.583	33	7.836		
	Total	318.972	35			
TCH8TH	Between Groups	1264.889	2	632.444	102.938	0.000
	Within Groups	202.750	33	6.144		
	Total	1467.639	35			
TGBFT	Between Groups	98.244	2	49.122	1.998	0.152
	Within Groups	786.727	32	24.585		
	Total	884.971	34			
TG1ST	Between Groups	100.722	2	50.361	3.331	0.048
	Within Groups	498.917	33	15.119		
	Total	599.639	35			
TG8TH	Between Groups	11687.167	2	5843.583	332.003	0.000
	Within Groups	580.833	33	17.601		
	Total	12268.000	35			
HDLBFT	Between Groups	105.056	2	52.528	6.901	0.003
	Within Groups	251.167	33	7.611		
	Total	356.222	35			
HDL1ST	Between Groups	51.722	2	25.861	4.870	0.014
	Within Groups	175.250	33	5.311		
	Total	226.972	35			
HDL8TH	Between Groups	197.722	2	98.861	17.178	0.000
	Within Groups	189.917	33	5.755		
	Total	387.639	35			
LDLBFT	Between Groups	123.500	2	61.750	69.667	0.000
	Within Groups	29.250	33	0.886		
	Total	152.750	35			
LDL1ST	Between Groups	77.167	2	38.583	18.233	0.000
	Within Groups	69.833	33	2.116		
	Total	147.000	35			
LDL8TH	Between Groups	794.889	2	397.444	204.666	0.000
	Within Groups	64.083	33	1.942		
	Total	858.972	35			

RESULTS

The data pertaining to various characters has been presented in Table no.2 and the corresponding ANOVA table has been presented in Table no.3. Regarding total cholesterol, it is evident from the mean table that, before treatment of drugs the three

groups were found to be statistically significant and also after treatment with Metformin and voglibose the data was recorded after 1 week and 8th week respectively. That data were subjected to statistical analysis using Analysis of Variance and Duncans' Multiple Range Test. It was revealed from the analysis of data table that, total cholesterol was found to be significantly lower ($p<.01$) in both the weeks of treatment. The DMRT test reveals that, the total cholesterol in group III (voglibose treatment) was statistically different from group II as well as group I. The mean along with standard errors Triglycerides values of before treatment and after treatment of 1st week and 8th week as been presented in Table no..2. It is evident from the table that, the means of the three groups of before treatment period vise control (GR-I). Metformin (GR II) and voglibose (GR III) were found to statistically non-significant, where as the means of the other two periods of study were found to be statistically significant ($P<0.01$) indicating the effects of drugs in the 1st week as well as 8thweek.The DMRT test reveals that TG in group III (voglibose treatment) was statistically different from group II as well as group I. The mean along with standard errors of HDL values of before treatment and after treatment of 1st week and 8th week has been presented in Table no.2 It is revealed from the table that, the means of the three groups were found to be statistically significant ($p<.01$) in the three respective period of study. This infers that the HDL has significant contribution to the study. The DMRT test reveals that HDL in group III (voglibose treatment) was statistically not different from group II but different from group I. The mean along with standard errors of LDL values of before treatment and after treatment of 1st week and 8th week has been depicted in table no.2. It is revealed from the table that, the means of the three groups were found to be statistically significant ($P<0.01$) in the three respective period of study. This infers that the LDL has significant contribution to the study. The DMRT test reveals that LDL in group III (voglibose treatment) was statistically different from group II as well as group I.

DISCUSSION

Diabetes mellitus is one of the major metabolic disorders with abnormalities in carbohydrate, lipid and protein metabolism [1].Diabetic patients are more prone to atheromatous complication such as ischemic heart disease [21].In diabetic lipid disorders may be due to lack of insulin (type I DM) or defect in its action (type II DM).Also in type II it may be a component of metabolic syndrome [4]. Dyslipidemia often precedes onset of type II diabetes mellitus. United Kingdom Prospective Study (UKPDS) has shown that hypertriglyceridemia is already present at the time of diagnosis. Normally insulin inhibits hormone sensitive lipase in adipose tissue. Insulin resistance in impaired glucose tolerance stage causes unrestricted lipolysis leading to increased fatty acid flux in the liver and ends in higher hepatic triglyceride synthesis. Also the activity of endothelial insulin dependent lipoprotein lipase activity is less resulting in diminished triglyceride rich lipoproteins. This results in hypertriglycemia [4].It is the HDL2 sub fraction which is decreased in type II DM and ultimately leads to coronary heart disease [4][3].The risk of CHD in diabetics is two to four times greater than in non diabetics with raised Total CH. The raised CH reflects all lipoproteins and just not only LDL. Diabetic patients have greater glycation of LDL and are more prone to oxidation. It is well known that insulin resistance and compensatory hyperinsulinemia are associated with an atherogenic plasma lipid profile with increased TG and decrease HDL. In type II DM patients beta cells of the pancreas are still able to produce insulin. Among OHA only metformin, acarbose, voglibose and piaglitazone has significant effect on lipid profile[25].Metformin being an extensively used OHA decreases insulin resistance and may have a beneficial effect on lipid profile indirectly. Alfa glucosidase inhibitor being an inhibitor of carbohydrate absorption spares beta cells of the pancreas and decreases the progress of the impaired glucose tolerance stage to type II DM. The lipid lowering effects of alfa glucosidase inhibitor is due to its glycemic control more than a direct action of the drug[11][12].A review on the effect of oral

antihyperglycemic agents on serum lipids with type IIDM found beneficial effects of voglibose on TG [22]. However Meta analysis was not performed. According to another study voglibose not only has a direct hypoglycemic effect through decrease absorption of carbohydrate but also a hypoinsulinemic and hypo lipidemic effect via improved insulin sensitivity [23]. Voglibose also reduces the progression of intimal medial thickness (IMT) and may be a candidate for an anti atherosclerosis drug for type II DM patients [24]. The present study indicated that voglibose decreases TG, TCH, LDL and increases HDL levels in alloxan induced diabetic rabbits. Hypercholestrolemia and hyper triglyceridemia have been reported to occur in alloxan induced diabetic rabbits [26] and a significant increase in our experiment was accordance with those studies. It was found that voglibose treatment causes an increase in HDL and decrease in LDL levels that may protect diabetic patients from atheromatous disease. Voglibose also decreases Total CH and TG more significantly than Metformin. These strong anti hyperlipidemic activity of voglibose could be through its control of hyperglycemia.

CONCLUSION

Voglibose an alfa glucosidase inhibitor having a beneficial effect on hyperlipidemia associated with hyperglycemia. Voglibose treatment tends to decrease the diabetes induce, rise in lipid levels and decrease the risks of coronary heart diseases. These results suggest that voglibose reduces progression of coronary heart disease along with impaired glucose tolerance stage and may be a candidate for an antiatherosclerotic drug for type II DM with dyslipidemia. Consequently we conclude that voglibose has not only direct hypoglycemic effect by decreasing carbohydrate absorption but also have the hypolipidemic effect via increasing insulin sensitivity.

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