Original Research Article

Study the effect of metformin, voglibose alone and in combination on body mass index in non-diabetic obese Indian subjects- A hospital based study

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Abstract

Background: Early detection and therapy of the obese adolescent with a family history of type 2 diabetes may interrupt the cycle of weight gain and insulin resistance that leads to glucose intolerance in adulthood. **Materials & Methods:** The objective of our study was to observe the effect of metformin and voglibose on BMI, as it provides a simple and convenient anthropometric index for classification of obesity. 60 non diabetic obese subjects were selected on the basis of inclusion and exclusion criteria, and divided into three groups of 20 subjects each. The first group received metformin 500 mg BD, second group received voglibose 0.3 mg and the third group received a combination of metformin 500 mg and voglibose 0.3mg. For the comparison we applied paired and unpaired t test. Paired t test was applied for intra group comparison and unpaired t test was applied for inter group comparison. **Results:** After six months of treatment with Metformin 500 mg BD alone, Voglibose 0.3mg BD alone and Metformin 500 mg with Voglibose 0.3 mg BD in combination, all three groups showed statistically significant reduction in BMI values from baseline. When we compared results of metformin group with voglibose group there was no statistically significant difference. But when we compared results of metformin alone with metformin and voglibose combination and voglibose alone with metformin and voglibose combination, the combination group showed statistically significant reduction in BMI base line values. **Conclusion:** Therefore, it can be concluded that Metformin + Voglibose combination is very effective in reducing body weight, but further long term studies with large sample size are needed to assess the safety and efficacy of Metformin+ Voglibose combination in treatment of obesity in non-diabetic population.

Keywords: Obesity, Anti-obesity drugs, Metformin, Voglibose, BMI, Indians.

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Introduction

Throughout most of the human history, obesity has been viewed as a sign of health and prosperity. But now it has been termed as an epidemic and social burden, with increasing prevalence worldwide.[1] Obesity is also defined as an abnormal growth of the adipose tissue due to an enlargement of fat cell size (hypertrophic obesity) or an increase in fat cell number (hyper plastic obesity) or a combination of both or is defined "as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired to produce adverse health consequences and is associated with increased morbidity and mortality". [2-3]

According to the World Health Organization estimates, 1.6 billion adults (aged 15 years and above) were overweight and 400 million were obese in 2005 and the figures are predicted to rise to 2.3 billion overweight and over 700 million obese adults by 2015.[4] Surprisingly, obesity is often neglected, though it is associated with a serious, life-threatening complications like increasing risk of cardio-metabolic illness.[5,6] According to National Family Health Survey (NFHS)-3 prevalence of overweight or obesity in India is 12.1% in males and 16% in females, and in Maharashtra it is 15.9% in Males & 18.1% in females.[7]

Body mass index (BMI) provides a simple and convenient anthropometric index for classification of obesity. The World Health Organization (WHO), the US Preventive Services Task Force and the International Obesity Task Force define overweight "as a BMI between 25.0 to 29.9 kg/m^2 and obesity as a BMI 30.0 kg/m2".[8, 9]

Table 1: Body Mass Index Classification[10]

Parameter	WHO Criteria	Indian Criteria
Normal	18.5-24.9 Kg/m^2	18.0-22.9 Kg/m^2
Over- weight	25.0-29.9 Kg/m^2	23.0-24.9 Kg/m^2
Obese	> 30 Kg/m^2	> 25 Kg/m^2

Therapeutic approach for a non-diabetic obese patient starts with comprehensive lifestyle management i.e. very low calorie diet, physical activity and behavior modification and if needed anti-obesity drugs. Bariatric surgery is suggested for those who are at greater risk of obesity. There are many examples of drugs used historically for weight loss that have been removed owing to significant side effects, like sibutramine & rimonabant. FDA approved orlistat as an anti-obesity drug in 1999. It reduces intestinal fat absorption by inhibiting pancreatic lipase. Orlistat is notorious for its gastrointestinal side effects which include steatorrhea. Though they are the most frequently reported adverse effect of the drug, but they tend to decrease with time. FDA approved few new anti obesity as adjunctive therapy for chronic weight management: lorcaserin approved in 2012; and phentermine/topiramate extended-release formulation also approved in 2012.[11]

Metformin, the biguanide, is most widely used for the treatment of type 2 Diabetes Mellitus (T2DM). In diabetic patients, it suppresses endogenous glucose production and may also act as an insulin sensitizer. It also helps diabetic patients to lose weight or at least keep their weight stable.[12,13] The weight loss effects have been attributed by lipolytic and anorectic effects; also suppressing glucose production by liver.[13] Metformin activates AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats**.** Recent studies suggests that the effect of metformin on AMP-activated protein kinase (AMPK) dependent lipolysis in adipocytes may lead to lower plasma levels of fatty acids and improve adipose tissue function.[14]

Voglibose is the recent alpha glycosidase inhibitor. Though voglibose has similar efficacy to acarbose, it has much weaker effect on alpha-amylase when given in a pharmacological dose. Hence, it has better tolerability.[15,16] It has shown strong anti-obesity and anti-diabetic activities and has been found to significantly reduce postprandial blood glucose concentration and weight in some animals.[17] It delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia. Administration of voglibose, increases the secretion of glucagon-like peptide (GLP)-1. GLP 1 is an incretin type of hormone, which causes early satiety. Also, it decreases plasma dipeptidyl peptidase-4 (DPP-4) activity.[18] Study by Xiaoling Cai et al shows weight reduction with Alpha Glucosidase inhibitors on Type 2 Diabetes Patients.[19] An animal study done by Hyun Ju Do shows weight reduction in non diabetic mice with voglibose.[20]

Some studies have revealed that there is significant weight reduction in non diabetic subjects with metformin.[21] Also some studies have revealed weight reduction with voglibse in T2DM patients. In a study done on non-diabetic animals with obesity, there was weight reduction with voglibose, considering the findings of above studies; we have undertaken this study to see the effect of voglibose on weight in non diabetic subjects.[22]

At present, no clinical studies have been reported of metformin and voglibose in head to head comparison for non-diabetic obesity. Therefore, the present study was planned to compare and evaluate the effect of metformin and voglibose on BMI in non-diabetics obese individuals.

Material and Methods

Present study was carried out in the Department of General Medicine in collaboration with the Department of Pharmacology at MGM Medical College and hospital, Aurangabad between September 2013 to

February 2014. The subjects enrolled for this study were selected after screening for HbA1c according to the inclusion and exclusion criteria. Written informed consent was obtained from each patient. Age group of 20-60 years of either sex, obese or overweight determined by a BMI of> 25 kg/m^2 and willing to participate were included in the study. Patients with HbA1c <5.7% or diabetic patients, pregnant and lactating women, subjects allergic to drugs & sensitive to drugs, subjects concurrently taking other medication which is known to affect the obesity and patients with gastrointestinal disorders like inflammatory bowel disease, deranged liver, kidney and thyroid function test were excluded. Institutional Ethics Committee permission and study participant's consent was taken.

Study Drugs: Tablet metformin (500 mg) and tab voglibose 0.3mg

Study Groups

Group A: Voglibose
Group B: Metformin
Group C: Combination (Voglibose+ Metformin)

Volunteers were assessed at baseline for HbA1c for screening of non-diabetic subjects. Healthy non-diabetic obese subjects were enrolled and assessed at baseline and at end of study for body mass index. After general physical examination of study participants' baseline investigations like HbA1c, FBG and PPBG were estimated. The statistical evaluation was done by Student's t-test with the help of SPSS (Statistical Package for Social Service version 19) value less than p<0.05 was taken as significant.

Results

Sixty non-diabetic obese subjects (n=60) volunteers completed the study. Evaluation was done at baseline and after 6 month. All the groups were matched in baseline characteristics i.e. age, sex and weight. The BMI decreased significantly when compared to baseline value in all three groups. For the result and calculation we applied student t test, both paired and unpaired. Intra-group comparison of voglibose and metformin at baseline and after six months was found to be significant but a highly significant result was found in combination group (voglibose+ metformin) [Table 2/Fig. 1].

Metformin and Voglibose

Inter group comparison between group metformin and voglibose showed no statistical difference in BMI (0.1±2.37) when compared by using unpaired t test and was found to be statistically non-significant with a p value > 0.05 [Table 3].

Metformin alone and in combination group (voglibose and metformin)

Inter group comparison between metformin group and combination group showed statistical difference in BMI (1.4 ± 1.97) when compared by using unpaired t test and was found to be statistically significant with a p value < 0.05 [Table 3].

Voglibose alone and in combination (Voglibose and Metformin)

Inter group comparison between Voglibose group and combination group showed statistical difference in BMI (1.5± 2.28) when compared by using unpaired t–test and was found to be statistically significant with a p value < 0.05 [Table 3].

Adverse Effects

Most common adverse drug reaction reported in all the three groups were related to gastrointestinal disturbances. In the 2 patients (10%) in metformin group had shown adverse drug reactions. In Voglibose group had 4 patients (20%) and in combination group 5 patients (25%). In Metformin group, adverse drug reaction seen was bloating of abdomen in 2 patients (10%). With voglibose group, gastrointestinal adverse drug reaction seen were nausea in 1 patient (5%), flatulence in 2 patients (10%), and diarrhea in 1 patient (5%). In combination group, adverse drug reaction seen were, nausea in 1 patient (5%), bloating of abdomen in 2 patients (10%), diarrhoea in 1 patient (5%) and abdominal pain in 1 patient (5%) [Table 4].

Table 2: Changes of BMI in study groups [metformin and voglibose alone and in combination before and after therapy]

Group	BMI			P value
	Mean value ± SD			
	Before therapy	After Therapy	Mean difference	
A	28.55± 2.19	27.84±2.08	1.26±1.07	0.00
B	28.84±2.73	27.41±2.83	1.44±0.68	0.00
C	28.94±2.005	25.93±1.86	3.00±1.03	0.00

Note: P< 0.05**: Statistically significant , P <0.001***: Statistically highly significant
Group A: Metformin, Group B: Voglibose, Group C: Combination (voglibose+ metformin)

Figure 1: Showing comparison of baseline values of BMI before and after therapy in three groups

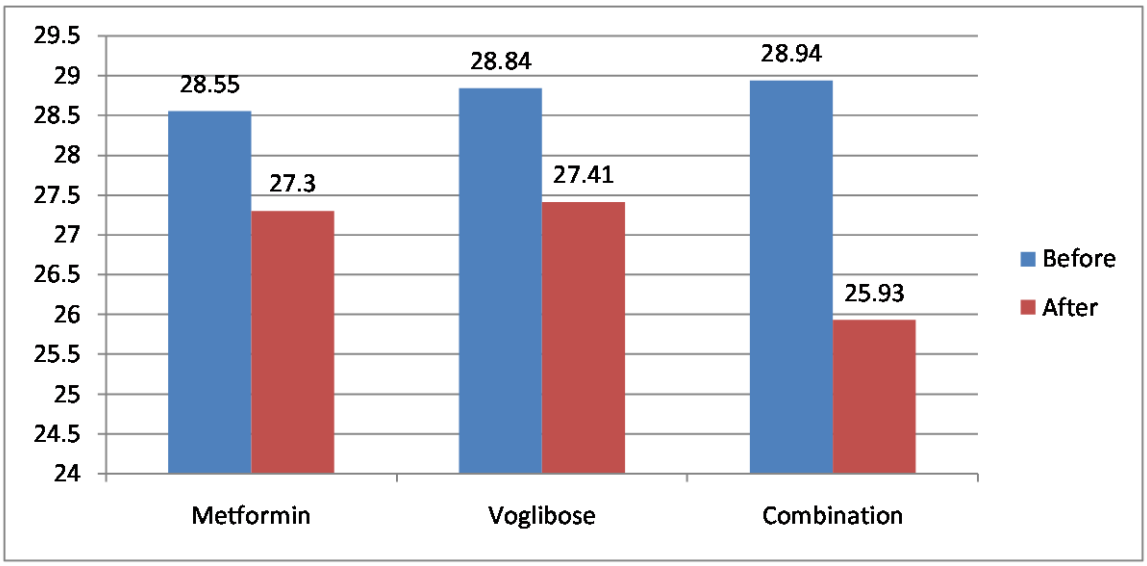

Table 3: Unpaired t- test for comparison of BMI

Groups	Mean Difference ± SD	P value
A Vs. B	0.1±2.37	0.88
A Vs. C	1.4 ± 1.97	0.035**
B Vs. C	1.5 ± 2.28	0.048**

(Note: P> 0.05*: Not Statistically significant, P< 0.05**: Statistically significant)

Table 4: Comparison of ADR's in treatment with metformin, voglibose and combination groups

ADR's	Group A	Group B	Group C
Nausea	-	5%	5%
Abdominal bloating	10%	-	10%
Flatulence	-	10%	-
Diarrhea	-	5%	5%
Abdominal Pain	-	-	5%
Total	10%	20%	25%

Discussion

Both the study drugs are widely used in the treatment of diabetic patients. Some studies have revealed effectiveness of metformin in weight reduction, [21] not only in diabetics but, also in non-diabetic patients also. Similarly, administration of voglibose in diabetic patients has shown weight reduction. Another study involving use of voglibose in non diabetic obese animals showed weight reduction.[18] Due to above considerations, this study was undertaken. Moreover, at present no clinical studies have been reported on metformin and voglibose in head to head comparison for non-diabetic obesity. Therefore, the present study was planned.

When we applied paired t-test for metfomin group, it showed significant reduction in BMI after six months of treatment as compared to baseline values. These findings are similar to a study conducted by C. Seifarth *et al* on non diabetic obese (n= 154) patients with a body mass index ≥27 kg/m^2 showed mean weight loss in the metformin treated group of 5.8±7.0 kg (5.6±6.5%) over 6 months.[21] Probable mechanisms of metformin for weight reduction is its lipolytic and anorectic action.22 Other possible mechanism is its actions it increases GLP 1. Also weight loss through AMP-activated protein kinase (AMPK) lead to lower plasma fatty acid level and improve adipose tissue function.[23, 24]

In TODY Study to manage T2DM in youth showed gastrointestinal disturbances were most common adverse event (41%) in metformin treatment group.[16] In our study though drug was well tolerated as there was only one type of ADR reported i.e. the bloating of abdomen in 2 patients.[25]

Similarly, there was significant reduction in BMI values from baseline in Voglibose group (0.3 mg BD) in our group after six months of treatment. (1.44 ±0.68) P < 0.00. Study by Xiaoling Cai *et al* [19] showed weight reduction from baseline was significantly more with voglibose treatment (n= 216) compared with placebo (n= 210) in Asians (WMD, 21.00 kg;). Also another study done by Hyun Ju Do, exhibited weight reduction in non diabetic obese mice with voglibose.[26]The probable weight reduction mechanism is increase in the secretion of glucagon-like peptide (GLP)-1, causing early satiety. Also it delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia.[18] In a Study by Iwamoto Y *et al* in Japanese patient with T2DM, the most common drug related ADRs with voglibose group were gastrointestinal disorders with an incidence of 32.8%167 in our study ADRs with voglibose group were, Nausea in 1 patient, flatulence in 2 patients, and diarrhoea in 1 patient.[27]

In our study we found significant weight reduction with combination group which is more as compared to other groups; this is because of additive effect of combination of Metformin with Voglibose. In this group, ADRs were seen i.e. nausea in 1 patient, bloating of abdomen in 2 patients, diarrhoea in 1 patient and abdominal pain in 1 patient.

Conclusion

After six months of treatment with Metformin 500mg BD alone, Voglibose 0.3mg BD alone, and Metformin 500mg with Voglibose 0.3mg BD in combination, all three groups showed statistically significant reduction in BMI values from baseline. When we compared results of metformin group with voglibose group there was no statistically significant difference. But when we compared results of metformin alone with metformin and voglibose combination and voglibose alone with metformin and voglibose combination, the combination group showed statistically significant reduction in BMI base line values.

There was only a single ADR associated with Metformin group i.e. bloatting of abdomen in 2 patients. In Voglibose group, there was Nausea in 1 patient, flatulence in 2 patients and diarrhea in 1 patient. While in the combination group, ADRs were nausea in 1 patient, bloting of abdomen in 2 patients, diarrhea in 1 patient and abdominal pain in 1 patient.

Although ADR's associated with the combination of Voglibose and Metformin are comparatively more but they are not serious and subside with time, therefore it can be concluded that, the use of Metformin and Voglibose in combination has greater efficacy in reducing the BMI in non- diabetic obese subjects than drugs when given alone. Therefore, it can be concluded that Metformin + Voglibose combination is very effective in reducing body weight, but further long term studies with large sample size are needed to assess the safety and efficacy of Metformin+ Voglibose combination in treatment of obesity in non-diabetic population

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