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Comparative Efficacy and Safety of Low- and High-dose Metformin, Voglibose, and Its Combination in Obese Subjects

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Abstract

Objective: To evaluate efficacy and safety of low-dose and high-dose metformin, voglibose, and its fixed dose combination in obese subjects.

Materials and Methods: ***An observational study among subjects between 20 and 40 years of age with body mass index (BMI) >25 kg/m^2, HbA1C <5.7%, and serum insulin level >25 pg/ml was conducted. Low dose consisted of Group I (n=20): metformin (500 mg BD); Group II (n=20): voglibose (0.2 mg BD); and Group III (n=20): FDC (metformin 500 mg + voglibose 0.2 mg BD), while the high dose consisted of Group IV (n=20): metformin (1000 mg BD); Group V (n=20): voglibose (0.3 mg BD); and Group VI (n=20): FDC (metformin 1000 mg + voglibose 0.3 mg BD). BMI and serum insulin levels were checked at baseline and after 6 months of therapy.***

Results: ***A total of 120 subjects were enrolled (69 men and 51 women). Baseline BMI (kg/m^2) of 29.70 (±1.59), 29.70 (±1.59), 29.70 (±1.59), 29.10 (±1.41), 29.80 (±1.64), and 29.00 (±1.52) in Group I–VI reduced to 28.45 (±1.76), 27.85 (±2.00), 27.55 (±1.57), 27.75 (±1.55), 28.65 (±1.66), and 26.50 (±1.63), respectively (p<0.05***

for all). Serum insulin level (mIU/L) at baseline in six groups significantly reduced from 33.95 (±4.81), 33.45 (±3.83), 33.50 (±4.57), 33.9 (±2.77), 34.4 (±4.36), and 34.2 (±3.96) to 30.055 (±4.01), 30.65 (±3.70), 26.65 (±4.14), 26.65 (±2.73), 30.35 (±3.83), and 22.25 (±3.78), respectively (p<0.05 for all). High dose had pronounced effect on BMI (p=0.0002) and serum insulin (p=0.001) compared with low dose (BMI p=0.25; serum insulin level p=0.005). Incidence of adverse event in low- and high-dose therapy was 8.3% and 16.7%, respectively. No serious adverse event was reported.

Conclusion: Metformin and voglibose monotherapy and combination therapy in low dose and high dose cause significant reduction in BMI and serum insulin levels. Combination therapy has more pronounced effect compared with monotherapy.

Keywords: ***BMI, metformin, serum insulin, voglibose***

Introduction

Obesity is one of the major public health problems, affecting every region of the globe. Worldwide, around 0.5 billion people are classified as obese and about 1.5 billion more as overweight.[1] According to a cross-sectional survey in five Indian cities, overall prevalence of obesity and overweight is 6.8% and 33.5%, respectively.[2] Obesity increases the likelihood of diseases such as cardiac disease, type 2 diabetes, obstructive sleep apnoea, certain types of cancer, and osteoarthritis. Excessive food intake, lack of physical activity, genetic susceptibility, endocrine disorders, medications, or psychiatric illness is some of the causes known to contribute to the development of obesity.[3] Pharmacotherapy may be considered for the prevention and management of obesity if lifestyle measures and exercise fail. Currently, only few weight-loss medicines with favourable side effect profile are available.[4] Metformin is a well-established, time-tested, and cost-effective anti-hyperglycaemic drug,[5,6] which has been shown to reduce weight in type 2 diabetes patients.[7] Obesity in non-diabetic patients is also linked to insulin resistance, hence improving insulin sensitivity may help in weight reduction with metformin therapy although the exact mechanism is not known.[8] In a randomized-controlled trial, metformin has shown to significantly reduce weight in non-diabetic patients.[9] In a recent review on anti-obesity drugs, metformin is not mentioned.[10] In another review, it is listed as a weight-reducing drug, but the scarcity of studies is underlined.[11] Voglibose, a alpha glycosidase inhibitor (AGI), has anti-obesity and anti-diabetic activities and shown to significantly reduce weight in animal studies.[12] A study by Cai et al. showed weight reduction with AGI in type 2 diabetes patients.[13] There has been no head-to-head comparison of metformin and voglibose in non-diabetic obesity.

Objectives of the Study

The objective of study was to evaluate efficacy and safety of low-dose and high-dose monotherapy with metformin, voglibose, and their fixed dose combination in obese subjects.

Materials and Methods

In this observational study, subjects of both gender between 20 and 40 years of age with BMI >25 kg/m^2, HbA1C <5.7%, and serum insulin level >25 pg/ml were enrolled. The patients with HbA1c >5.7%, pregnant and lactating women, patients with known allergy to study drugs, and those concurrently taking other medications having known to affect obesity were not enrolled in the current study. Smoker, alcoholic, tobacco chewer, or those having hypothyroidism, gastrointestinal disorders such as inflammatory bowel disease, gastric deranged liver function test, or kidney function test were also excluded from the study. The study was conducted per ICH GCP guidelines at MGM Medical College & Hospital, Aurangabad, in collaboration with Department of Medicine after taking IEC approval.

A total of 120 subjects were enrolled and divided into low-dose arm and high-dose arm (n=60 each).

The subjects in low-dose arm (Category A) received following medications:

- Group I (*n*=20): metformin (500 mg BD)
- Group II (*n*=20): voglibose (0.2 mg BD)
- Group III (*n*=20): FDC (metformin 500 mg + voglibose 0.2 mg BD)

Similarly, the subjects in high-dose arm (Category B) received following medications:

- Group IV (*n*=20): metformin (1000 mg BD)
- Group V (*n*=20): voglibose (0.3 mg BD)
- Group VI (*n*=20): FDC (metformin 1000 mg + voglibose 0.3 mg BD)

All subjects were assessed at baseline and at the end of 6 months for change in BMI and serum insulin levels.

Statistical Analysis

Paired '*t*' test was used to assess difference between before and after treatment values within each group, while ANOVA test was used to measure difference among the groups. Unpaired 't' test was used to assess difference between the groups. *P-Value*<0.05 was considered as statistically significant. The analysis was done using SPSS version 17.

Results

A total of 120 subjects were enrolled in the study. The male-to-female ratio in low-dose and high-dose therapy was 58.3%:41.7% and 56.7%:43.3%, respectively (Table 1). The distribution of patients according to the age group and gender in all six groups is given in Table 1. Low-dose metformin and voglibose monotherapy and their fixed dose combination significantly reduced BMI after treatment. Similarly high-dose metformin and voglibose monotherapy and their fixed dose combination significantly reduced BMI after 6 months of treatment (Table 2). Six-month treatment with low-dose metformin monotherapy, low-dose voglibose monotherapy, and their fixed-dose combination significantly reduced serum insulin after treatment. Similarly high-dose metformin and voglibose monotherapy and their fixed-dose combination significantly reduced serum insulin levels after 6 months of treatment (Table 3). High-dose therapy showed significantly pronounced effect on BMI and serum insulin (Table 4). Fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg resulted in significantly higher BMI reduction compared with FDC of metformin 500 mg

Table 1 | Demographic data

Age group (years)	Gender	Group I *N* (%)	Group II *N* (%)	Group III *N* (%)	Group IV *N* (%)	Group V *N* (%)	Group VI *N* (%)
20–30 years	**M**	6 (30%)	7 (35%)	8 (40%)	7 (35%)	9 (45%)	6 (30%)
	F	7 (35%)	8 (40%)	4 (20%)	6 (30%)	3 (15%)	9 (45%)
31–40 years	**M**	5 (25%)	4 (20%)	5 (25%)	4 (20%)	5 (25%)	3 (15%)
	F	2 (10%)	1 (5%)	3 (15%)	3 (15%)	3 (15%)	2 (10%)
Total	**120**	20 (100%)	20 (100%)	20 (100%)	20 (100%)	20 (100%)	20(100%)

Table 2 | BMI (before and after therapy)

Category	Group	BMI Mean (±SD) kg/m^2			*p*-Value
		Before therapy	After therapy	Mean difference	
Category A	**I**	29.70 (±1.59)	28.45 (±1.76)	1.25 (±1.07)	0.000**
	II	29.70 (±1.59)	27.85 (±2.00)	1.05 (±1.47)	0.005*
	III	29.70 (±1.59)	27.55 (±1.57)	1.65 (±0.59)	0.000**
Category B	**IV**	29.10 (±1.41)	27.75 (±1.55)	1.35 (±0.49)	0.000**
	V	29.80 (±1.64)	28.65 (±1.66)	1.15 (±0.37)	0.000**
	VI	29.00 (±1.52)	26.50 (±1.63)	2.50 (±0.83)	0.000**

***p*<0.001 paired 't' test.

Table 3 | Serum insulin (before and after therapy)

Category	Group	Serum insulin Mean (±SD) mIU/L			*p*-Value
		Before therapy	After therapy	Mean difference	
Category A	I	33.95(±4.81)	30.055(±4.01)	3.90 (±1.21)	0.000**
	II	33.45 (±3.83)	30.65 (±3.70)	2.80 (±1.36)	0.000**
	III	33.50 (±4.57)	26.65 (±4.14)	6.85 (±1.46)	0.000**
Category B	IV	33.9 (±2.77)	26.65 (±2.73)	7.25 (±2.53)	0.000**
	V	34.4 (±4.36)	30.35 (±3.83)	4.05 (±1.19)	0.000**
	VI	34.2 (±3.96)	22.25 (±3.78)	11.95(±2.21)	0.000**

***p*<0.001 paired 't' test.

Table 4 | Intergroup comparison of BMI and serum insulin level (ANOVA)

	BMI		Serum insulin level	
	F	*p*-Value	*F*	*p*-Value
Category A	1.413	0.25	05.93	0.005
Category B	9.764	0.0002	26.9	0.001

Table 5 | Comparison of change in BMI (high dose vs. low dose)

Group comparison	Difference Mean (±SD)	*t* value	*p*-Value
I vs. IV	0.7 (±1.6)	1.49	0.14
II vs. V	0.9 (±1.86)	1.45	0.16
III vs. VI	1.1 (±3.97)	2.13	0.039

Table 6 | Comparison of change in serum insulin level (high dose vs. low dose)

Group comparison	Difference Mean (±SD)	*t* value	*p*-Value
I vs. IV	3.5 (±3.44)	3.13	0.003
II vs. V	0.2 (±3.78)	0.251	0.80
III vs. VI	4.3 (±3.97)	3.51	0.001

plus voglibose 0.2 mg (Table 5). Metformin 1000 mg BD resulted in significantly higher reduction in serum insulin levels compared with metformin 500 mg BD. Fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg resulted in significantly better reduction in serum insulin compared with FDC of metformin 500 mg plus voglibose 0.2 mg (Table 6).

The overall incidence of adverse event in low-dose and high-dose therapy was 8.3% and 16.7%, respectively. Fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg resulted in adverse events in 25% of patients. All adverse events were related to gastrointestinal tract. Nausea was the most common adverse event followed by vomiting, abdominal pain, and diarrhoea (Table 7). No subject reported serious adverse event.

Discussion

Obesity, a public health problem, is affecting every region of the world[14] including India.[15] India is facing the double burden of undernutrition and overnutrition today. Undernutrition is more prevalent in rural areas, whereas overweight and obesity are

Table 7 | Adverse effects

	Category A			Category B		
	Group I	Group II	Group III	Group IV	Group V	Group VI
Nausea	1 (5%)	1 (5%)	1 (5%)	2 (10%)	1 (5%)	2 (10%)
Vomiting	–	–	1 (5%)	1 (5%)	1 (5%)	1 (5%)
Abdominal pain	–	–	1 (5%)	–	–	1 (5%)
Diarrhoea	–	–	–	–	–	1 (5%)
	1 (5%)	1 (5%)	3 (15%)	3 (15%)	2 (10%)	5 (25%)

more prevalent in urban areas. Overweight and obesity are associated with an increased burden of non-communicable diseases, premature mortality, and social and psychological adverse effects. Anti-obesity drugs are used as adjunct because of their limited long-term success.[16]

Metformin is the first-line treatment for type II diabetes particularly in overweight and obese people. It is also widely used for non-diabetic obesity aiding weight loss. The weight loss caused by metformin is attributed to the suppression of glucose production by liver, anorectic effect, lipolytic effects, and prolongation of GLP-1 action causing early satiety. With appropriate use, metformin causes few adverse effects mainly gastrointestinal upset.[17]

Voglibose delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycaemia and hyperinsulinaemia and has anti-obesity and anti-diabetic activities.[18]

Overall, the literature comparing metformin and voglibose is scanty, and no clinical studies have compared metformin versus voglibose in head-to-head clinical trial among non-diabetic obese subjects. Therefore, the present study was planned to evaluate and compare the effect of metformin and voglibose on BMI and serum insulin in non-diabetic obese subjects.

Fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg twice daily resulted in overall mean BMI loss of 2.50 ± 0.83 ($p< 0.001$) after 6 months of treatment compared with baseline. Our findings are similar to a study conducted by Seifarth et al. on non-diabetic obese ($n= 154$) subjects with a body mass index ≥27 kg/m^2, where the mean weight loss in metformin-treated group was 5.8±7.0 kg over 6 months.[19] Cai et al. have shown significantly more weight reduction with voglibose treatment ($n= 216$) compared with placebo ($n= 210$) in Asian type 2 diabetics.[12] Weight reduction with voglibose in diabetic patients has also been shown by Negishi et al.[20]

Similarly, fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg twice daily, resulted in significant reduction (11.95 ± 2.21mIU/L) in mean serum insulin after 6 months of treatment ($p< 0.001$). Study done by Negishi et al.[20] and Shinozaki et al.[21] showed significant reduction in serum insulin levels with voglibose. Similarly Tankova et al. showed reduction in serum insulin levels with metformin.[22]

Five patients (25%) receiving fixed-dose combination of metformin 1000 mg plus voglibose 0.3 mg twice daily complained about gastrointestinal side effects. In a Japanese study conducted by Iwamoto et al., gastrointestinal disorders were reported by 32.8%, and these adverse events were the most common drug-related adverse events with voglibose in the study.[23] In TODY study, gastrointestinal disturbances were most common adverse event (41%) among metformin-treated group.[24]

To our knowledge, this is the first study assessing efficacy and safety of metformin and voglibose for weight loss in outpatient setting. The strong link between weight gain and insulin resistance is undisputed today with compelling evidence that insulin resistance being stated as a major contributor to abdominal obesity. Verdict is yet to be out if insulin resistance is the cause or consequence of obesity.[25]

Improving insulin resistance helps in weight loss by the multiple mechanisms: Improved insulin sensitivity results in less postprandial hypoglycaemia episodes due to sluggish post prandialinsulin secretion and delayed insulin peak. Less postprandial hypoglycaemic events result in less carbohydrate cravings, which lead to less compensatory carbohydrate intake.[26] Moreover, metformin-induced insulin-stimulated glucose disposal in the skeletal muscle, reduction in hepatic glucose output, inhibition of gluconeogenesis, and reduction in intestinal glucose absorption,[27] reduction in appetite and anorectic component,[28] decrease in leptin levels, and rise in GLP-1 levels[29] may contribute to the weight loss.

Hyperinsulinaemia can cause body weight gain, while AGIs are known to reduce insulin levels. Reduction in insulin level and rise in the secretion of glucagon-like peptide (GLP)-1, delay in the digestion and absorption of carbohydrates might be responsible for the reduction in BMI observed in this study.[30]

The results of this study show that metformin

and voglibose represent a valuable option for the management of obese non-diabetic people. Open-label study design and small sample size are the limitations of our study. Studies with large sample size are needed to confirm results of our study.

Conclusion

Metformin and voglibose alone and in combination in low dose and high dose have significant effect on reducing BMI and serum insulin levels. Fixed-dose combination of metformin and voglibose has more pronounced effect on BMI and serum insulin levels.

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