ORIGINAL RESEARCH

To investigate the impact of metformin, voglibose as individual interventions, and their combined effect on body mass index (BMI) in non-diabetic individuals with obesity

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ABSTRACT

Aim: To investigate the impact of met for min, voglibose as individual interventions, and their combined effect on body mass index (BMI) in non-diabetic individuals with obesity.

Material and Methods: The research included individuals of both sexes, aged between 20 and 58 years, who were classified as obese or overweight based on a body mass index (BMI) more than 25 kg/m2. Participants were required to express their willingness to take part in the study. metformin (500 mg) and voglibose 0.3mg tab were used. All the 90 patients were divided into 3 groups. Group A: Voglibose, Group B: Metformin and Group C: Combination (Voglibose+ Metformin).

Results: The study observed a substantial difference in the comparison of voglibose and metformin within the same group at the beginning and after six months. However, the combination group (voglibose + metformin) showed an even more significant outcome. The intergroup comparison between the metformin and voglibose groups revealed no significant difference in BMI (0.57±0.04) when analysed using an unpaired t-test. The results were judged to be statistically non-significant, with a p-value greater than 0.05. A statistical analysis was conducted to evaluate the BMI between the Voglibose group and the combination group. The results of an unpaired t-test revealed a statistically significant difference in BMI (mean ± standard deviation: 1.86±0.78) between the two groups, with a p-value of less than 0.05 .The intergroup comparison between the metformin group and the combination group revealed a statistically significant difference in BMI (2.43±0.98) when analysed using an unpaired t-test. The p-value was determined to be less than 0.05, indicating statistical significance.

Conclusion: We concluded that the Metformin 500mg BD alone, Voglibose 0.3mg BD alone, and a combination of Metformin 500mg with Voglibose 0.3mg BD, exhibited a statistically significant decrease in BMI values compared to their initial baseline measurements. Upon comparing the outcomes of the met for min group with the voglibose group, no statistically significant difference was seen.

Keywords: Metformin, Voglibose, BMI, Non-diabetic, Obesity

Introduction

Throughout the majority of human history, obesity has been seen as an indicator of good health and socioeconomic well-being. However, it is now classified as an epidemic and a significant societal burden, with a rising frequency on a global scale [1]. Obesity can be characterised as an atypical expansion of adipose tissue resulting from either an enlargement in the size of fat cells (known as hypertrophic obesity), an increase in the number of fat cells (known

as hyperplastic obesity), or a combination of both. Alternatively, it can be described as a state of abnormal or excessive accumulation of fat in adipose tissue, to the extent that it may impair health and lead to negative health outcomes, including heightened morbidity and mortality [2-3]. Based on estimations provided by the World Health Organisation, it was determined that in 2005, around 1.6 billion individuals aged 15 years and above were classified as overweight, while 400 million were classified as obese. Projections indicate that these numbers are expected to increase to 2.3 billion overweight adults and over 700 million obese adults by the year 2015[4]. Remarkably, obesity is often disregarded despite its correlation with severe and sometimes fatal repercussions, such as an elevated susceptibility to cardio-metabolic diseases [5,6]. Based on data from the National Family Health Survey (NFHS)-3, the prevalence of overweight or obesity in India is reported to be 12.1% among men and 16% among females. In the state of Maharashtra, the corresponding figures are 15.9% among males and 18.1% among females [7]. The body mass index (BMI) offers a straightforward and easy anthropometric measure for categorising obesity. The definition of overweight and obesity is provided by reputable organisations such as the World Health Organisation (WHO), the US Preventive Services Task Force, and the International Obesity Task Force. According to these organisations, overweight is characterised by a body mass index (BMI) ranging from 25.0 to 29.9 kg/m2, while obesity is defined as a BMI of 30.0 kg/m2 [8, 9]. The therapeutic strategy for an obese patient without diabetes involves implementing a thorough lifestyle management plan. This plan often includes a very low calorie diet, engaging in physical activity, and making behavioural modifications. In some cases, the use of anti-obesity medications may also be considered. Bariatric surgery is recommended for those who are at an elevated risk of developing obesity. Numerous instances can be found in history when medications used for the purpose of weight reduction have been withdrawn due to the manifestation of notable adverse effects, such as sibutramine and rimonabant. The Food and Drug Administration (FDA) granted approval for orlistat as a pharmaceutical intervention for the treatment of obesity in the year 1999. The inhibition of pancreatic lipase leads to a reduction in the absorption of fat in the intestines. Orlistat is well-known for its gastrointestinal adverse effects, notably include the occurrence of steatorrhea. Although they are the most often reported side effect of the medication, it is observed that their occurrence tends to diminish with time. The FDA has granted approval for a limited number of novel anti-obesity medications to be used as supplemental treatment for chronic weight control. Specifically, lorcaserin was authorised in 2012, and a formulation of phentermine/topiramate in extended-release form was also approved in the same year [10,11]. Metformin, a medication classified as a biguanide, is extensively used for the management of type 2 Diabetes Mellitus (T2DM). In individuals diagnosed with diabetes, it has been seen to inhibit the generation of glucose inside the body and maybe enhance the sensitivity of insulin. Additionally, it has been seen that weight loss or weight maintenance may be beneficial for those with diabetes [12,13]. The observed effects of weight loss have been ascribed to the lipolytic and anorectic properties, as well as the inhibition of hepatic glucose synthesis [13]. Metformin induces the activation of AMP-activated protein kinase (AMPK), a hepatic enzyme that assumes a crucial function in insulin signalling, overall energy homeostasis, and the regulation of glucose and lipid metabolism. According to recent research, it has been suggested that the impact of metformin on the activation of AMP-activated protein kinase (AMPK) in adipocytes may result in a reduction in circulating fatty acid levels and an enhancement in the functionality of adipose tissue[14]. Voglibose is a novel alpha glycosidase inhibitor that has emerged in recent times. While voglibose has comparable effectiveness to acarbose, its impact on alpha-amylase is far less pronounced when administered at a medicinal dosage. Therefore, it exhibits improved tolerability [15,16]. The compound has shown potent anti-obesity and anti-diabetic effects, leading to a significant decrease in postprandial blood glucose levels and weight in several animal models [17]. The process of carbohydrate digestion and absorption is delayed, resulting in the inhibition of postprandial hyperglycemia. The administration of voglibose has been shown to enhance the production of glucagon-like peptide (GLP)-1. GLP-1 is classified as an incretin hormone that elicits a sensation of early satiety. Additionally, it has been seen to result in a reduction in plasma dipeptidyl peptidase-4 (DPP-4) activity [18]. The research conducted by Xiaoling Cai and colleagues demonstrates the efficacy of Alpha Glucosidase inhibitors in promoting weight loss among individuals diagnosed with Type 2 Diabetes [19]. A research conducted by Hyun Ju Do investigated the effects of voglibose on weight loss in non-diabetic mice [20]. Several trials have shown a significant decrease in body weight among individuals without diabetes who were administered metformin[21]. Additionally, some studies have shown that voglibose may lead to weight loss in people with type 2 diabetes mellitus (T2DM). A research was conducted on non-diabetic animals exhibiting obesity to investigate the impact of voglibose on weight reduction. Based on the aforementioned results, the present investigation was performed to examine the effects of voglibose on weight in non-diabetic individuals [22]. Currently, there is a lack of clinical research that have reported on the direct comparison of metformin and voglibose for the treatment of non-diabetic obesity.

Consequently, the current research was designed to assess and compare the impact of metformin and voglibose on body mass index (BMI) in non-diabetic patients who are obese.

Material and Methods

The present investigation was conducted inside the Department of Pharmacology. The participants included in this research were chosen based on their HbA1c levels, after a thorough assessment of the inclusion and exclusion criteria. Each patient provided written informed consent. The research included individuals of both sexes, aged between 20 and 58 years, who were classified as obese or overweight based on a body mass index (BMI) more than 25 kg/m2. Participants were required to express their willingness to take part in the study. Exclusion criteria encompassed individuals meeting the following conditions: having a HbA1c level below 5.7% or being diagnosed with diabetes, being pregnant or lactating, displaying allergies or sensitivities to drugs, currently taking medications known to impact obesity, and having gastrointestinal disorders such as inflammatory bowel disease, impaired liver or kidney function, or abnormal thyroid function test results. The researchers obtained clearance from the Institutional Ethics Committee and obtained consent from the study participants.

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

Study Groups

Group A: Voglibose

Group B: Metformin

Group C: Combination (Voglibose+ Metformin) : The participants were evaluated at the beginning of the study to measure their HbA1c levels in order to screen for those without diabetes. The research included individuals who were obese but did not have diabetes. These participants were evaluated at the beginning of the trial and again at the conclusion in order to measure their body mass index. Following a comprehensive physical examination, baseline investigations including as HbA1c, FBG, and PPBG were conducted on the research subjects. The statistical analysis was conducted using the Student's t-test, using the SPSS software (version 25.0) for data processing. A significance level of $p<0.05$ was used to determine statistical significance.

Results

A total of 90 obese individuals without diabetes (n=90) participated as volunteers in the research. The evaluation was conducted during the first assessment and again after a period of 6 months. All the groups were carefully selected to ensure that they had similar baseline characteristics, including age, sex, and weight. The body mass index (BMI) exhibited a substantial reduction in all three groups when compared to their respective baseline values. To get the results and do the necessary calculations, we used the student t-test, using both paired and unpaired analyses. The study observed a substantial difference in the comparison of voglibose and metformin within the same group at the beginning and after six months. However, the combination group (voglibose + metformin) showed an even more significant outcome, as shown in Table 1.

Table 1: Changes of BMI in study groups [metformin and voglibose alone and in combination before and after therapy

	BMI			
Group	**Before therapy**	**After Therapy**	Mean difference	**P value**
A	28.77±1.58	27.98±1.36	0.79±0.11	0.001
B	29.01±2.55	27.65±1.58	1.36±0.26	0.001
C	29.33±2.06	26.11±1.77	3.22±0.89	0.001

Metformin and Voglibose : The intergroup comparison between the metformin and voglibose groups revealed no significant difference in BMI (0.57±0.04) when analysed using an unpaired t-test. The results were judged to be statistically non-significant, with a p-value greater than 0.05 [Table 3].

Metformin alone and in combination group (voglibose and metformin) : The intergroup comparison between the metformin group and the combination group revealed a statistically significant difference in BMI (2.43±0.98) when analysed using an unpaired t-test. The p-value was determined to be less than 0.05, indicating statistical significance [Table 3].

Voglibose alone and in combination (Voglibose and Metformin) : A statistical analysis was conducted to evaluate the BMI between the Voglibose group and the combination group. The results of an unpaired t-test revealed a statistically significant difference in BMI (mean ± standard deviation: 1.86±0.78) between the two groups, with a p-value of less than 0.05 [Table 3].

Table 2: Unpaired t- test for comparison of BMI

Groups	Mean Difference± SD	Pvalue
AVs. B	0.57±0.04	0.71
AVs. C	2.43±0.98	0.04
BVs. C	1.86±0.78	0.03

Adverse Effects : The gastrointestinal problems were the most often reported adverse medication reactions across all three groups. Out of the four patients (13.33%) in the metformin group, adverse medication responses were seen. The Voglibose group consisted of 8 patients, accounting for 26.67% of the total sample, whereas the combined group had 10 patients, representing 33.33% of the whole sample. In the cohort receiving Metformin, a total of four patients (13.33%) had the adverse medication response of abdominal bloating. In the voglibose group, gastrointestinal adverse medication reactions were seen, including nausea in 2 patients (6.67%), flatulence in 4 patients (13.33%), and diarrhoea in 2 patients (6.67%). In the combined group, the observed adverse medication reactions were nausea in two patients (6.67%), stomach bloating in four patients (13.33%), diarrhoea in two patients (6.67%), and abdominal discomfort in two patients (6.67%). Table 3 presents the relevant data.

Table 3: Comparison of ADR's in treatment with metformin, voglibose and combination groups

ADR's	Group A	Group B	Group C
Nausea	-	2(6.67%)	2(6.67%)
Abdominalbloating	4(13.33%)	-	4(13.33%)
Flatulence	-	4(13.33%)	-
Diarrhea	-	2(6.67%)	2(6.67%)
AbdominalPain	-	-	2(6.67%)
Total	4(13.3%)	8(26.67%)	10(33.33%)

Discussion

Both study medicines are often used in the management of individuals with diabetes. Several studies have shown the efficacy of metformin in promoting weight loss, not only in individuals with diabetes but also in non-diabetic people [21]. In a similar vein, the administration of voglibose to individuals with diabetes has shown a decrease in body weight. A further investigation examining the administration of voglibose in non-diabetic obese animals demonstrated a decrease in body weight [18]. This research was conducted in response to the aforementioned factors. Furthermore, it is important to note that there is currently a lack of clinical research that have investigated the direct comparison between metformin and voglibose in the context of non-diabetic obesity. Consequently, the current investigation was designed. When we conducted paired t-test for metfomin group, it indicated substantial decrease in BMI after six months of therapy as compared to baseline values. The results obtained in this study align with the findings of a previous investigation done by C. Seifarth et al. The aforementioned study focused on a cohort of non-diabetic obese individuals (n=154) with a body mass index equal to or more than 27 kg/m2. The research revealed that the metformin-treated group saw an average weight reduction of 5.8±7.0 kg (equivalent to 5.6±6.5% of their initial body weight) over a period of six months [21]. The potential mechanisms through which metformin may contribute to weight loss include its lipolytic and anorectic effects [22]. Another potential mechanism is the augmentation of GLP-1 activity. Furthermore, it has been shown that weight loss achieved by the activation of AMP-activated protein kinase (AMPK) is associated with a reduction in plasma fatty acid levels and an enhancement in adipose tissue functionality [23, 24]. The TODY Study, which aimed to address the management of type 2 diabetes mellitus (T2DM) in young individuals, revealed that gastrointestinal disturbances were the prevailing adverse event (41%) seen in the metformin therapy group [16]. In our trial, the medicine demonstrated a high level of tolerability, with just one adverse drug reaction (ADR) seen. Specifically, this ADR manifested as abdominal bloating and was recorded in two individuals [25]. In a similar vein, our study observed a noteworthy decrease in baseline BMI values among the Voglibose group (0.3 mg BD) following a six-month period of therapy. The statistical analysis yielded a significant result, with a p-value of less than 0.001, indicating that the observ ed effect is highly unlikely to have occurred by chance. The estimated value of 1.36 The research conducted by Cai et al. [19] shown that the decrease in weight from the first measurement was much greater among individuals of Asian descent who received voglibose therapy (n= 216) in comparison to those who received a placebo (n= 210) (weighted mean difference, 21.00 kg;). Another research conducted by Hyun Ju Do demonstrated the efficacy of voglibose in inducing weight loss in obese mice without diabetes [26].The likely mechanism for weight loss is an elevation in the release of glucagon-like peptide (GLP)-1, which leads to a sensation of early satiety. Additionally, it has been shown that this substance has the ability to impede postprandial hyperglycemia by delaying the digestion and absorption of carbs [18]. A study conducted by Iwamoto Y et al examined the prevalence of drug-

related adverse drug reactions (ADRs) in Japanese patients with type 2 diabetes mellitus (T2DM). The results indicated that gastrointestinal illnesses were the most often seen ADRs in the voglibose group, with an incidence rate of 32.8%. In our trial, adverse drug reactions (ADRs) seen in the voglibose group included nausea in two patients, flatulence in four patients, and diarrhoea in two patients [27]. In our research, we observed a significant decrease in weight among participants in the combination group, surpassing the reductions seen in the other groups. This outcome may be attributed to the synergistic impact resulting from the combined administration of Metformin and Voglibose. Within this cohort, adverse drug reactions (ADRs) were seen. Specifically, two patients experienced nausea, four patients reported bloating of the belly, two patients exhibited symptoms of diarrhoea, and two patients complained of stomach discomfort.

Conclusion

We concluded that the Metformin 500mg BD alone, Voglibose 0.3mg BD alone, and a combination of Metformin 500mg with Voglibose 0.3mg BD, exhibited a statistically significant decrease in BMI values compared to their initial baseline measurements. Upon comparing the outcomes of the metformin group with the voglibose group, no statistically significant difference was seen.

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