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Significance of Orlistat in management of dyslipidemia, systolic blood pressure and body mass index

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Abstract. – OBJECTIVE: The current study intends to find out the efficacy of Orlistat in the management of hyperlipidemia, Systolic Blood Pressure (SBP) and Body Mass Index (BMI).

MATERIALS AND METHODS: This retrospective study has evaluated the lipid profiles of the patients, who have been using metformin therapy for Type 2 diabetes. The study has obtained data regarding the parameters like triglyceride, Total cholesterol (TC), LDL cholesterol, HDL cholesterol and LDL/HDL ratio, systolic blood pressure and Body Mass Index (BMI). Random distribution of patients was done into placebo and Orlistat groups. The placebo group received only metformin, and patients in the Orlistat group received Orlistat along with metformin. After 24 weeks, the follow-up study was done, and statistical analysis was conducted.

RESULTS: The study found that the Orlistat group has significant improvement ($p<0.05$) more improvement in LDL cholesterol, HDL cholesterol, Total cholesterol, LDL/HDL Ratio and Triglycerides, while BMI and systolic blood pressure did not show a significant difference between placebo and Orlistat group.

CONCLUSIONS: This study has concluded that Orlistat can be used for significant improvement in lipid profile. The study also found that Orlistat may not have a significant effect on reducing BMI and blood pressure without adequate lifestyle modification.

Key Words:
Obesity, Dyslipidemia, Hypertension, Orlistat, Metformin.

Introduction

According to World Health Organization (WHO), obesity is defined as the accumulation of excessive fat which poses risk to health and is characterized by BMI>30. It negatively affects several end organs, including the liver and cardiovascular organ. Obesity has been positively correlated with an increase in lifestyle-associated factors. Evidence shows that lifestyle-related factors like hypertension and low level of physical activity are highly associated with obesity[1].

Over the years, the global prevalence of obesity has reached an alarming height and accounts for nearly 5% of all disabilities and approximately 7% of all deaths in a worldwide scenario. Numerous studies show that increased adiposity is positively associated with End Stage Renal Disease (ESRD), different cardiovascular problems, and Type 2 diabetes mellitus. Demographic impressions show a distinct correlation between increased blood pressure and eventual damage of the terminal organs[2,3]. According to research conducted in 2013, it is estimated that approximately 50% of the global population has obesity, which leads to several other complicated conditions. After 1980, the overall burden of obesity reached more than 45% among children and more than 25% among adults. It is estimated that almost 2 billion people worldwide are obese or overweight[4,5].

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A higher number of adipocytes triggers the sympathetic pathway and the Renin-Angiotensin-Aldosterone System (RAAS), leading to volume overload. The autonomic nervous system and the baroreceptors are stimulated, and consequently, peripheral resistance, stroke volume, and cardiac output are increased. In addition, there is an afterload elevation, causing the blood pressure to rise and left ventricular hypertrophy. This structural remodeling causes neointimal hyperplasia and smooth muscle hyperplasia, creating mechanical stress on the inner walls of the arteries. As a consequence, the carotid intima-media thickness is developed[6,7]. Figure 1 depicts the complex pathological relationship between Obesity, hyperlipidemia and cardiovascular features[7].

A different pathophysiological pathway shows that the increased levels of amino acids in obese people are responsible for activating the intracellular rapamycin complex 1 (mTOR C1)/S6 kinase (S6-K) the mechanism inside the liver[8]. The amino acids inside the liver regulate the metabolism and mobilization of the lipid from the liver to the adipose tissue *via* a neuronal mechanism. The mTOR C1/S6 K mechanism mediates the process of lipid metabolism. This process can decrease triglyceride (TG) hydrolysis by reducing the fatty-lipoprotein lipase expression. Consequently, the serum TG is raised. This mechanism is specifically active in the case of an over-supply of nutrients and can vividly explain the phenomenon of hypertriglyceridemia caused by obesity[9]. Figure 2 depicts the interconnection between obesity and increased levels of TG due to increased amino acids.

A BMI >30 kg/m^2 indicates the need for pharmacological intervention and management of obesity. Physical activity and dietary adjustments can be used as adjunctive to achieve a distinct and desired outcome. Currently, four categories of drugs are commonly used in managing obesity and related hypertriglyceridemia: Benzphetamine, Phendimetrazine, Phentermine, and Diethylpropion[9,10].

Significant bodyweight reduction can be very effective in managing obesity-related hypertriglyceridemia and hypertension. For example, Orlistat is effective for people with obesity-related hypertension. On the other hand, Lorcaserin has less efficacy in lowering body weight but has satisfactory patient compliance[11]. In cases of dyslipidemia, Orlistat was found to have a clinically significant effect on lipid profile parameters. However, there are debates about the pharmacological effect of Orlistat on lipid profile parameters, blood pressure, and the management of obesity. Some works mentioned that Orlistat might contribute to weight loss, while some mentioned that Orlistat could efficiently control lipid profile but have no effect on weight loss[8-11].

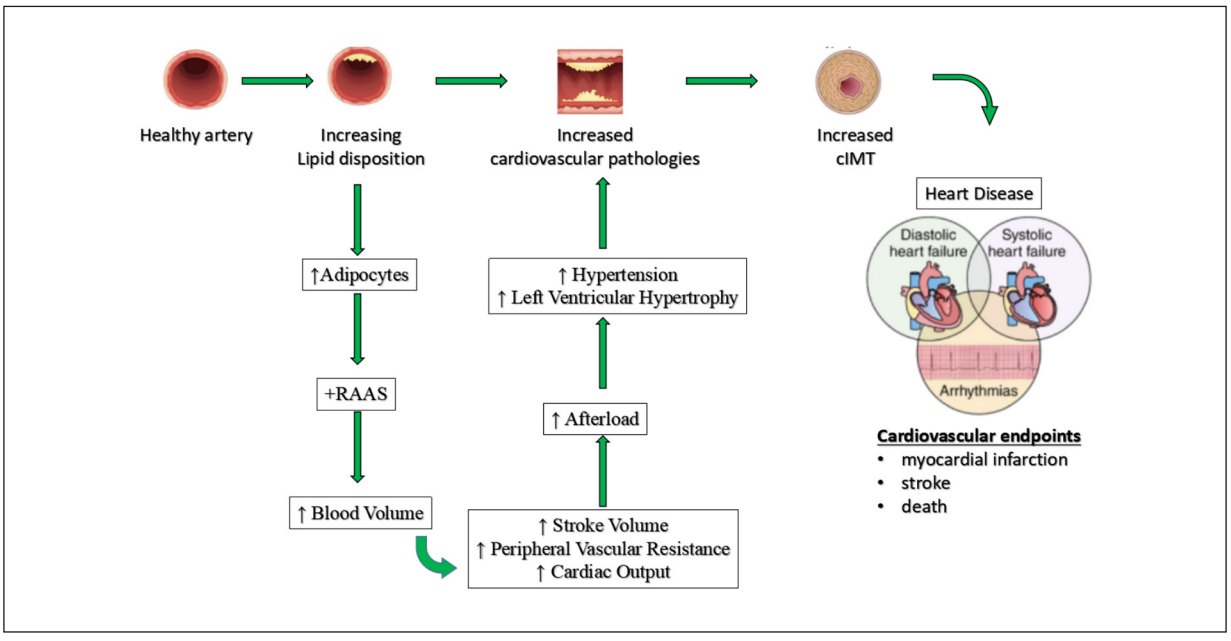

Figure 1. Pathological relationship between obesity, hyperlipidaemia and cardiovascular features. RAAS, Renin-Angiotensin-Aldosterone System; cIMT, Carotid intima-media thickness.

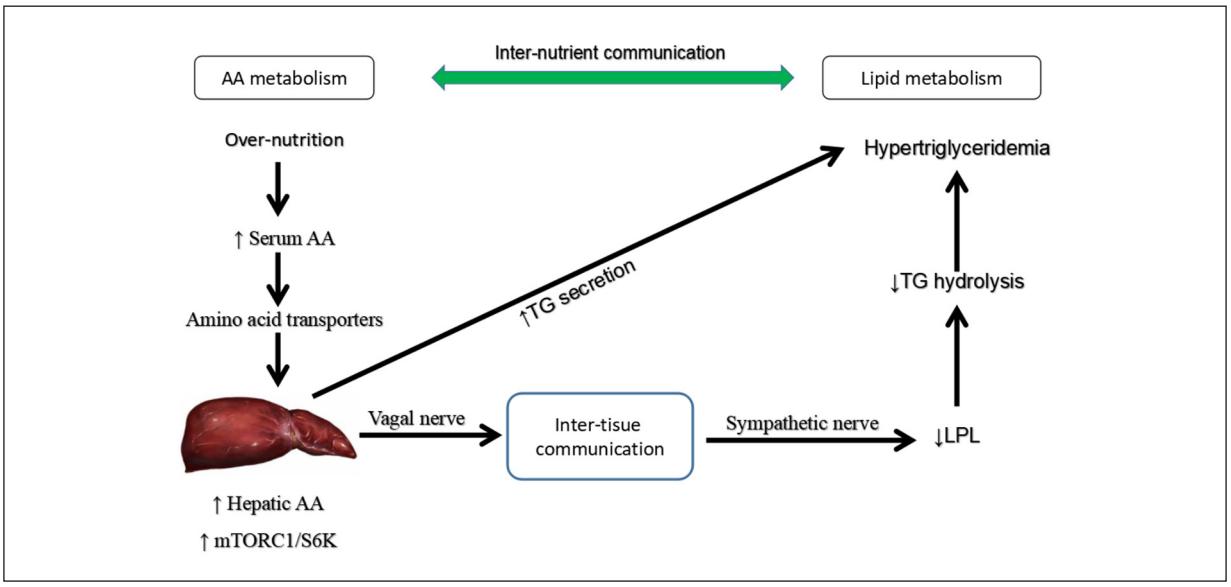

Figure 2. Pathophysiologic mechanism of hypertriglyceridemia due to elevated amino acids in obese individuals.

This current study investigates the clinical improvement in lowering LDL cholesterol, effect on HDL cholesterol level, the ratio of LDL and HDL and the level of triglycerides. Further this study investigates the efficacy of Orlistat on reduction of BMI and SBP.

Materials and Methods

Study Design

This is a retrospective study conducted in the Hail region of Saudi Arabia. The study evaluated lipid profiles and blood pressure in patients with Type 2 diabetes. These patients had an HbA1c between 7% and 11% and received 1 g of metformin for 24 weeks. The study has obtained data regarding their drug treatment and lipid profiles, including triglyceride, Total Cholesterol (TC), LDL cholesterol, HDL cholesterol, LDL/HDL ratio, systolic blood pressure, and BMI. The study considered 200 patients in total, of which 100 patients received the metformin treatment only and no Orlistat treatment (placebo group), while other 100 patients received 120 mg of Orlistat (Orlistat group) along with metformin. Both the drug treatment was given for 24 weeks. The selection of the patients in the placebo group or Orlistat group was random. Statistical analysis was conducted on the data obtained for each group before the treatment and after 24 weeks of treatment.

The initial information regarding the patients of both groups included patients' history, physical examination, laboratory results, serum lipids, and blood pressure. Blood pressure was obtained for three consecutive days in the morning (about 8 am), which constituted the initial measurement. The same assessments were repeated after 24 weeks for effective analysis, which was considered as the follow-up measurements. Changes in the results of the laboratory measurements, including lipid profiles and blood pressure, were studied. The statistical analysis was conducted between the Orlistat and placebo groups.

Inclusion and Exclusion Criteria

The included patients were aged between 40 to 65 years. The study only included the patients with Type 2 diabetes mellitus who were on metformin drug treatment, those who gave consent, and those who had followed our study protocol completely. The included patients also had dyslipidemia. Patients with chronic conditions like renal, hepatic, or endocrine disorders and poorly managed hypertension may disrupt the study outcome and evaluation. The patients who had a history of bariatric surgery, substance abuse, or were on weight loss medications before or during the study, have been excluded from this study.

Statistical Analysis

The study conducted a statistical analysis using SPSS 25 (IBM Corp., Armonk, NY, USA) and

Microsoft Excel. The study employed ANOVA for effective analysis between the groups (placebo and Orlistat). The descriptive measurements have been expressed as mean±standard deviation. For each lipid profile parameter, the change in a parameter (measurement during follow-up study-measurement during the initial study) was analyzed between the placebo and Orlistat groups for significance. The level of significance was considered to be α=0.05 (p<0.05).

Results

The study obtained the baseline characteristics of the patients in each group. Table I shows the details of the findings. The mean value of age in the placebo and Orlistat groups was 52.35±0.6 years and 53.65±0.8 years, respectively. The study found 62 males and 38 females in the placebo group while 58 males and 42 females were in the Orlistat group. BMI of placebo and Orlistat groups were found to be 31.58±2.68 kg/m^2 and 31.44±2.56 kg/m^2, respectively.

The study found that the change in LDL cholesterol, HDL cholesterol, Total cholesterol, LDL/HDL Ratio and Triglycerides were found to have a significant difference between the placebo and Orlistat groups (p<0.05). The study added that Systolic Blood Pressure and BMI have no significant difference between the placebo and Orlistat group (p>0.05). The study has found that LDL cholesterol has reduced from 3.19±0.05 mmol/L to 3.14±0.06 mmol/L in the placebo group while it has reduced from 3.21±0.06 mmol/L to 2.81±0.04 mmol/L in Orlistat group, which is statistically more significant (p<0.05) than the placebo group. The study also noted a significant increase in HDL cholesterol in the Orlistat group as compared to the placebo group. Again, Total Cholesterol increased in the placebo group from 5.39±0.061 mmol/L to 5.49±0.07 mmol/L, while in the Orlistat group it reduced from 5.39±0.062 mmol/L to 5.14±0.05 mmol/L. Therefore, the patients in the Orlistat group have shown significant improvement (p<0.05) in Total Cholesterol. The study, further, has shown significant improvement in LDL/HDL ratio and triglyceride in the Orlistat group (p<0.05) as compared to the placebo. However, the systolic blood pressure and BMI have improved both in the placebo and Orlistat group, there is no significant (p>0.05) difference between these two groups. Table II shows the detailed findings of the lipid profile test, systolic blood pressure and BMI, before and after 24 weeks.

Discussion

The study found significant changes in the parameters like LDL cholesterol, HDL cholesterol, Total cholesterol, triglycerides, and LDL/HDL ratio between initial and follow-up results in the placebo and Orlistat groups (p<0.05). Although Systolic Blood Pressure and BMI have improved more in the Orlistat group than in the placebo group, the change in these parameters is insignificant (p>0.05). There are published studies[10-12], which have shown that Orlistat (an approved drug in Saudi Arabia) has been used to manage an elevated LDL/HDL ratio. Some studies[11-13] have shown that Orlistat also improves BMI and blood pressure. However, in our work, the improvement in BMI and blood pressure was insignificant between patients of placebo and Orlistat groups, despite substantial improvement in these parameters. It has been noted that physical activity levels also contribute to improving dyslipidemia. Similar findings have been shown by another studies[12-14]. Improvement in LDL/HDL ratio, an increase of HDL and decrease of LDL by Orlistat have been documented by literature. Further, few studies[15-17] have shown that a slight reduction in cholesterol and triglyceride levels can be achieved

Table I. Baseline characteristics of the patients in placebo group and orlistat group.

Parameters	Placebo group N = 100	Orlistat group N = 100
Age (years)[a]	52.35 ± 0.6	53.65 ± 0.8
Sex[b]		
Male	62	58
Female	38	42
Body Mass Index[a] (kg/m^2)	31.58 ± 2.68	31.44 ± 2.56
Fasting Blood Glucose[a] (mmol/l)	11.2 ± 0.3	11.4 ± 0.2

[a]Expressed as mean ± standard deviation; [b]Expressed as number of patients.

Table II. Result of the lipid profile test, systolic blood pressure and BMI, before the treatment and after 24 weeks of treatment.

Parameters	Initial (before the treatment)		Follow-up (after 24 weeks of treatment)		*p*-value[a]
	Placebo	Orlistat	Placebo	Orlistat	
LDL cholesterol (mmol/l)	3.19 ± 0.05	3.21 ± 0.06	3.14 ± 0.06	2.81 ± 0.04	$p < 0.05$
HDL cholesterol (mmol/l)	0.981 ± 0.023	0.982 ± 0.022	1.05 ± 0.019	1.09 ± 0.021	$p < 0.05$
Total cholesterol	5.39 ± 0.061	5.39 ± 0.062	5.49 ± 0.07	5.14 ± 0.05	$p < 0.05$
LDL/HDL Ratio	3.52 ± 0.09	3.49 ± 0.09	3.08 ± 0.08	2.85 ± 0.07	$p < 0.05$
Triglycerides	2.64 ± 0.089	2.79 ± 0.112	2.65 ± 0.14	2.480 ± 0.11	$p < 0.05$
Systolic Blood Pressure	131.3 ± 0.9	131.8 ± 0.9	130.8 ± 0.89	129.58 ± 0.91	$p > 0.05$
BMI	31.58 ± 2.68	31.44 ± 2.56	30.74 ± 1.98	29.58 ± 1.58	$p > 0.05$

LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; BMI, Body Mass Index; [a]level of significance is 0.05.

with Orlistat. The probability of reduced lipoproteins can be increased by the combined effect of losing body weight and Orlistat therapy of shorter duration. In our study, it has been seen that BMI has been reduced in all the patients. The combined effect of improvement in BMI and Orlistat therapy contributes significantly to the improvement of various cholesterol levels including LDL, HDL, LDL/HDL ratio and Total Cholesterol.

According to a few studies[14,16,17], saturated and unsaturated fats are neither good for the vessels nor bad for them. Other researchers[15,16] have found that reducing saturated or trans-fat by more than a few percent results in a drop in LDL cholesterol of more than 0.05 mmol/L. In this method, it has been observed that cardiovascular risks may decrease by 10% upon reducing the 10% LDL serum level. Some studies pointed out[16-18] that dietary fish oils can help decrease triglyceride levels. Plant sterols are considered to be beneficial for lowering LDL. Some studies[18-20] have shown an association between Orlistat treatment and improvement in lipid profiles. Studies[21,22] using larger data sets have also demonstrated a high correlation between the status of cholesterol levels and ischemic heart disease. Studies[17,18] indicated that the individuals' cholesterol levels improved after receiving lifestyle counselling and appropriate modification, including personalized intervention.

The present study revealed the analytical significance of Orlistat treatment in managing hyperlipidemia. The study has highlighted that Orlistat can significantly affect the improvement of lipid profiles. However, the study could not show a significant effect on reducing BMI and proposed that lifestyle and diet modification should be followed along with Orlistat treatment to reduce BMI significantly. A similar conclusion has been noticed from other works[23], which state that Orlistat should accompany lifestyle modifications to reduce BMI effectively.

Limitations

The study has some limitations. The study was conducted on 200 patients from one source due to which the results cannot be conclusive for the global population. The study also did not consider different cardiovascular indices or factors and did not evaluate the safety profile of the Orlistat.

Conclusions

This study has concluded that Orlistat can be prescribed for significant improvement in lipid profile parameters including LDL cholesterol, HDL cholesterol, Total Cholesterol, LDL/HDL Ratio and Triglycerides. The study has concluded that Orlistat may not have a significant effect on reducing BMI and blood pressure without adequate lifestyle modification. However, there is need to conduct more evidence on a variety of population to support our conclusion. Hence, managing lipid profile and obesity must include lifestyle and diet modification in addition to the drug treatment with Orlistat.

In this study, the patients were on metformin therapy due to their elevated HbA1c levels. The study suggests that there is a need to conduct studies with Orlistat monotherapy, and studies should be conducted on more diverse patients with other underlying conditions, especially renal or hepatic conditions. This would be helpful to chart out the applicability of Orlistat and determine its uses among patients with renal or hepatic conditions.

Overall, this study has highlighted the clinical significance of Orlistat in improving lipid profiles and concludes that Orlistat can be prescribed for improving lipid profiles in obese individuals with Type 2 diabetes. Further trials are required to study the interaction with other drugs and comparative efficacy with other lipase inhibitors.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Authors' Contribution
We declare that this work was done by the authors named in this article, and all the authors have contributed equally for this research.

Ethics Approval
The Ethical Committee approved this study from REC at the University of Hail (approval number: H-2021-195). The study was conducted in accordance with The Declaration of Helsinki as amended in 2013.

Informed Consent
The whole study process was explained to the patients thoroughly and required consent was obtained from each one of them before starting the data collection.

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Data Availability
The data will be available on request.

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