Original Article

Effect of rimonabant on the components of metabolic syndrome: A randomized, controlled study done on Punjabi population

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Abstract

The objectives of this study were to study the total and differential effect of Rimonabant on weight parameters, lipid profile, glycemic profile, and blood pressure and to evaluate its safety profile in obese population of Punjab. **Materials and Methods:** This was a randomized open controlled study, carried out on 100 subjects that included Punjabi adults (18-70 years) who were obese or overweight (with associated risk factors) according to Asia pacific guidelines. Treatment group ($n = 50$) was given Rimonabant 20 mg once-daily, and control group ($n = 50$) was given placebo for 12 weeks. Alterations in weight and lipid parameters, Fasting blood sugar (FBS), and blood pressure were recorded. Psychiatric adverse events were monitored by HADS score. Analysis was done using SPSS software. **Results:** Statistically significant difference was observed in two groups in reduction in weight, waist circumference, body mass index. Overall reduction in number of patients in the obese category was 20% in group 1 and 6.25% in group 2. In lipid parameters, significant changes were observed in triglycerides (TG), HDL cholesterol, and total cholesterol: HDL ratio ($P < 0.001$). No significant change was observed for LDL cholesterol and total cholesterol. Effect on Fasting Blood Sugar (FBS) was also significant. Moderate decrease in systolic blood pressure and no significant change was observed in diastolic blood pressure. Using multivariate regression model, Rimonabant was found to have weight-loss independent effect on lipid parameters with triglycerides having the maximum percentage difference between regression coefficients. No significant correlation was observed between changes in lipid parameters and weight loss. Amongst the lipids, changes in triglycerides and HDL cholesterol correlated best. Decrease in FBS correlated with weight loss but not to lipid parameters. Adverse event profile was comparable in both groups. Depressive symptoms were noted in 3 subjects in treatment group with 1 requiring termination of treatment. Frequency of anxiety symptoms was same in both groups with none showing tendency towards suicide. **Conclusions:** This is the first study of Rimonabant on Punjabi population and reports the depressive adverse events to be occurring in low frequency and of mild intensity in this group. Thus, it provides a clue to the need for further studies of cannabinoid receptor antagonists on larger samples in such ethnically predisposed populations to reevaluate the safety profile and its genetic correlation. It also suggests need for further research on differential effect of antagonism of cannabinoid receptors in CNS and adipose tissue and its use to produce drug that targets metabolic derangements by selective action on adipose tissue receptors.

Key words: Rimonabant, Metabolic Syndrome, Punjab, Obesity

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INTRODUCTION

Body composition of South Asians is conducive to development of the metabolic syndrome. Approximately 20-25% of urban South Asians have evidence of the metabolic syndrome.[1] In India, there is a steady growth in the number of obese Indians towards epidemic proportions. High risk ethnicity and high

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propensity to central obesity predispose Indians to a higher risk of type 2 diabetes and metabolic syndrome even at lower levels of BMI.[2] Certain communities in India like the Punjabi Bhatia community have inordinately high tendency to develop obesity, type 2 diabetes, and the metabolic syndrome.[3] The National Family Health Survey-3 for Punjab showed that nearly 37.5% women and 30.3% men in Punjab are obese.[4]

Anti-obesity drug, Rimonabant, is a selective antagonist of type 1 cannabinoid receptors (CB1) and acts on CB1 receptors in CNS to regulate appetite. Other proposed mechanisms are actions on receptors in the GIT that may modulate satiety as a peripheral means of regulating food intake or on those expressed in the adipose tissue that may improve metabolic derangements often seen in the obese population, thus decreasing insulin resistance, coronary artery disease, and dyslipidemia.

Though found to have a favorable effect on the cardiometabolic risk profile in obese subjects, Rimonabant has been facing controversies since the outset as regards the psychiatric adverse events associated with its use and ban was imposed by the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, India in December, 2009.[5] There is no earlier study to assess the effect of the drug in the Punjabi population; therefore, this study was done to assess its efficacy and safety profile in this ethnically susceptible group.

The objectives of this study are to study the total and differential effect of Rimonabant on weight parameters, lipid profile, glycemic profile, and blood pressure in obese population of Punjab, to evaluate the direct effect of Rimonabant on lipid profile independent of weight loss and to evaluate the safety profile of drug with special emphasis on psychiatric manifestations. This study also aims to find correlation of different components of metabolic syndrome to each other.

MATERIALS AND METHODS

Study design: This study was a randomized open controlled study, carried out in a tertiary care hospital in Punjab. 101 subjects were randomly assigned to treatment with either placebo or Rimonabant 20 mg one tablet given daily on empty stomach half an hour before meals for 12 weeks along with dietary and exercise protocol.

Subjects included were those in the age range of 18-70 years with Body Mass Index (BMI) $\geq$25 kg/m^2 (obese as per Asia Pacific guidelines)[6] or with BMI $\geq$ 23 kg/m^2 (overweight) with either one of risk factors: Hypertension or dyslipidemia (LDL $\geq$ 130, HDL $<$ 40 in men or $<$50 in women, TG $\geq$ 150 mg/dl), or diabetes mellitus type 2 or fasting blood sugar $\geq$ 110 mg%. Exclusion criteria were pharmacologic therapy for dyslipidemia within 6 weeks before screening, on treatment with very low caloric diet within 6 months before screening, psychiatric illness – severe depression, suicidal attempt, eating disorder, severe hypertension – systolic BP $\geq$ 160 mm Hg and/or diastolic BP $\geq$ 100 mm Hg (stage-2 hypertension according to JNC-7), uncontrolled thyroid dysfunction, hepatic impairment, hematologic abnormality, renal impairment, history of hashish/marijuana abuse, any malignant disorder within 5 years, pregnancy/lactation, epilepsy/seizure disorder on anti-epileptic treatment, patient who has quit smoking within past 6 months, patients on medicines altering weight, and patient with history of multiple sclerosis.

Study was conducted from January 2008 to December 2008 on eligible subjects after taking their informed consent and approval from the ethics committee. Weight variables (body weight, BMI, waist circumference, waist hip ratio) and blood pressure (systolic and diastolic) were measured at baseline, 6 and 12 weeks. Metabolic measures were assessed at 12 weeks, which included triglycerides, total cholesterol, HDL, LDL, total cholesterol/HDL ratio, and FBS. The safety assessment included standard adverse-event reporting, vital signs, ECG changes, and psychiatric monitoring according to the Hospital Anxiety and Depression Scale (HADS) with cut-off score of 10 at any time for stopping drug.

Data was compiled and analyzed statistically using the software SPSS version-13. For testing the statistical significance of the difference between two groups, paired *t*-test was applied. *P* value of $<$0.001 was taken as level of significance. ANOVA was used for testing the significance of variation in the sample. Pearson's correlation coefficients between all the parameters were obtained for both the groups. A multivariate linear regression model was applied for estimating the effect of various factors on lipid profile independent of weight loss.

RESULTS

The study completion rate was 100% in the control group and 98% in the treatment group with one

drop-out at 6 weeks. Sex distribution was comparable in the two groups with 56% males in control and 54% in treatment group. Mean age was also comparable in two groups (52 years). As compared with a weight loss of 1.46 kg in the group receiving placebo, the group receiving 20 mg of Rimonabant had a loss of 5.3 kg [Figure 1]. The proportion of patients who had a weight loss equal to or greater than 5% was 4% in the placebo group and 84% in the group receiving 20 mg of Rimonabant, whereas the proportion of those who had a weight loss equal to or greater than 10% was 8% in the group receiving 20 mg of Rimonabant [Figure 2]. Twenty percent of the patients in the control group actually gained the weight lost at 6 weeks by 12 weeks.

There was statistically significant difference between treatment and control groups for reduction in waist circumference of 3.11 cm vs. 1.02 cm [Figure 3], BMI of 2.00 vs. 0.56 kg/m² [Figure 4], and waist: Hip ratio of 0.03 vs. 0.01 [Figure 5]. As per BMI criteria, total reduction in number of obese patients was 20% in treatment group and 6.25% in control group [Figure 6]. In the treatment group, out of all female patients, 77.27% (17 out of 22) lost more than 5% weight and 13.63% lost more than 10% weight. Out of males, 89.28% (25 out of 28) lost >5% weight and 3.57% lost >10% weight. However, no significant effect of sex could be observed on degree of weight loss on the whole.

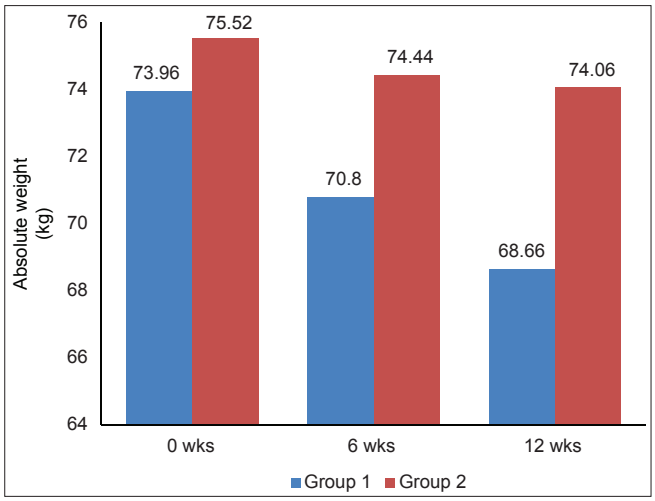

Figure 1: Absolute Weight from 0 to 12 weeks at 6 weekly intervals for the study groups

Amongst the lipid parameters, significant changes were observed over 12 weeks with reduction in triglyceride levels by 11.72% in treatment and 1.37% in control group. The increase in HDL cholesterol levels was 15.80% and 4.37%, respectively ($P < 0.001$). Reduction in total cholesterol (4.6% vs. 1.12%) and LDL cholesterol (4.58% vs. 0.66%) was not found statistically significant. Overall, decrease in total cholesterol: HDL ratio was found to be significant (18.13% vs. 4.75%). Differential effect on lipid profile is shown in Figure 7.

For other parameters, there was a statistically significant reduction in FBS levels (16% vs. 6.6%), modest decrease in systolic blood pressure ($P < 0.05$), and no significant change in diastolic blood pressure.

On applying ANOVA test, f-ratios were found to be significant for all variables, except changes in diastolic BP, LDL, and total cholesterol levels.

A multivariate linear regression model was used to study the effect of Rimonabant on lipid profile independent of weight loss. Regression coefficients of triglycerides on weight loss are −0.538 in group-1 against −0.481 in group-2, thereby showing that triglycerides are 11.18% more reduced in treatment group (calculated as-$(\beta_1/\beta_2 - 1) \times 100$). The coefficients of HDL, LDL, and total cholesterol on weight loss in treatment group

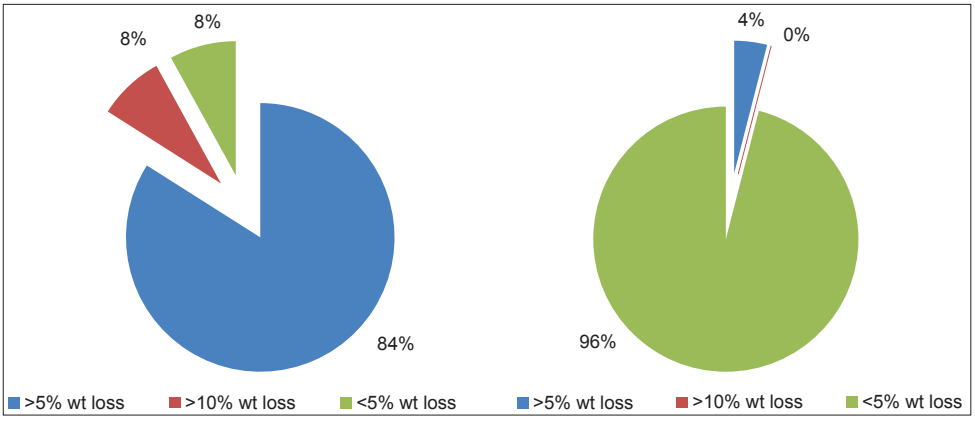

Figure 2: (a) Percentage of patients with ≥5% and ≥10% weight loss at 12 weeks in treatment group (b). showing percentage of patients with ≥5% and ≥10% weight loss at 12 weeks in control group

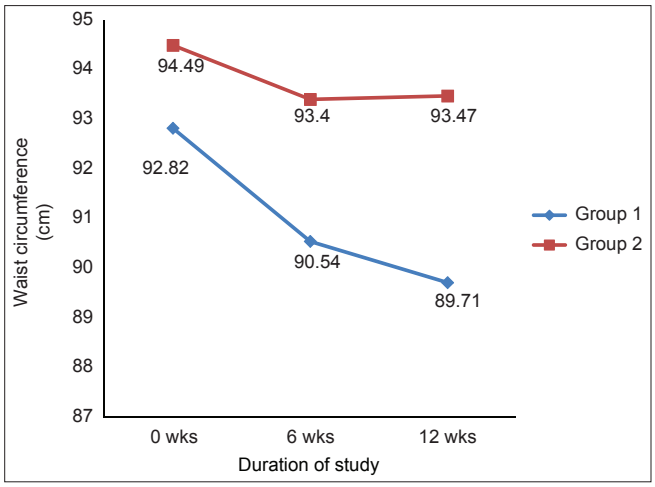

Figure 3: Changes in waist circumference from 0 to 12 weeks at 6 weekly intervals for the study groups

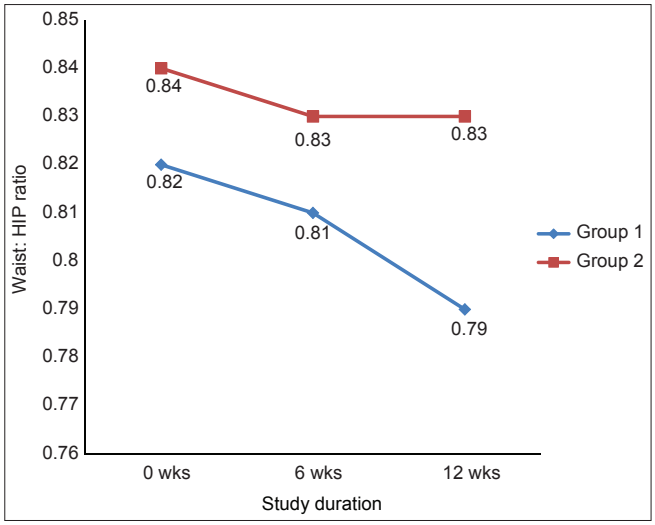

Figure 5: Changes in waist: Hip ratio from 0 to 12 weeks at 6 weekly intervals for the study groups

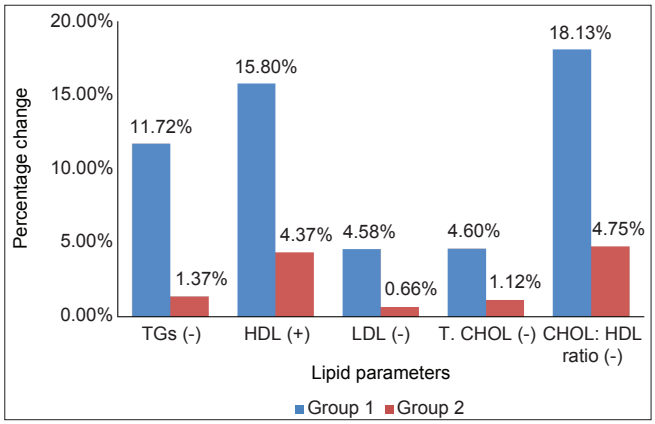

Figure 7: Percentage changes in the lipid parameters- Triglycerides, HDL Cholesterol, LDL Cholesterol, Total Cholesterol and Total Cholesterol: HDL ratio from 0 to 12 weeks in the two study groups

were 0.703, −0.292, and −0.159, respectively. In control group, the regression coefficients could not be found

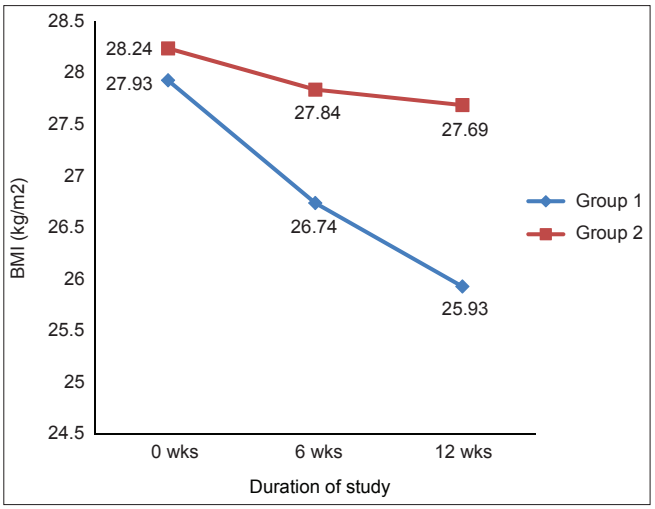

Figure 4: Changes in BMI from 0 to 12 weeks at 6 weekly intervals for the study groups

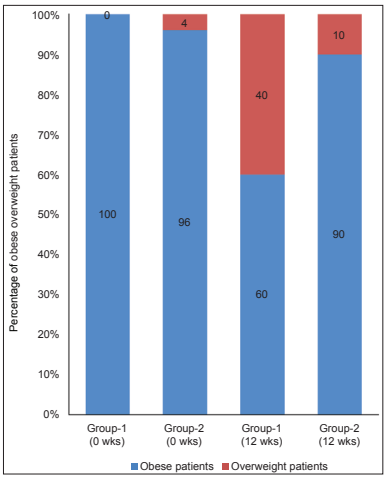

Figure 6: Change in the obesity status of subjects/distribution of obese and overweight subjects in the two study groups

statistically significant, showing that the lipid profile was not affected by weight loss alone.

Pearson's correlation coefficients between the different parameters/components of metabolic syndrome for the two study groups were obtained. On studying the correlation between different anthropometrics parameters, it was found that weight loss is highly correlated (r = 0.601) to decrease in waist circumference in treatment group as compared to control group (r = 0.465). Insignificant correlation coefficients obtained between lipid parameters and weight loss in control group show that weight loss alone does not correlate to favorable alterations in lipid profile. Among the individual lipid parameters, it was found that reduction in triglycerides and increase in HDL levels were highly correlated to each other (r = 0.501) in treatment group. Correlation between other parameters is weak. No significant

correlation was obtained in the control group. Fasting blood glucose correlated most with weight loss in the treatment group. No correlation was obtained with changes in lipid parameters.

The total number of adverse events reported in treatment group was 28 and in control group it was 23 [Table 1]. Depressive symptoms were noticed in 3 patients in group 1 at 6 weeks and none in group 2. Out of the 3 patients in group 1, who had increase in HADS depression sub-score, 2 remained below the cut-off of 10, but third patient who was noted to have a score of 11 at 6 weeks had to discontinue treatment. Anxiety symptoms occurred equally, with one patient in each of the two groups, though HADS score remained below 10. No tendency towards suicide was observed in either group. The increase in depression and anxiety sub scores using HADS was noticed to occur in first 6 weeks in whichever case they did increase after which they stabilized.

Anorexia and nausea/vomiting were more frequent in subjects given Rimonabant (in 15.7% and 13.7% cases) than in those taking placebo (8% and 8% cases). Overall, the adverse effect profile was comparable in both the groups. Other adverse events noticed were diarrhea, fatigue, and headache, which were more in the control group.

DISCUSSION

The mean age of the patients was 52 years in both the groups i.e., treatment (group 1) and control (group 2). Treatment group had 56% males and 44% females, and control group had 54% males and 46% females. There is equal distribution in both the sexes in the groups, thereby ruling out any bias due to sex. The baseline mean weight was almost the same in both the groups, i.e. 73.96 kg in group-1 and 75.52 kg in group-2.

Table 1: The adverse event profile for the two study groups

Adverse events	Treatment group		Control group	
	f	% age	f	% age
Depression	3	5.88	-	-
Anxiety	1	1.96	1	2
Nausea/vomitting	7	13.7	4	8
Anorexia	8	15.7	4	8
Diarrhea	1	1.96	2	4
Fatigue	3	5.88	5	10
Headache suicide	5	9.88	7	14
Total adverse events	28		23	

In the present study, Rimonabant, in a dose of 20 mg once-daily, caused a mean weight loss of 5.3 kg at 12 weeks as against 1.46 kg with placebo over the same time period. This is similar to the results shown by Despres[7] in RIO-Lipids, Pi Sunyer[8] in RIO-NA, and Van Gaal[9] in RIO-Europe trials. The weight reduction was slightly less (4.25 kg) at 12 weeks in RIO-Diabetes group.[10] This could be because the other trials had overweight/obese patients under study, but RIO-Diabetes was specially designed to study effect on diabetic patients who are generally more resistant to weight loss.[11]

There were 84% patients in group-1 who lost more than 5% of weight at base line, out of which 8% lost more than 10% of their baseline weight. In comparison to this, 4% of patients in group-2 lost more than 5% and none lost more than 10% of baseline weight, creating a marked difference between the groups. Similar results were shown by earlier trials though absolute values cannot be compared because duration of the published trials was longer than our study.

In the treatment group, out of all female patients, 77.27% (17 out of 22) lost more than 5% weight and 13.63% lost more than 10% weight. Out of males, 89.28% (25 out of 28) lost $>5\%$ weight and 3.57% lost $>10\%$ weight. But, no significant effect of gender was observed on degree of weight loss on the whole.

In the present study, there was also statistically significant reduction in waist circumference. The mean reduction was 3.11 cm in group-1 and 1.02 cm in group-2 after 12 weeks of treatment, the mean difference between two groups being 2.09 cm. This difference is comparable to that observed in RIO trials.[7-9] Though the reduction in waist circumference was observed in control group also, which could be because of diet control and exercise, it is less as compared to treatment group and the difference is significant. Waist to hip ratio also decreased by 3.66% in group 1 compared to 1.2% in group 2, which is highly significant.

In our study, reduction in BMI of 7.2% in group-1 was observed as against 1.97% in group-2. Though BMI has been taken as basis of patient selection in earlier studies, there are no published results available on reduction in BMI.[8,9] Following the WHO Asia-Pacific guidelines on obesity, in our study, a 40% reduction in number of obese individuals (BMI $>$ 25 kg/m^2) was observed in group 1 as against 6.25% reduction in the number in group 2. But, this cannot be compared because of lack of any published studies on Indian population.

As such, anthropometric parameters change according to weight loss. On studying the correlation between different anthropometrics parameters, it was found that weight loss is highly correlated (r = 0.601) to decrease in waist circumference in treatment group as compared to group-2 (r = 0.465). Significant correlation of waist circumference reduction with weight loss has been shown by Han and associates.[12] Weight loss was also found to be highly correlated to BMI and weakly to waist: Hip ratio.

Thus, a significant decrease in all obesity parameters was observed in the treatment group, confirming the efficacy of the drug in reducing obesity and achieving the ideal target weight loss (5-10%) and favorable anthropometric measures.

Rimonabant has shown a favorable effect on the lipid parameters. Triglyceride level reduction in group 1 was 21.68 mg/dl (11.71%) and in group 2 was 2.51 mg/dl (1.38%), thus mean change compared to control of 10.33%, which is highly significant. This is comparable to net reduction of 9% observed by Despres in RIO lipids at 12 weeks.[7]

After 12 weeks of treatment, mean increase in HDL levels was 5.97 mg/dl (15.8%) in group 1 as against 1.70 mg/dl (4.3%) in group 2. The difference between two groups is highly significant. This is comparable to results of RIO-Lipids trial.[7]

The decrease in LDL levels was 7.07 mg/dl (4.6%) in group 1 against 1.06 (0.66%) in group 2, but the significance of the difference could not be established statistically. Similarly, total cholesterol came down by 10.56 mg/dl (4.61%) in group 1 against 2.63 mg/dl (1.12%) in group 2. This difference also did not come out to be significant. It shows that though Rimonabant did cause some reduction in levels of LDL and total cholesterol in our study, the effect is not that significant. Similar results have been shown by Despres,[7] Pi Sunyer,[9] Scheen,[10] and Van Gaal[8] in four RIO trials and ADAGIO–Lipids[13] though comparison of absolute values cannot be made because of longer duration of the trials.

These changes in levels of HDL-C and total cholesterol translated into a reduction in total cholesterol: HDL-C ratio of 18.13% in group 1 and 4.75% in group 2, thus a net difference of 13.38% between the two groups, which comes out to be highly significant. Similar pattern was also observed by Despres in RIO-Lipids trial.[7]

Multivariate linear regression model was used to study the effect of Rimonabant on lipid profile independent of weight loss. Regression coefficients of triglycerides on weight loss are -0.538 in group-1 against −0.481 in group-2, thereby showing that triglycerides are 11.8% more reduced in treatment group. The coefficients of HDL, LDL, and total cholesterol on weight loss in treatment group were 0.703, −0.292, and −0.159, respectively. In control group, the regression coefficients could not be found statistically significant, showing that the lipid profile was not affected by weight loss alone. Thus, the changes in the lipid profile in the treatment group were mainly because of the direct effect of Rimonabant.

Similar results were obtained by Van Gaal[8] in RIO-Europe trial and Pi Sunyer[9] in RIO-NA trial on lipid profile after making adjustments for weight loss. Difference in statistical values from earlier studies could be because of smaller sample size and secondly, because of different population characteristics, that is, our study was done in Punjabi Indian population as compared to data available in American and European population.

Further, the insignificant correlation coefficients obtained between lipid parameters and weight loss in control group show that weight loss alone does not correlate to favorable alterations in lipid profile. This is in concordance with results of analysis done by Orchard[14] who showed that though the lifestyle measures reduce weight and waist circumference, they do not reduce abnormalities in HDL cholesterol and triglycerides effectively.

Further, on studying correlation among the individual lipid parameters, it was found that reduction in triglycerides and increase in HDL levels were highly correlated to each other (r = 0.501) in treatment group. Correlation between the other parameters is weak. Thus, HDL and triglyceride changes go hand in hand. No significant correlation was obtained in the control group, which could be the reason for insignificant regression coefficients in multivariate regression analysis as explained earlier.

This pattern of change in lipid profile i.e., reduction in triglycerides, increase in HDL-C, and total cholesterol: HDL-C ratio is particularly effective in curbing the lipid derangement of classical lipid-triad that occurs in central obesity and metabolic syndrome and is characteristically found in obese Indian population, thus establishing the efficacy of Rimonabant in modifying the same.

A favorable effect on glycemic control was also noticed after the treatment, mean reduction in fasting blood

glucose levels was 19.82 mg/dl (16%) in group 1 against 6.48 (5.04%) in group 2. Though decrease was also observed in those on placebo (group 2), it was less as compared to group 1, and the difference was highly significant statistically. The reason for the decrease in control group could be the "Hawthorne Effect," which is described as follows: Patients enrolled in any trial invariably show an improvement in glycemic control because of the greater attention paid to them and because they may also want to show their interest in the study.[15]

On studying correlation of fasting blood glucose with other variables, it was found to be maximum correlated with weight loss in the treatment group. No correlation was obtained with changes in lipid parameters.

Another component of metabolic syndrome, hypertension, was also assessed by monitoring blood pressure (BP). Rimonabant (group 1) decreased systolic BP by 7.34% against 4.29% decrease in group 2. The difference came out to be statistically significant at $P < 0.05$ though not highly significant. Difference in diastolic BP, reduction of 4.71% in group 1 vs. 4.47% in group 2, was not found to be significant. Thus, Rimonabant has modest effect on systolic and no effect on diastolic BP in our study. This is comparable to the small but significant ($P < 0.05$) decrease observed by Scheen[10] in RIO Diabetes and Despres[7] in RIO-Lipids trial. But, the overall effect is less as compared to weight and lipid control.

The total number of adverse events reported in group 1 was 28 and in group 2, it was 23. Depressive symptoms were noticed in 3 patients in group 1 at 6 weeks and none in group 2. Out of the 3 patients in group 1, who had increase in HADS depression sub-score, 2 remained below the cut-off of 10, but third patient who was noted to have a score of 11 at 6 weeks had to discontinue treatment. Anxiety symptoms occurred equally, with one patient in each of the two groups, though HADS score remained below 10. No tendency towards suicide was observed in either group. Anorexia and nausea/vomiting were more frequent in group 1 (in 15.7% and 13.7% cases) than in group 2 (in 6% and 8% cases, respectively). Overall, the adverse effect profile was comparable in both the groups.

Rimonabant has been shown to increase incidence of depression in a meta-analysis by Christensen and in RIO trials.[16] The patients in our study who had increase in HADS depression scores had high levels of triglycerides at baseline, favoring the relation between high baseline triglycerides and incidence of depression occurring with the use of drug as suggested by Christensen. Also, the increase in depression and anxiety sub scores using HADS was noticed to occur in first 6 weeks in whichever case they did increase after which they stabilized, indicating need of monitoring psychiatric profile in early phase of treatment.

In the present study, effect of the drug on this ethnic population as regards both the efficacy and adverse event profile was found to be different as compared to earlier trials that have published data mainly from the Caucasian population. It indicates that Rimonabant is an effective drug for controlling weight and lipid parameters and other components of metabolic syndrome simultaneously. It may be useful to target all the risk factors at one go and thus, has a potential role in curbing the obesity and related comorbidities in the Indian Punjabi population.

There are certain drawbacks in this study that should be acknowledged. Firstly, because the study was done on a small sample of Punjabi population and for a smaller duration, the effects cannot be exactly extrapolated for the entire population. Secondly, effects on body composition were mainly based on anthropometric measurements that do not give the exact estimate of metabolic risk as compared to absolute and differential body fat percentage measurements. Analysis of psychiatric adverse effects was done mainly for depression and anxiety symptoms and also grades of the severity could not be studied since the drug was stopped at HADS scores of 10 because of ethical considerations.

Earlier studies and trials conducted in Caucasians with Rimonabant reported significant psychiatric adverse events including depression, anxiety, and attempts to suicide, on the basis of which use of drug was banned in India. But, our study conducted on the Indian population reports of negative results for the adverse effects of the drug that have been creating controversies since its launch. Psychiatric events noticed in this study have occurred in lesser frequency and of milder intensity, thus demanding further studies on the use of Cannabinoid receptor antagonists in such ethnic populations before imposing a ban universally.

CONCLUSIONS

Rimonabant alters all the parameters included in criteria of metabolic syndrome to a varying extent, thus reducing the comorbidities associated with the syndrome phenotype. In addition to the beneficial

effect on various cardiometabolic risk factors in the genetically predisposed population of Punjabi ethnicity, the study reports the depressive adverse events to be occurring in low frequency and of mild intensity, onset being in early phase of initiation and no progression later. Since the results of our study are different from earlier studies done on Caucasian population, it provides a clue to the need for further studies of cannabinoid receptor antagonists on larger samples in such ethnically predisposed populations to reevaluate the safety profile and its genetic correlation.

We hypothesize that this variation in effects could be because of differential distribution of the cannabinoid receptors in the adipose tissue and CNS or because of variation in the degree of increase in endocannabinoid tone in the adipose tissue in susceptible populations and thus the resultant different effect of the CB-1 receptor antagonist on this population. Further research is needed to study the differential effect of antagonism of cannabinoid receptors in CNS and adipose tissue and then exploiting this differential effect to produce drug that targets metabolic derangements by selective action on adipose tissue receptors. Another area is to discover measures to decrease CNS penetrability of the endocannabinoid antagonist and thus, its adverse effects, though this might decrease its central action of decreasing appetite but retain its peripheral metabolic effects.

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Disclaimer

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