

## **Comparison between duration dependent effects of Simvastatin and Gemfibrozil on dyslipidemia in patients with type 2 diabetes**

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### **Abstract**

**Objective:** To observe the duration dependent effects of two important classes of lipid lowering drugs i.e. simvastatin and gemfibrozil in type 2 diabetic patients with dyslipidemia in Pakistani population.

**Methods:** Seventy type 2 diabetic patients with newly diagnosed dyslipidemia were enrolled and were divided randomly into two groups each, with 35 patients. Group I patients was given tablets Simvastatin 20 mg once daily and group II patients received tablet Gemfibrozil 600 mg twice daily. The study period comprised of 12 weeks. Fasting lipid profile and fasting blood sugar was analyzed on week 0 (day of inclusion), week 6 and week 12.

**Results:** At week 12 simvastatin decreased serum LDL cholesterol by 36.97 percent ( $P<0.001$ ). In contrast gemfibrozil did not reduce it significantly with a reduction of only 1.33 percent ( $P=N.S$ ). Simvastatin reduced serum total cholesterol and serum triglyceride by 29.88 percent ( $P<0.001$ ) and 21.78 percent ( $P<0.001$ ) respectively and increased serum HDL cholesterol by 16.67 percent ( $P<0.001$ ). While gemfibrozil decreased serum total cholesterol by 9.14 percent ( $P<0.001$ ) and serum triglyceride by 30.84 percent ( $P<0.001$ ). Gemfibrozil raised serum HDL cholesterol levels by 18.08 percent ( $P<0.001$ ).

**Conclusion:** Significant changes were observed in all lipid parameters with both simvastatin and gemfibrozil with regard to duration of treatment. Simvastatin was found to be more effective in lowering serum total cholesterol and LDL cholesterol levels in comparison to gemfibrozil, which was found to be more effective in lowering serum triglyceride and elevating serum HDL cholesterol levels. Both of these drugs were well tolerated and none of the patients exhibited any significant adverse effects. Both can be given as monotherapy in patients with type 2 diabetes mellitus and abnormal lipid profile (JPMA 55:324;2005).

### **Introduction**

Coronary heart disease is a leading cause of morbidity and mortality and high blood cholesterol is one of its major risk factors.<sup>1-2</sup> The incidence and prevalence of coronary heart disease are markedly increased in patients with

type 2 diabetes mellitus accounting for more than 70 percent of deaths in western countries.<sup>3</sup> The prevalence of coronary heart disease in Pakistan is as high as in western world.<sup>4</sup> Patients with type 2 diabetes have a two to four-fold excess risk of coronary artery disease as compared to

non-diabetic patients.<sup>5-7</sup> The causal role of an elevated serum cholesterol level in the genesis of atherosclerosis and its clinical sequelae is now well-established.<sup>8</sup> A question of particular importance is the relative role of various lipoprotein abnormalities in determining the cardiovascular risk in diabetic individuals. Although clinical trials of cholesterol have shown that lowering of LDL cholesterol in diabetic patients does reduce the incidence of coronary vascular disease, the relative importance of LDL, compared with the characteristic dyslipidemia consisting of elevated triglyceride, decreased HDL cholesterol and LDL particles of altered composition in diabetic patients is still a subject of debate.<sup>9</sup> Increase in the serum triglyceride and decrease in serum high density lipoprotein (HDL) cholesterol levels have been identified as being of unique importance in patients with type 2 diabetes mellitus. These changes in lipoprotein can occur in the absence of significant hyperglycemia and are not necessarily restored to normal with the institution of good glycemic control.<sup>10</sup> Simvastatin was found to substantially reduce total and LDL cholesterol concentration and their efficacy and safety in reducing coronary artery disease morbidity and mortality was established in primary and secondary prevention studies.<sup>11</sup> Gemfibrozil has been proven very effective in reducing coronary artery disease events in patients with combined hyperlipidemia in the Helsinki Heart Study.<sup>12</sup>

The present study investigated the duration dependent effects of simvastatin and gemfibrozil on dyslipidemia in patients with type 2 diabetes mellitus.

## Patients and Methods

This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Post Graduate Medical Centre (JPMC), Karachi.

Seventy Type 2 diabetic patients with newly diagnosed dyslipidemia were selected from Medical OPD and Diabetic OPD of Jinnah Post Graduate Medical Centre Karachi.

The Inclusion criteria were patients with Type 2 diabetes mellitus above 25 years age of either sex with newly diagnosed dyslipidemia, (serum LDL-cholesterol above 130 mg/dl, serum triglyceride above 150 mg/dl, serum total cholesterol above 200 mg/dl, and serum HDL-cholesterol below 40 mg/dl). The Exclusion criteria were, patients having history of allergy to Simvastatin or Gemfibrozil, pregnant or lactating women, patients with Type 1 diabetes mellitus, patients having history of myocardial infarction, coronary artery bypass grafting, proven coronary artery disease, unstable angina, clinically manifest heart failure, patients with acute liver disease or hepatic dysfunction or impaired renal function and patients who were on systemic steroids, androgens, cyclosporine, immunosuppressant drugs or any other drug with reported interaction with anti lipidemic drugs or

any other concurrent medical illness.

The selected patients were divided into two groups with 35 patients in each group.

Patients in-group I were provided tablets Simvastatin 20 mg and were advised to take one tablet daily in the evening. Patients in group II were given tablet Gemfibrozil 600mg twice daily with meals. Each patient in both the groups was advised and given a written diet and exercise plan. The study duration was of 12 weeks.

After explaining the limitations, consent was obtained from all study participants before being enrolled in the study. They were instructed to come for follow-up at fortnightly intervals. Patients were asked about drug compliance and adverse effects at each visit. Lipid profile and serum glucose determinations were done at day of inclusion i.e. week 0 and repeated at weeks 6 and 12.

All laboratory analyses were done in the central laboratory of Jinnah Postgraduate Medical Centre Karachi. The serum total cholesterol (TC) and triglyceride (TG) were measured by enzymatic colorimetric procedures. Serum HDL-C was isolated initially by precipitating low-density lipoprotein cholesterol (LDL-C) and Very low-density lipoprotein cholesterol (VLDL-C) with phosphotungstate/Magnesium chloride. An aliquot of the supernatant was then assayed for HDL cholesterol content. LDL-C was calculated by the Friedwald equation,

$[LDL\text{-}chol] = [Total\ chol] - [HDL\text{-}chol] - ([TG]/5)$ .  
Whereas all concentrations are measured in mg/dl.

## Statistical Analyses

All data was fed in SPSS version 10.0 and analyzed. Mean  $\pm$  SEM of each category of lipid profile for each group was calculated. Paired t test was used to compare the mean values of various lipid fractions at various points in time (0 week, 06 week and 12 week) for each group separately. P value of less than 0.05 was considered statistically significant.

## Results

From the initial 70 patients included in the study 11 were lost to follow up. Of these 11 patients, 6 dropped out in Gemfibrozil group, (4 due to gastric upset and diarrhea, and 2 for unknown reason). Five patients dropped out in Simvastatin group (03 due to generalized weakness and muscle pain and 02 for unknown reasons).

Thus 59 of the 70 patients completed the study. The changes in the levels of all the lipid constituents in both groups, taking simvastatin or gemfibrozil, are shown in Table.

The total decrease of serum total cholesterol in 12 weeks, of the simvastatin group was 29.8%. In contrast the

**Table. Changes in Mean Lipid Values from Week 0, Week 6 and Week 12.**

Lipid profile	Drugs	Week 0 ( mg/dl )	Week 6 ( mg/dl )	P Value	Week 12 ( mg/dl )	P value
T. Chol	DR1 (n=31)	241.63 ± 7.59	197.45 ± 6.87	< 0.001	169.43 ± 6.19	< 0.001
	DR2 (n=29)	236.09 ± 6.37	224.45 ± 6.58	< 0.001	214.21 ± 6.61	< 0.001
TG	DR1 (n=31)	303.49 ± 32.45	279.58 ± 32.12	< 0.001	237.40 ± 26.46	< 0.001
	DR2 (n=29)	317.43 ± 21.75	269.35 ± 19.28	< 0.001	219.52 ± 17.48	< 0.001
HDL	DR1 (n=31)	31.43 ± 0.90	33.74 ± 1.05	< 0.001	36.67 ± 1.11	< 0.001
	DR2 (n=29)	34.46 ± 0.95	35.84 ± 1.06	< 0.001	40.69 ± 1.09	< 0.001
LDL	DR1 (n=31)	187.97 ± 7.25	156.23 ± 6.41	< 0.001	118.47 ± 4.19	< 0.001
	DR2 (n=29)	165.17 ± 4.97	165.90 ± 5.45	N.S	162.97 ± 5.76	N.S

DR1: Simvastatin; DR2: Gemfibrozil; Chol: Total Cholesterol; TG: Triglyceride; HDL: High Density lipoprotein; LDL: Low Density Lipoprotein;  
 ± : Indicates Standard Error of mean; All observations were measured in mg/dl; Figures in Parenthesis indicates number of patients.

gemfibrozil group had a figure of 4.93%.

Similarly the fall in serum triglycerides in 12 weeks in subjects of the simvastatin group was 21.78% and that of the gemfibrozil group was 30.84%. Serum HDL increased in the simvastatin group by 16.7% after 12 weeks whereas the gemfibrozil group showed a rise by 18.1%.

Simvastatin reduced LDL levels by 36.97% whereas gemfibrozil did not have any effect on the LDL (Figure).

simvastatin and gemfibrozil and lovastatin<sup>13-15</sup> have yielded results comparable to those reported in our study. In all these studies statin was found to be a powerful lipid lowering agent and significantly reduced all lipid parameters in contrast to gemfibrozil, which significantly decreased serum triglyceride and elevated serum HDL cholesterol levels but is ineffective in lowering LDL cholesterol levels. According to the current concepts LDL particles start the atherogenic process by entering the arterial intima where they become oxidized and degraded and then deposit cholesterol, initiating formation of the lipid core of the lesion. It is now known that LDL particles of type 2 diabetic patients may be more atherogenic partly because of the common occurrence of elevated triglyceride levels accompanied by LDL particles of small size and increased density. Small dense LDL may penetrate the arterial endothelium more avidly than normal sized LDL and may be more susceptible to oxidation and glycation of apolipoprotein, all of which may add to atherogenicity.<sup>16</sup> In the present study simvastatin produced significantly greater reduction in serum LDL cholesterol from baseline to week 6 and week 12 as compared to gemfibrozil which did not show any significant change in serum LDL levels. These changes in LDL cholesterol are consistent with those observed in previous comparative trials.<sup>13,14</sup>

Figure. Percentage Changes in Lipid Profile from Week 0 - Week 12 with DR1 and DR2.

## Discussion

This study demonstrates significant lipid lowering effects of simvastatin on all lipid parameters as compared to gemfibrozil, which was found to have significant effects on serum triglyceride and serum HDL, moderate effects on serum total cholesterol but no significant effect on serum LDL levels.

Direct comparison studies involving gemfibrozil and

Miller M et al<sup>17</sup> reported similar changes in all lipid parameters as observed in our study but they used simvastatin in a higher dose, 40mg and the duration of their study was 24 weeks. The reason for the improvement shown by our study participants, could be due to the genetic difference, the advised diet and exercise.

We have observed marked reduction in serum

triglyceride and increase in HDL cholesterol levels with gemfibrozil as compared to simvastatin which is in accordance with the study of Garg A and Grundy SM<sup>18</sup> who observed similar changes but also reported a significant increase in the LDL, which was not significant in our study.

Both simvastatin and gemfibrozil demonstrated acceptable safety profile and good tolerance in patients with type 2 diabetes.

The landmark survival trials with statins (the Scandinavian Simvastatin Survival Study [4S]<sup>11</sup>, the West of Scotland Coronary Prevention Study [WOSCOPS]<sup>19</sup> for primary coronary artery disease prevention), and long term Intervention with Pravastatin in Ischemic Heart Disease [LIPID]<sup>20</sup>, showed that considerable reduction in LDL cholesterol levels has a clear benefit for high risk patients. The biggest reduction in coronary mortality (42%) was induced by a 35% reduction in LDL cholesterol by Simvastatin, in comparison with placebo, in the 4S.<sup>11</sup> The LDL cholesterol reduction seen in the present study, by simvastatin was in accordance with that reported in the previous trials.

The Veterans Affairs High-Density Lipoprotein Intervention trial (VA-HIT)<sup>21</sup> showed that treatment with Gemfibrozil resulted in a significant elevation in HDL cholesterol and a reduction in serum triglyceride levels, with no changes in LDL cholesterol, which coincided with a significant reduction in the coronary artery disease event rate (22%). The changes observed in serum triglyceride and serum HDL cholesterol in our study are similar to that reported in VA-HIT.

It can be concluded from the study that simvastatin is an effective drug to decrease serum cholesterol, serum triglyceride, serum LDL and to increase serum high density lipoprotein cholesterol concentrations. In contrast Gemfibrozil is more effective in decreasing serum triglyceride concentration and to increase serum HDL cholesterol concentration. Moreover duration of therapy has significant effect on lowering the lipid parameters as we have observed gradual changes in all lipid parameters with both simvastatin 20 mg once daily and gemfibrozil 600 mg twice daily on week 6 and week 12.

None of these drugs had any adverse effect on blood glucose levels and therefore can be given as monotherapy in type 2 diabetic patients with abnormal lipid profile.

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