

# Effect of statins and fibrates on plasma creatine phosphokinase in Mexican patients with hypercholesterolemia

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## ABSTRACT

Combination therapy to treat dyslipidemia has become popular in patients with coronary heart disease; however, it can also increase the risk of serious adverse effects, like myalgias and rhabdomyolysis. We analyzed the characteristics of 527 Mexican patients with hypercholesterolemia to assess the effect of statins and fibrates on plasma creatine phosphokinase (CPK) after three months of treatment. Atorvastatine, pravastatin and rosuvastatin showed a statistically significant difference in CPK ( $p < 0.05$ ). Four patients (0.75%) had moderate and transitory up to 3 times the CPK upper limit range, all of them referring myalgias. Although statins and fibrates treatments are safe, monitoring CPK plasma levels during treatment is still advisable.

**Key words:** Creatine phosphokinase, statins, fibrates, hypercholesterolemia.

## RESUMEN

La terapia de combinación para el tratamiento de la dislipidemia ha sido habitual en pacientes con enfermedad coronaria. Sin embargo, también puede aumentar el riesgo de efectos adversos graves, como las mialgias y la rabdomiólisis. En este estudio analizamos las características de 527 pacientes mexicanos con hipercolesterolemia para evaluar los efectos de las estatinas y fibratos en la actividad plasmática de creatina fosfoquinasa (CPK) después de tres meses de tratamiento. Atorvastatina, pravastatina y rosuvastatina mostraron una diferencia estadísticamente significativa en niveles de CPK ( $p < 0.05$ ). Cuatro pacientes (0.75%) presentaron de manera moderada y transitoria niveles de CPK de hasta 3 veces el límite superior, los pacientes refirieron mialgias. Aunque los tratamientos con estatinas y fibratos son seguros, vigilar los niveles en plasma de CPK durante el tratamiento sigue siendo recomendable.

**Palabras clave:** Creatina fosfoquinasa, estatinas, fibratos, hipercolesterolemia.

## INTRODUCTION

Coronary heart disease is one of the most frequent causes of mortality in the western world.<sup>1</sup> The non symptomatic form of the disease is even more prevalent.<sup>2</sup> Several clinical studies have shown that a decrease in serum cholesterol concentration helps to

avoid the onset of clinical manifestations and retard the progress of arteriosclerosis, decreasing the total mortality rate.<sup>3,4</sup>

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) play a prominent role in the treatment of dyslipidemia. Overall, statins are well tolerated, with a low occurrence of adverse ef-

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fects. However, serious reactions to statins have been reported, although they are rare (e.g., rhabdomyolysis 0.3-13.5 cases/million statin prescriptions). The concomitant use of statins with other lipid-lowering drugs like fibrates is recommended as an alternative treatment of severe dyslipidemias or in patients not responding to statin treatment alone; however, this could also increase the risk of serious adverse effects.<sup>5</sup> Statins have also been associated with another form of muscular disease, a non-inflammatory myopathy, where increased activity of serum creatine phosphokinase (CPK) has been reported without evidence of rhabdomyolysis or muscle inflammation.<sup>6-10</sup> Others researchers have described patients who had statins associated myopathy with normal CPK.<sup>11-13</sup> Rhabdomyolysis is characterized by marked increase in CPK (>10 times the upper limit of normal), and possible myoglobinemia and myoglobinuria, renal failure and death. Symptoms may include spontaneous myalgias, muscle tenderness, weakness, malaise and fever.<sup>14</sup>

The aim of our study was to investigate the effect of statins and fibrates treatments on plasma CPK in Mexican patients with hypercholesterolemia.

## METHODS

### Subjects and study design

We carry out a clinical trial with 527 Mexican patients with hypercholesterolemia. The informed consent obtained based on the Declaration of Helsinki and Nuremberg code from all subjects included in this study was approved by the Hospital Ethics Committee. This study was carried out in patients participating in the program called PROCCAM from the "Hospital Regional de Petróleos Mexicanos" located in Ciudad Madero, Tamaulipas, Mexico. Patients in this program were first treated with exercise and diets, if those measures were ineffective, treatment based on lipid-lowering drugs was indicated.

All patients treated with statins or fibrates for over three months for dyslipidemia management were included, and registered under the international disease codes (ICD) E780, E781 and E782 for hypercholesterolemia, hypertriglyceridemia and mixed hyperlipidemia, respectively.<sup>15</sup>

Data collected on these patients included: name, age, gender, associated pathologies, statins and fibrates administered in combination with other drugs and their adverse effects. Presence of symptoms for myopathy was also considered.

### Blood sampling and biochemical analysis

Blood samples were taken at 7:00 am from patients with hypercholesterolemia in conditions of fasting for 14 h and a diet monitored by three day to measure plasma CPK baseline before and after treatment with lipid-lowering drugs. Blood samples were drawn using vacutainer test tubes without anticoagulant (Becton-Dickinson, Mexico City, Mexico). Samples were allowed to clot and then centrifuged for 15 minutes.

Enzymatic method (Pointe Scientific, Inc. USA) were used to determinate the concentrations of total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) after dextran sulphate precipitation. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation. Triglycerides (TG) were measured by enzymatic method (Pointe Scientific, Inc. USA) with correction for glycerol.<sup>16</sup> CPK, TC, HDL-C and TG were measured in automated equipment SYNCHRON CX9 PRO (Beckman Coulter, California, USA).

In accordance with National Cholesterol Education Program (NCEP) of the United States of America (USA), patients with hypercholesterolemia have values of TC  $\geq$  200 mg/dL, HDL-C  $\leq$  40 mg/dL and LDL-C  $\geq$  160 mg/dL (two qualifying lipid determinations could not differ by more than 15% from each other) and patients with hypertriglyceridemia have values of TG  $\geq$  150 mg/dL. CPK reference upper limit value of 170 IU/L for women and 200 IU/L for men.<sup>16,17</sup>

### Statistical analysis

Descriptive statistics are means  $\pm$  standard deviation (SD) and frequencies and percentages. Paired *t*-test was used to establish if there were statistically significant differences between groups using Statistica software version 6.0. A *p*-value  $<$  0.05 was considered significant.

## RESULTS

A total of 1,465 files of patients diagnosed with dyslipidemia were revised. 527 (36%) were treated with lipid-lowering drugs, while the rest 938 (64%) were managed only with diet and exercise or treated for other concomitant pathologies. The general baseline characteristics of the 527 patients are shown in *table I*, with a mean age of  $61.65 \pm 9.64$  years, formed by 32% women and 68% men.

The most common used lipid-lowering drugs during the treatment were atorvastatin 10 mg/day (35.5%), followed by bezafibrate 200 mg/day (31.1%), rosuvastatin 10 mg/day (9.7%) and pravastatin 10 mg/day (9.1%).

In this study, we have shown that the changes observed in total cholesterol in patients with hypercholesterolemia after three months of treatment with statins were statistically significant,  $285.6 \pm 129.4$  mg/dL vs.  $234.1 \pm 45.8$  mg/dL ( $p < 0.05$ ). With respect to the NCEP of USA recommended goals for LDL cholesterol levels,<sup>17</sup> only 25.6% of the patients reached the goals related to primary prevention and 23.1% for secondary prevention.

Table II shows the mean plasma CPK after three months of treatment with lipid-lowering drugs. When analyzing CPK, using a reference upper limit value of 170 IU/L for women and 200 IU/L for men,<sup>16</sup> the frequency of CPK greater than 200 IU/L was 12.5%, both in women and men. Gender differences analysis revealed a 14.5% rise in women and 13.3% in men ( $p > 0.05$ ). However, significantly high CPK (3 times the upper normal limit) was found only in 0.8% of men and 0.2% of women.

The CPK activity reached with atorvastatin (10 mg/day) treatment was 355, 506, 1,217 IU/L for the three patients respectively, and for simvastatin, (10 mg/day) 522 IU/L in one patient. Of these four patients, three had long-term type 2 diabetes mellitus and chronic renal failure with less than 30% adequate renal function. Additionally, two of the patients had hypothyroidism. In spite of using low doses of atorvastatin, the increase in the CPK to more

than 3 times the normal upper limit caused to discontinue the treatment.

## DISCUSSION

We found out that the CPK mean values were not statistically significant different from the CPK baseline values after three months of treatment with lipid-lowering drugs simvastatin and fibrates ( $p > 0.05$ ). However, atorvastatin, pravastatin and rosuvastatin treated patients showed a statistically significant difference in CPK baseline values ( $p < 0.05$ ). Four patients (0.75%) were found to have myopathy, two of them treated with atorvastatin (10 mg/day), one with simvastatin (10 mg/day) and another with atorvastatin (10 mg/day) and bezafibrate (200 mg/day).

We did not find statistical significant differences in CPK caused by fibrates and statins treatments ( $p > 0.05$ ). We found only significantly high CPK (3 times the normal upper limit) in 0.8% men and 0.2% women. It has been reported that approximately 5% of the patients treated with statins or fibrates have a moderate and transitory up to 3 times the upper limit of CPK.<sup>18-20</sup> Normally; this has no clinical implications, although some patients might develop myositis and rhabdomyolysis.<sup>21,22</sup>

In other studies, the percentage of adverse effects increased to 5% or more when treatment included fibrates, or there were concomitant diseases. Murdock and others assessed the efficacy and safety of combining gemfibrozil with pravastatin, and simvastatin at different dosages. They concluded that the risk of toxicity was very low and it was safe to consider combining the use of both drugs.<sup>23,24</sup>

The four cases of myopathies were treated with a combination of statins and fibrates as well as pa-

**Table I.** Baseline characteristics of the patients.

Characteristic	Value
Gender	
Female (%)	32
Male (%)	68
Age (years)	$61.65 \pm 9.64$
Creatine phosphokinase (IU/L)	$101.4 \pm 57.7$
Total cholesterol (mg/dL)	$285.6 \pm 129.47$
Triglycerides (mg/dL)	$368.6 \pm 367.9$
Hypercholesterolemia (%)	29.24
Hypertriglyceridemia (%)	25.64
Mixed hyperlipidemia (%)	45.12
Hypothyroidism (%)	13.79
Type 2 diabetes mellitus (%)	57.47
Hypertension (%)	59.77
Cardiopathy (%)	31.03
Chronic renal failure (%)	18.39

**Table II.** CPK activity after three months of statins and fibrates treatment.

Treatment	CPK (UI/L)	<i>p</i>
Statins		
Pravastatin 10 mg/day	$120.96 \pm 56.33$	< 0.05
Simvastatin 10 mg/day	$102.43 \pm 60.61$	> 0.05
Simvastatin 40 mg/day	$105.93 \pm 65.76$	> 0.05
Atorvastatin 10 mg/day	$127.22 \pm 152.85$	< 0.05
Rosuvastatin 10 mg/day	$132.27 \pm 84.20$	< 0.05
Fibrates		
Bezafibrate 200 mg/day	$134.18 \pm 219.88$	> 0.05
Bezafibrate 400 mg/day	$147.89 \pm 77.75$	> 0.05
Ciprofibrate 100 mg/day	$183.43 \pm 176.00$	> 0.05

tients having one or more risk diseases such as type 2 diabetes mellitus, chronic renal failure or hypothyroidism. Two patients became asymptomatic after the withdrawal of the drug although CPK remained elevated; this situation has been reported in patients with hypothyroidism.<sup>6</sup>

Finally, with respect to the recommended goals for NCEP regarding LDL-C, only 25.6% and 23.07% of the patients in primary and secondary prevention achieved the goals, unlike other data reported, for example, Jones et al, compared rosuvastatin with other lipid-lowering agents and obtained that Adult Treatment Panel III LDL-C goals were achieved by 82% of patients treated with rosuvastatin 10 mg compared with 69% of patients treated with atorvastatin 10 mg.<sup>25</sup>

The studies 4S, COMPELL, POLARIS and STELLAR provide evidence that the use of hypolipidemic drugs, including statins, decrease cardiovascular events, including death. In these studies, women had a greater decrease of coronary events in comparison to men with the use of statins, finding that more women than men were given statins and fibrates.<sup>25-29</sup> In our study, we found this percentage greater for men (68.3%) than for women (37.1%).

Statins and fibrate have been shown to reduce LDL-C levels in patients with hypercholesterolemia. In this study, our population after three months of treatment did not show clinically relevant increase in plasma CPK during treatment with statins and fibrate. The muscle-related side effects reported with lipid-lowering drugs were rare (0.75%) to the lowest effective dose with appropriate monitoring of symptoms and CPK activity. However, plasma CPK should be measured frequently to assess muscle damage during treatment. Additionally, minor muscle complains without elevated CPK might not need to stop drug intake.

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