ORIGINAL ARTICLE

Effects of bisphosphonates on lipid metabolism

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Abstract

OBJECTIVES: Bisphosphonates are widely used for the treatment of metabolic bone disorders and their effects on lipid metabolism have also been investigated. Some studies reported that bisphosphonates have beneficial effects on serum cholesterol levels. In this study we aimed to assess the effects of bisphosphonates on lipid levels in hyperlipidemic patients who received bisphosphonates because of osteoporosis.

METHODS: 49 female patients (age: 54.2 ± 7.2 years) with diagnosis of osteoporosis and hyperlipidemia were enrolled. Patients received alendronate 10 mg/day and they were followed up for 6 months. Pretreatment total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1 and apolipoprotein B levels were measured and compared with post-treatment levels.

RESULTS: Pretreatment and post-treatment levels of total cholesterol were 255.2 ± 34.3; 233.02 ± 37.0 mg/dL, triglyceride levels were 153.0 ± 57.3; 129.1 ± 54.4 mg/dL, and LDL levels were 170.7 ± 30.5; 160.0 ± 34.2 mg/dL, respectively. Reductions in total cholesterol, triglyceride and LDL-cholesterol levels were statistically significant; whereas differences in HDL-cholesterol, apolipoprotein-A1 and apolipoprotein-B levels were not significant.

CONCLUSIONS: Data from our study suggest that alendronate therapy may have beneficial effects on lipid metabolism. Thus, when hyperlipidemia is detected in patients receiving bisphosphonates, it is considered reasonable to follow the patient for a while before initiating antihyperlipidemic agent to prevent unnecessary use of drugs.

INTRODUCTION

Bisphosphonates are widely used for the treatment of metabolic bone disorders and especially osteoporosis due to their inhibitory effects on bone resorption (Delmas and Meunier 1997; Liberman *et al*. 1995; Ringe *et al*. 2002; Vasikaran *et al*. 2001). Bisphosphonates are pyrophosphate analogues in which the oxygen bridge has been replaced by a carbon with various side chains (Rodan and Fleisch 1996). While it is recognized that their target site of action are bone cells, other effects of these drugs apart from bone metabolism have also been investigated (Sato *et al.* 1991). Although their precise mechanism of action is unknown, studies showed that bisphosphonates inhibit squalen syn-

Table 1: Pre-treatment and post-treatment plasma levels of lipid parameters.

	BEFORE TREATMENT	AFTER TREATMENT	P
Total Cholesterol (mg/dL)	255.2 ± 34.3	233.02 ± 37.0	<0.005
Triglyceride (mg/dL)	153.0 ± 57.3	129.1 ± 54.4	<0.05
HDL-Cholesterol (mg/dL)	53.9 ± 11.6	53.2 ± 10.7	>0.05
LDL-Cholesterol (mg/dL)	170.7 ± 30.5	160.0 ± 34.2	<0.05
Apolipoprotein-A1 (mg/dL)	146.3 ± 24.6	144.9 ± 21.3	>0.05
Apolipoprotein-B (mg/dL)	124.2 ± 13.0	122.8 ± 17.0	>0.05

thase and cholesterol biosynthesis (Amin *et al.* 1992). On the basis of these data concerning metabolic effects of bisphosphonates, their effects on lipid metabolism have been started to be investigated with more interest. Some studies reported that bisphosphonates have remarkable and unexpected effects on serum cholesterol levels (Adami *et al.* 2000). It was also demonstrated that squalen synthase inhibitors reduce plasma triglyceride levels through an LDL receptor-independent mechanism (Hiyoshi *et al.* 2001). However, another study was reported that bisphosphonates have no effect on serum cholesterol levels (Frolik *et al.* 1996).

According to these data about the mechanism of action of bisphosphonates, their effects on lipid metabolism have attracted more attention; however few studies assessing their effects on serum cholesterol and triglyceride levels have been published and relevant data are conflicting. In this study, we aimed to assess the effects of bisphosphonates on lipid metabolism and serum cholesterol and triglyceride levels.

MATERIALS AND METHODS

Study Design

Forty-nine female patients (mean age: 54.2 ± 7.2 years) who visited an outpatient osteoporosis clinic were enrolled. Inclusion criteria were, diagnosis of osteoporosis by bone mineral density measurement (T-score: < –2.5) and decision to initiate bisphosphonates and also detection of hyperlipidemia by biochemical analyses. Patients who received bisphosphonate or a drug that affect lipid metabolism during past 6 months were excluded. After patients were informed, diet for hyperlipidemia was planned and patients were monitored for 2 months. Then, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1 and apolipoprotein B levels of patients were measured and bisphosphonate therapy was initiated with continuing the diet.

Patients used alendronate 10 mg/day for their osteoporosis and they were followed up for 6 months. Total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1 and apolipoprotein B levels were measured again after treatment and compared with pretreatment levels. Statistical analysis was performed with SPSS 14.0 program by using Student's T test.

Bone mass measurements

Bone mineral density were measured at the anteroposterior spine (L1–L4) and at the hip (femoral neck, trochanter, intertrochanter region, Ward's triangle, and total hip) using dual-energy x-ray absorptiometry on a Hologic model 4500 C (Hologic Inc., Waltham, MA).

Blood samples

Blood samples was obtained from the antecubital vein. The blood samples were centrifuged immediately at 3000 rpm 10 min +4°C. Total cholesterol, HDL-cholesterol, and trigliserid were determined with Architect C 8000 (Abbott, USA) using commercial Abbott kits (cat no: 7B62-20, 3K33-20, 7D74-20, respectively). LDL-cholesterol were calculated using total cholesterol, HDL-cholesterol and VLDL values, automatically. Apolipoprotein A1 and apolipoprotein B levels were measured by immunoturbidimetry.

RESULTS

Pre-treatment levels of plasma lipids were: total cholesterol: 255.2 ± 34.3 mg/dL, triglyceride: 153.0 ± 57.3 mg/dL, HDL-cholesterol: 53.9 ± 11.6 mg/dL, LDL-cholesterol: 170.7 ± 30.5 mg/dL, apolipoprotein-A1: 146.3 ± 24.6 mg/dl and apolipoprotein-B: 124.2 ± 13.0 mg/dl. Post-treatment levels were found that total cholesterol: 233.02 ± 37.0 mg/dL, triglyceride: 129.1 ± 54.4 mg/dL, HDL-cholesterol: 53.2 ± 10.7 mg/dL, LDL-cholesterol: 160.0 ± 34.2 mg/dL, apolipoprotein-A1: 144.9 ± 21.3 mg/dL and apolipoprotein-B: 122.8 ± 17.0 mg/dL. Statistically significant decreases in plasma total cholesterol ($p<0.005$), triglyceride ($p<0.05$) and LDL-cholesterol ($p<0.05$) levels were found. However, there is no significant difference in plasma HDL-cholesterol, apolipoprotein-A1 and apolipoprotein-B levels ($p>0.05$) [Table 1].

DISCUSSION

Bisphosphonates are potent inhibitors of bone resorption used for the treatment and prevention of metabolic bone disorders and the mechanism of effects of these drugs were studied widely. Several studies showed that bisphosphonates inhibit mevalonate pathway in osteoclasts (Reszka *et al.* 2001; Suri *et al.* 2001). Other effects

of these drugs apart from bone metabolism have also paid attention; one of these effects is related to lipid metabolism. Some experimental studies demonstrated that bisphosphonates inhibit the squalen synthase enzyme and cholesterol biosynthesis (Ciosek *et al.* 1993; Magnin *et al.* 1995; Risser *et al*. 1997). It was shown that squalen synthase plays an important role in cholesterol biosynthetic pathway and studies on squalene synthase inhibitors to treat hyperlipidemia are ongoing (Hiyoshi *et al*. 2000). Recent studies reported that bisphosphonates exert their effects by inhibiting farnesyl phosphate synthase, an enzyme which is involved in cholesterol synthesis (Bergstrom *et al.* 2000; Dunford *et al.* 2001; Rodan and Reszka 2002). It was also shown that these effects are related with bisphosphonates having nitrogen in their structures (so called aminobisphosphonates), and bisphosphonates lacking an amino group (such as etidronate and clodronate) did not affect sterol biosynthesis (Adami *et al.* 2000; Rodan and Reszka 2002). However, although etidronate did not affect lipid levels, it was shown that this drug can regress atherosclerosis and reduce plaque thickness (Zhu *et al.* 1994).

Few clinical studies were done on the basis of these data. Adami et al. reported a decrease in serum total cholesterol, triglyceride, LDL-cholesterol and apolipoprotein-B levels and an increase in HDL-cholesterol and apolipoprotein-A1 levels in patients receiving bisphosphonates (Adami *et al.* 2000). Another study reported an increase in lipoprotein(a) levels and a decrease in apolipoprotein-A1 and apolipoprotein-B levels (Lippi *et al.* 1998). In contrast with these findings, some studies suggesting no effect of bisphosphonates on lipids were published. A study by Frolik et al. has compared the effects of different treatments and it was shown that estrogen and selective estrogen receptor modulators (SERMs) decreased serum cholesterol levels, but alendronate had no effect on cholesterol levels (Frolik *et al.* 1996). Also another study showed that clodronate did not influence cholesterol concentrations in plasma (Ylitalo *et al.* 1994).

In our study we aimed to evaluate lipid parameters in hyperlipidemic patients using alendronate and to assess effects of bisphosphonates on serum lipid levels. After a 6-month treatment period, statistically significant decrease was found in serum total cholesterol, triglyceride and LDL-cholesterol levels. However any significant change was observed in HDL-cholesterol, apolipoprotein-A1 and apolipoprotein-B levels. Although discordant results were reported in studies evaluating these effects, there are many results suggesting that bisphosphonates have effect on lipid metabolism. Despite inadequate knowledge about the mechanism of action, it was demonstrated that bisphosphonates affect cholesterol biosynthesis. The recent elucidation of bisphosphonate action at the cellular level on the mevalonate pathway has led to interest in its effects on lipoprotein metabolism, which may prove to be of clinical significance of these drugs (Vasikaran 2001). Data from our study suggest that alendronate therapy has beneficial effects on lipid metabolism. However, as relevant data are insufficient, further studies are needed to clarify these issues.

In conclusion, while administration of these drugs for the treatment of hyperlipidemia is not considered, they may have useful effects on hyperlipidemia in patients with metabolic bone disorders. Thus, when hyperlipidemia is detected in patients using bisphosphonates, it is considered reasonable to follow the patient for a while before initiating antihyperlipidemic agent to prevent unnecessary use of drugs. And also, these results may be useful to choice of the drug for osteoporosis treatment when there is accompanying hyperlipidemia.

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