

Received: 2015.05.20
Accepted: 2016.01.06
Published: 2016.03.13

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 160-164
DOI: 10.12659/AJCR.894712

Successful Improvement of Metabolic Disorders, Including Osteopenia, by a Dopamine Agonist in a Male Patient with Macro-Prolactinoma

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 43
Final Diagnosis: Prolactinoma
Symptoms: —
Medication: —
Clinical Procedure: Treatments by a dopamine agonist
Specialty: Endocrinology and Metabolic

Objective: Unknown etiology





Background: Bone metabolic disorders in patients with prolactinoma have not been fully characterized. The case presented herein illustrates potential causal associations between prolactinoma and osteopenia, with a reversal of the disorder by treatment with a dopamine agonist.

Case Report: A 43-year-old male with macro-prolactinoma [PRL 7770 ng/mL] was referred to our hospital. He suffered was overweight [body mass index (BMI) 29.4 kg/m²] and had impaired glucose tolerance, hypertriglyceridemia, and osteopenia. The patient was administered cabergoline, a dopamine D2 receptor agonist, and the dose was gradually increased up to 9 mg/week over the period of 1 year. One year later, the patient's serum PRL levels decreased to within the normal range (19.1 ng/mL), and his pituitary tumor mass decreased to 1/4 of its initial size. His weight, dyslipidemia, and impaired glucose tolerance improved within 1 year. A marked increase in the bone mineral density (BMD) at the second to fourth lumbar spine (from 0.801 g/cm² to 0.870 g/cm², +8.6%) and at the femoral neck (from 0.785 g/cm² to 0.864 g/cm², +10.1%) were observed despite the presence of unresolved hypogonadism.

Conclusions: Treatments with dopamine agonists represent a beneficial strategy for patients with prolactinoma accompanied with bone loss, in addition to their established efficacy in shrinkage of the size of pituitary tumors, normalization of PRL levels, and improvement of metabolic disorders.

MeSH Keywords: Bone Diseases, Metabolic • Dopamine • Dyslipidemias • Glucose Intolerance • Obesity • Prolactin

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/894712>

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Background

Recent studies have shown that prolactinoma is associated with metabolic disorders, such as obesity, dyslipidemia, and glucose intolerance [1–4], and that these metabolic disorders are improved by treatment with dopamine agonists [1,4]. Patients with prolactinoma, particularly male patients, have a high prevalence of osteoporosis or osteopenia compared to patients without prolactinoma [5]. However, bone metabolism in these patients has not been fully characterized. We report a patient diagnosed with macro-prolactinoma accompanied with

osteopenia in addition to known metabolic disorders, including dyslipidemia, hyperglycemia, and being overweight, which were successfully improved by treatment with a dopamine agonist.

Case Report

A 43-year-old male patient with a large pituitary tumor was referred to our hospital. He suffered from headaches for 6 months. Magnetic resonance imaging (MRI) of his head was performed, which revealed an enlarged pituitary gland with a

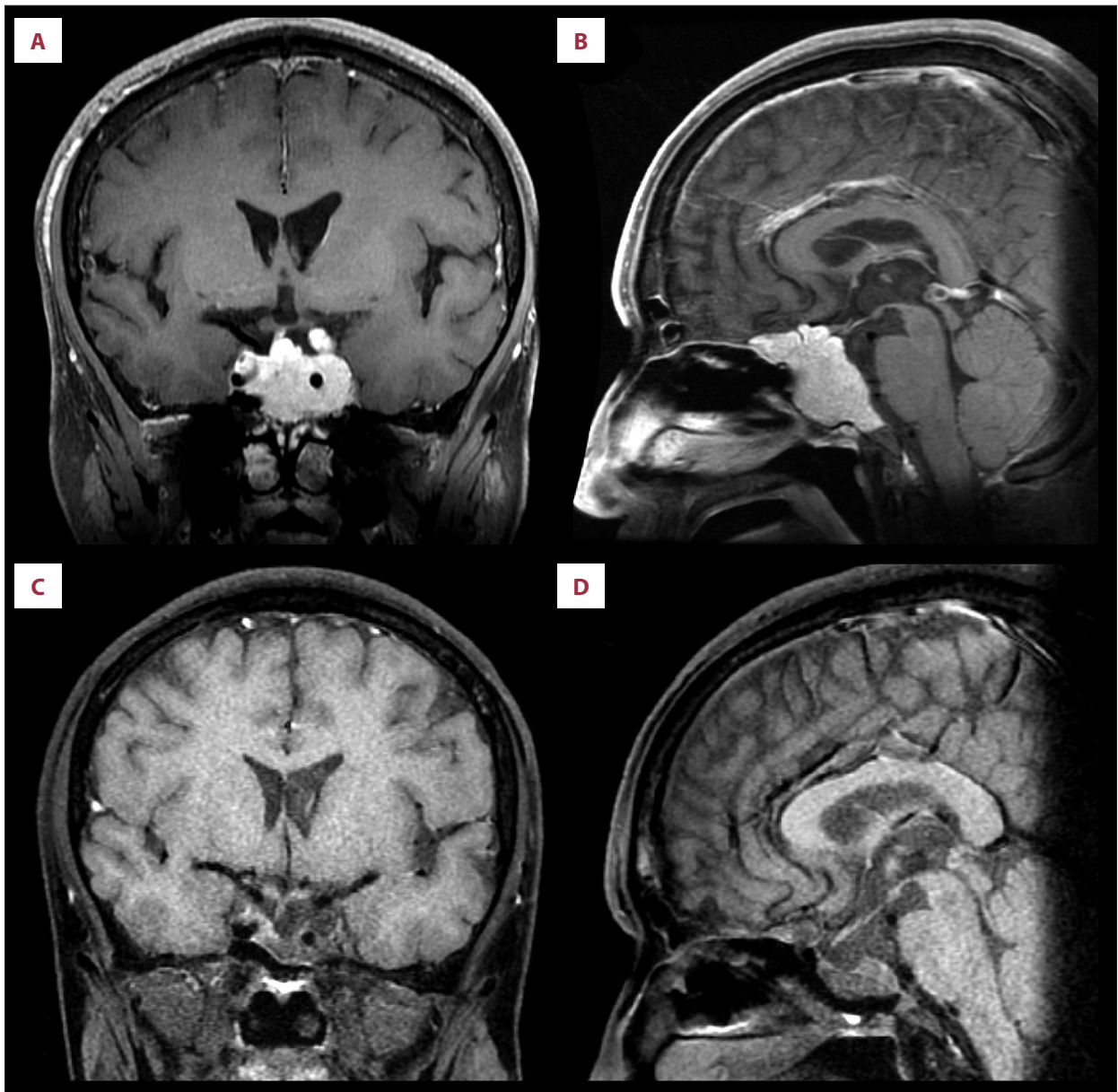


Figure 1. Gadolinium-enhanced magnetic resonance imaging. (A, B) Before cabergoline treatment, a large pituitary tumor invades the cavernous sinus and surrounds internal carotid arteries (Lt.>Rt.). (C, D) After 1 year of cabergoline treatment, the pituitary tumor decreased to one-quarter of its initial size.

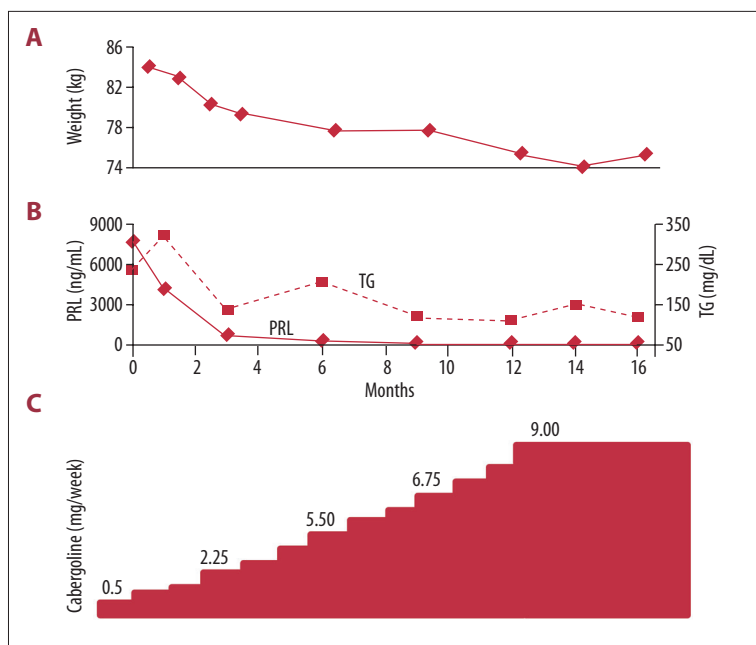


Figure 2. Body weight (A), PRL, and TG (B), and cabergoline dosage (C) throughout our follow-up period.

mass invading the cavernous sinus and engulfing the internal carotid arteries (Figure 1A, 1B). He had no family history of pancreatic tumor, pituitary tumor, or urolithiasis considered as type 1 multiple endocrine neoplasias (MEN). He had discontinued therapy for dyslipidemia, which had been diagnosed at 35 years of age, and had undergone a cholecystectomy due to cholelithiasis at 40 years of age. Physical examination showed no signs of galactorrhea or visual field defects, with the exception of the patient being overweight (BMI: 29.4 kg/m²).

His blood screen test showed dyslipidemia [triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C): 236 mg/dL and 190 mg/dL, respectively] and prominent hyperprolactinemia (PRL 7770 ng/mL). The decreased basal levels and diminished peak values of LH and FSH after a loading test of luteinizing hormone-releasing hormone (LHRH), concomitant with a low free testosterone level (4.0 ng/mL), indicated that he had been affected by hypogonadotropic hypogonadism [basal levels: LH 0.9 mIU/mL, FSH 1.8 mIU/mL; peak levels: LH 10.6 mIU/mL at 30 min, FSH 3.1 mIU/mL at 90 min]. His osteopenia was diagnosed based on decreased BMD of the second to fourth lumbar spine (L2–4) and the femoral neck (FN) (T-score: –2.1 SD and –0.6 SD, respectively). An oral glucose tolerance test (OGTT) confirmed impaired glucose tolerance with a 120 min glucose level of 213 mg/dL. However, HbA1c was normal (5.2%). According to these clinical findings, he was diagnosed with macroprolactinoma, hypogonadotropic hypogonadism, osteopenia, dyslipidemia, and impaired glucose tolerance.

The dopamine agonist cabergoline was administered at an initial dose of 0.5 mg/week and then increased 0.75 mg/week every month, up to 9 mg/week over the period of a year. It has

been reported that cavernous sinus invasion and male sex were associated with dopamine agonist-resistance [6], suggesting that our patient, with markedly high PRL level and large tumor, could be resistant to treatments with dopamine agonists, and his PRL level seemed not to be normalized by the usual doses of cabergoline. Ono et al. have shown that high-dose cabergoline treatment of prolactinoma (the highest dose; 12 mg/week) is effective in poor responders [7]. Therefore, we treated our patient with these high doses of cabergoline. No adverse effects of cabergoline, such as nausea or appetite loss, were observed. One year later, his serum PRL levels decreased to within the normal range (19.1 ng/mL) (Figure 2), and the size of the pituitary tumor decreased to one-quarter of its initial size (Figure 1C, 1D). His serum TG levels gradually improved after administration of a low dose of cabergoline (Figure 2). His free testosterone level (6.2 ng/mL) and peak LH and FSH concentrations after LHRH loading (10.2 mIU/mL at 30 min and 7.6 mIU/mL at 90 min) after 1 year of treatment with cabergoline indicated that his hypogonadotropic hypogonadism had not sufficiently improved. However, his BMD values were markedly increased at L2–4 (from 0.801 g/cm² to 0.870 g/cm², +8.6%) and at the femoral neck (from 0.785 g/cm² to 0.864 g/cm², +10.1%) (Figure 3A), accompanied with an increase in bone turnover markers (bone alkaline phosphatase (BAP): 53.6 to 74.2 µg/L; urinary NTX 38.5 to 56.3 nMBCE/mMcr) (Figure 3B). His body weight decreased from 84.0 kg to 74.1 kg over the year (Figure 2). His glucose level after 75-g OGTT at 120 min was improved (129 mg/dL), and the hyperinsulinemia was also ameliorated (Figure 4). Three years later, the BMD at L2-4 and the femoral neck only slightly increased (0.881 g/cm² and 0.855 g/cm², respectively), while bone turnover markers decreased to near-normal levels (BAP: 23.5 µg/L; urinary NTX 42.3 nMBCE/mMcr),

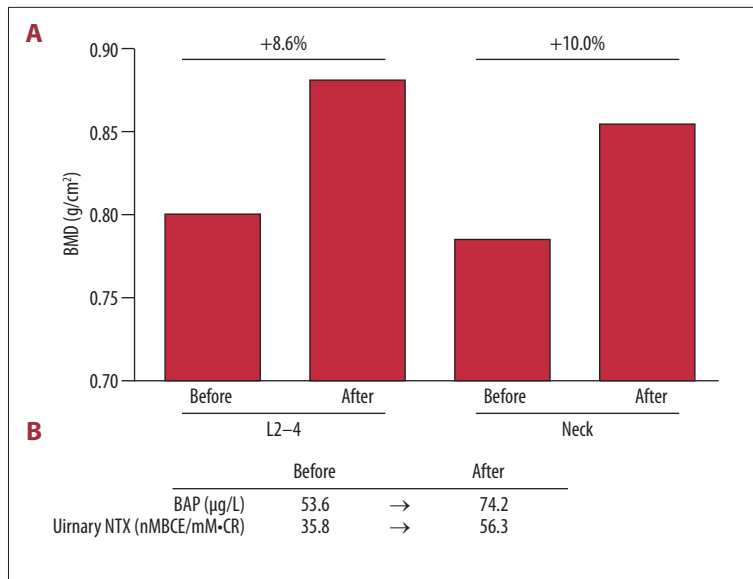


Figure 3. (A) Lumbar spine and femoral neck BMD scores in bars, at baseline, and at end of 1-year treatment with cabergoline. (B) Bone turnover indices at baseline versus at end of 1-year treatment with cabergoline

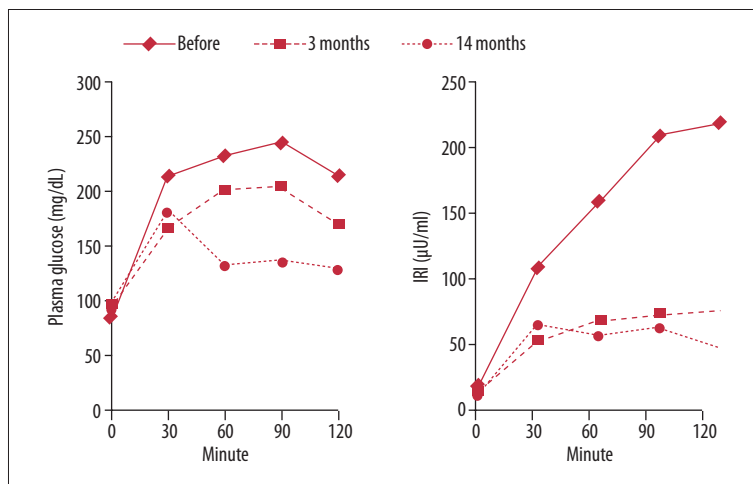


Figure 4. OGTT indices. Plasma glucose and insulin levels. Solid lines indicate pre-Cabergoline treatment. Broken lines indicate after 3 months. Dotted lines indicate after 14 months of Cabergoline.

and the free testosterone level recovered to within the reference range (8.6 ng/mL).

Discussion

As previous studies have demonstrated, our patient had metabolic disorders, i.e., dyslipidemia, glucose intolerance, and being classified as overweight [1–4], which were markedly improved with cabergoline treatment [4]. A notable finding in this case was a marked increase in BMD after treatment with a dopamine agonist. To the best of our knowledge, this is the first case report of reversed osteopenia in a patient with prolactinoma who was treated with cabergoline.

Hypogonadotropic hypogonadism is a well-known complication in patients with hyperprolactinemia and causes increased bone turnover compared to subjects without prolactinoma [8].

Men with prolactinoma have a high prevalence of osteopenia and osteoporosis, as determined by bone mineral density [5], and this bone loss in patients with prolactinoma is primarily caused by hypogonadism [5]. However, our case showed that 1-year treatment with a dopamine agonist markedly increased BMD, without a matching and correspondent reversal of hypogonadism. This observation demonstrates that hypogonadism was not a dominant cause of decreased BMD in our patient. Several *in vitro* studies have shown that osteoblasts express PRL receptor [9] and that PRL administration suppresses mRNA levels of Runt-related transcription factor 2 (Runx2), a key transcriptional factor for osteoblastic differentiation [10], alkaline phosphatase activity [11], and osteocalcin mRNA expression [11]. These findings suggest that PRL may directly deteriorate bone formation via inhibition of proliferation and differentiation of osteoblasts. Furthermore, PRL promotes mRNA expression of osteoclast differentiating factors, including receptor activator of nuclear factor- κ B ligand

(RANKL), and inhibits osteoclastogenesis inhibitory factors, such as osteoprotegerin [11], which acts as a decoy receptor for RANKL. These reports imply that PRL indirectly promotes bone resorption through osteoblast-derived factors. Mice that are homozygous for a deletion of dopamine transporters exhibit decreased bone mass and deteriorated bone strength compared to wild-type animals [12]. Mutant mice deficient of dopamine β -hydroxylase, which converts dopamine to epinephrine or norepinephrine, had increased BMD [13], which may indicate that dopamine enhances osteogenesis. In our case, treatment with a dopamine agonist improved bone mineral density concomitant with increased BAP and urinary NTX levels, suggesting that treatment with a dopamine agonist primarily accelerates bone formation by decreasing PRL levels. In a tentatively similar manner to that observed in mice [11], cabergoline might contribute to this bone density increase.

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Conclusions

The generally overlooked bone metabolic disorders, as well as the classical characteristics of prolactinoma, were remarkably reversed by treatments with dopamine agonists. *In vitro* studies have demonstrated that prolactin and dopamine affect bone metabolism. These observations suggest that dopamine agonists might also favorably affect bone loss in patients with prolactinoma.

Conflict of Interest

None.