Parathyroid Hormone (1–34) Improves Bone Mineral Density and Glucose Metabolism in Spontaneously Diabetic Torii-Leprfa Rats

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(Received 10 July 2011/Accepted 11 August 2011/Published online in J-STAGE 25 August 2011)

ABSTRACT. The Spontaneously Diabetic Torii-Leprfa (SDT-fa/fa) rat, a model of obese type 2 diabetes, shows obesity, hyperglycaemia and low bone mineral density (BMD). The objective of this study was to evaluate the effects of parathyroid hormone (1–34) [PTH(1–34)] on BMD and glucose metabolism in the SDT-fa/fa rat. SDT-fa/fa rats showed obesity with hyperglycaemia and decreased serum osteocalcin levels and the tibial BMD. A 4-week treatment of PTH(1–34) (20 μg/kg/day) increased the serum osteocalcin levels and the tibial BMD, and decreased the serum glucose levels without changing the serum insulin levels. These findings indicate that PTH(1–34) improved not only BMD but also glucose metabolism in SDT-fa/fa rats. This study suggests that PTH(1–34) is a novel agent for the treatment of diabetic osteoporosis.

KEY WORDS: bone mineral density, glucose metabolism, obese type 2 diabetes mellitus, osteocalcin, parathyroid hormone.


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Hyperglycaemia is a negative factor for bone metabolism and causes osteoblast dysfunction. Diabetic model animals show low bone turnover and decreases in both bone mass and bone strength [11]. In humans, patients with diabetes mellitus show low bone turnover and have a high risk of hip fracture [3]. Parathyroid hormone (PTH) is an attractive agent for the treatment of osteoporosis. Intermittent PTH injections stimulate new bone formation and remarkably increase bone mass in animals. In a study on humans, recombinant human PTH(1–34) increased bone turnover and bone mineral density (BMD), and decreased the risk of vertebral and nonvertebral fractures in postmenopausal osteoporosis [7]. As a diabetic animal model, PTH(1–34) improved bone formation, BMD and bone strength in streptozotocin-induced type 1 diabetic rats [10]. However, the effects of PTH(1–34) on bone in type 2 diabetes have not been reported in animals or humans. The Spontaneously Diabetic Torii-Leprfa (SDT-fa/fa) rat is well known as a model of obese type 2 diabetes, and the rats eventually develop obesity, hyperglycaemia, hyperlipidaemia and diabetes-associated complications such as osteoporosis [4, 6]. The objective of the present study was to investigate the effects of PTH(1–34) on BMD and glucose metabolism in the SDT-fa/fa rat.

Male 8-week-old SDT-fa/fa rats from our colonies were used. Age-matched male Sprague-Dawley rats (Charles River Laboratories Japan, Yokohama, Japan) were used as control animals. All animal procedures and protocols complied with the guidelines for animal experimentation set by the Ethics Committee for Animal Use at Japan Tobacco Inc. The rats were maintained at 23 ± 3°C on a 12-hr/12-hr light-dark cycle with ad libitum access to a standard diet (CRF-1; Oriental Yeast, Tokyo, Japan) and water. The rats were injected subcutaneously with either vehicle (0.1% bovine serum albumin solution) or human PTH(1–34) (Peptide Institute, Osaka, Japan) (20 μg/kg/day) dissolved in vehicle once daily for 4 weeks.

Blood samples were collected from the tail vein. Serum glucose, insulin and osteocalcin levels were measured using commercial kits [4]. The BMD of the whole right tibia was measured using quantitative computed tomography (QCT) [4].

All data are presented as means ± SE. Differences among the groups were tested by the following method. Bartlett’s homogeneity of variance test was performed, followed by Tukey’s multiple comparison test for data with equal variances and the Steel-Dwass multiple comparison test for data with unequal variances. Differences were considered significant for values of P<0.05 (two-sided).

To evaluate the effects of PTH(1–34) on bone formation in SDT-fa/fa rats, serum osteocalcin, a bone formation marker, was measured. The serum osteocalcin levels were significantly decreased in SDT-fa/fa rats compared with control rats (Fig. 1A). PTH(1–34) significantly increased the serum osteocalcin levels (SDT-fa/fa, 25.6 ± 2.8 ng/ml vs. SDT-fa/fa+PTH(1–34), 38.3 ± 2.2 ng/ml). The tibial BMD was measured by QCT. The BMD was significantly decreased in SDT-fa/fa rats compared with control rats (Fig. 1B). PTH(1–34) significantly increased the BMD in SDT-fa/fa rats compared with control rats (SDT-fa/fa, 532 ± 4
mg/cm³ vs. SDT-fa/fa+PTH(1–34), 593 ± 8 mg/cm³).

The body weight and serum glucose levels were significantly increased in SDT-fa/fa rats compared with control rats (Fig. 2A and 2B). In addition, the serum insulin levels were slightly increased in SDT-fa/fa rats compared with control rats (Fig. 2C). PTH(1–34) significantly decreased the serum glucose levels (SDT-fa/fa, 852 ± 29 mg/dl vs. SDT-fa/fa+PTH(1–34), 753 ± 18 mg/dl), but had no effects on the body weight and serum insulin levels.

In this study, we evaluated the effects of PTH(1–34) on BMD and glucose metabolism in SDT-fa/fa rats. Treatment with PTH was reported to strongly increase BMD in patients with postmenopausal osteoporosis [7] and glucocorticoid-induced osteoporosis [9]. However, the effects of PTH on BMD in patients with diabetes mellitus have not been reported. This study demonstrated that PTH(1–34) remarkably increased the tibial BMD in SDT-fa/fa rats. Similarly, PTH(1–34) increased the BMD and bone strength in type 1 diabetic rats [10]. Based on these data, PTH may be a promising agent for preventing bone fractures in patients with diabetes mellitus.

PTH stimulates bone formation, thereby leading to increased bone mass. In this study, we confirmed that PTH(1–34) stimulated bone formation by measuring the serum osteocalcin levels. Recently, osteocalcin has been suggested as a novel regulator of glucose metabolism. Lee
et al. [5] described that osteocalcin-knockout mice showed hyperglycaemia and hypoinsulinaemia. Osteocalcin has three glutamic acid residues that undergo post-translational modification by gamma-carboxylation. Undercarboxylated osteocalcin has less than three carboxylated residues. In rodent studies, undercarboxylated osteocalcin decreased the blood glucose levels, and increased the serum insulin levels and insulin sensitivity in the pancreas [1]. In addition, treatment with undercarboxylated osteocalcin decreased the blood glucose levels in type 2 diabetic mice [2]. In humans, it was reported that lower levels of carboxylated osteocalcin predicted an increase in insulin resistance [8]. From these data, it is suggested that an osteocalcin inducer has the potential to be an agent for the treatment of diabetes mellitus. It is well known that PTH increases the blood osteocalcin levels in animals and humans. This study demonstrated that PTH(1–34) decreased the serum glucose levels with an increase in serum osteocalcin, a carboxylated osteocalcin, in SDT- fa/ fa rats. Therefore, it is suggested that PTH will improve glucose metabolism in diabetes mellitus. Furthermore, since PTH(1–34) did not affect the serum insulin levels in SDT- fa/ fa rats, it is speculated that the improving effect of PTH(1–34) on glucose metabolism is caused by a decrease in insulin resistance.

This study is the first to evaluate the effects of PTH(1–34) on bone mass and glucose metabolism using SDT- fa/ fa rats. Considering our results, PTH(1–34) improves not only BMD but also glucose metabolism in diabetes mellitus and has the potential to be a novel agent for the treatment of diabetic osteoporosis.

REFERENCES