4. The Pathophysiology and Etiology of Diabetic Osteopenia

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Diabetic osteopenia is recognized as one of the major complications of diabetes mellitus. Because of the increasing population of aged people and diabetic patients in present Japan, it has been predicted that a greater number of diabetic patients will suffer from this complication than in the past. Prevention of the occurrence of this complication will become increasingly important not only for the quality of life in aged patients with diabetes, but also for the sociomedical aspects of all human beings. Accordingly, the results of our studies on the pathophysiology and etiology of diabetic osteopenia are summarized here.

1. Prevalence of diabetic osteopenia

Since 1948 when Albright (1) first pointed out abnormalities of bone metabolism in diabetes mellitus, there have been conflicting reports concerning the prevalence of this complication. Various results have been obtained according to differences in race, sex, type of diabetes, and methods used for measurement. To evaluate the prevalence of diabetic osteopenia in Japan, a nation-wide survey was conducted using microdensitometry of the second metacarpal bone (2). Of approximately ten thousand cases, 20.1% of diabetic patients were found to have osteopenia, whereas the prevalence in the age-matched controls was only 7.9% (p<0.01).

2. Pathophysiological aspects of diabetic osteopenia

Bone \(\gamma\)-carboxyglutamic acid-containing protein (BGP) is known to be one of the major non-collagenous proteins in bone matrix, and its plasma levels have been found to be a sensitive indicator of bone turnover. To investigate the pathophysiology of diabetic osteopenia, plasma levels and bone content of BGP were measured in streptozotocin (STZ)-induced IDDM rats (3). Plasma BGP in IDDM rats was \(19.6 \pm 2.8\) (mean \(\pm\) SE) ng/ml, significantly lower than the value of \(89.2 \pm 14.0\) in controls (\(p<0.01\)). Bone BGP content per femur also was significantly decreased in IDDM rats compared to controls (\(669 \pm 58\) \(\mu\)g vs \(1,241 \pm 126\); \(p<0.01\)) (Fig. 1). The decreased BGP content is consistent with the hypothesis that BGP synthesis is impaired in IDDM. Accordingly, we postulated that the low turnover is one of the pathological features of diabetic osteopenia. The effect of long-term insulin therapy on low bone turnover in IDDM was then investigated by pancreatic transplantation treatment in...
STZ-induced IDDM rats. This succeeded in reversing the decreased plasma BGP and the osteopenia observed in untreated IDDM rats (p<0.01). The improvement of the diabetic state by insulin therapy is, therefore, essential for the prevention of deterioration in diabetic osteopenia. Since the presence of insulin receptors has been shown recently in osteoblastic cells (4), insulin might have a direct stimulatory effect on skeletal tissue in IDDM via insulin receptors, reversing the decrease in bone turnover and resulting low plasma BGP.

In addition, plasma levels of BGP were also found to be reduced in NIDDM model rats with hyperinsulinemia. In Wistar fatty rats, plasma BGP was 47.2±4.7 ng/ml, significantly lower than the value of 100.8±5.4 in their lean littermates (p<0.01). Bone BGP content also was significantly decreased in Wistar fatty rats (p<0.01). It seems likely, therefore, that impaired bone turnover is a common characteristic of diabetic osteopenia in both IDDM and NIDDM.

Circulating levels of BGP and the severity of diabetic osteopenia were assessed simultaneously in clinically proven NIDDM patients. Plasma BGP in NIDDM of both sexes was 3.9±0.3 ng/ml, which was significantly decreased compared to the values of 6.9±0.2 and 8.5±0.3 in age-matched controls of males and females, respectively (p<0.01). This evidence shows clearly that bone turnover is decreased in human diabetic subjects similar to that in diabetic animals. Since plasma BGP is found to be already reduced in patients without osteopenia and since this protein has been suggested to be involved in the process of bone mineralization (5), the decreased BGP might contribute to the pathogenesis of diabetic osteopenia. On the other hand, it has been shown that serum BGP levels are elevated in postmenopausal osteoporosis (6), and our study using microdensitometry revealed that the densitometer pattern of diabetic osteopenia differs in several ways from that of osteoporosis. It seems likely, therefore, that diabetic osteopenia is a different clinical entity from osteoporosis.

3. Etiology of diabetic osteopenia

It was shown in a nation-wide survey that there is a negative correlation between the mean daily sunlight energy and the prevalence of diabetic osteopenia (7). This suggests that an altered vitamin D metabolism is a causative factor in diabetic osteopenia. The plasma levels of vitamin D metabolites were, therefore, measured in diabetic patients (8). In IDDM, plasma 1,25(OH)2D and 24,25(OH)2D were significantly decreased (p<0.01), and the latter was also significantly reduced in NIDDM (p<0.01). Accordingly, differences in the pathogenesis or severity of diabetes might influence alterations of vitamin D metabolism.

In addition, 1,25(OH)2D3, an active vitamin D metabolite, is known to exhibit its biological action by binding with a specific 1,25(OH)2D3 receptor in the target organs such as intestine, kidney, and bone. We examined, therefore, genetically diabetic db/db mice to evaluate 1,25(OH)2D3 receptors in intestine and kidney (9). This model is characterized by obesity, hyperglycemia, and temporary hyperinsulinemia and closely resembles human NIDDM. The number of specific 1,25(OH)2D3-binding sites in intestine and kidney was 118±11 fmol/mg protein and 34.6±7.1, respectively, in diabetic mice, which was significantly lower than the values of 199±11 and 63.3±5.7 in controls (p<0.01). On the other hand, there were no significant differences in the equilibrium dissociation constants of intestinal and renal receptors between control and diabetic mice. These results clearly demonstrate decreased concentrations of 1,25(OH)2D3 receptors in intestine and kidney of db/db mice. Alterations in the vitamin D endocrine system including an altered bone metabolism in diabetes probably result, at least in part, from the decrease in 1,25(OH)2D3 receptors in the target organs. Recent studies have revealed that 1,25(OH)2D3 stimulates transcription of the BGP gene and BGP synthesis, and that the 1,25(OH)2D3-responsive element is located within the promoter for BGP (10, 11). A quantitation of BGP and 1,25(OH)2D3 receptor mRNA content and its in vitro transcription rate in diabetic osteoblasts would be helpful to elucidate the role of alterations of the vitamin D endocrine system in the pathogenesis of diabetic osteopenia. Further studies will be necessary for the establishment of a means of prevention and treatment of this complication.

REFERENCES

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5. Pathogenesis and Correspondence of Diabetic Retinopathy
—Approach from Polyol Metabolism

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In recent years, interest in the etiology of diabetic retinopathy has been increasingly focused on the possible links with the polyol pathway, as demonstrated in animal studies (1-9) and clinical observations (5, 6, 10-13). If aldose reductase (AR) activity in the polyol pathway is involved in the development of some diabetic complications, then its inhibition might result in the prevention of diabetes-associated complications. The present study is comprised of animal experiments and a clinical trial to attempt to confirm the above-mentioned hypothesis.

Prevention of diabetic retinopathy by aldose reductase inhibitor in fructose-fed diabetic rats

Streptozotocin diabetic rats and normal rats were maintained from 1 to 8 months on a 72% fructose diet and treated with aldose reductase (AR) inhibitor (ONO-2235: 50 mg/kg/day) as mentioned previously (7, 14).

Effect of fructose feeding and AR inhibitor on the electroretinogram (ERG)

Streptozotocin-diabetic rats were maintained on a 72% fructose diet for 4 wk and some were treated with an AR inhibitor. Prolongation of the peak latencies of the oscillatory potentials in the b-wave of the ERG was observed in both the laboratory chow-fed and the fructose-fed diabetic rats, and tended to persist more in the fructose-fed diabetic rats than in the laboratory chow-fed diabetic rats. This prolongation of peak latencies observed in 0₃ and 2(0₁ + 0₂ + 0₃ + 0₄) from either the fructose-fed or the laboratory chow-fed diabetic rats was significantly reversed upon treatment with ONO-2235.

Histological and biochemical observations

In the results of the examination of trypsin digestion after a 7-8 month experimental period, the changes were more severe in fructose-fed diabetic rats. In fructose-fed diabetic rats, there was a