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High Incidence of Obesity and Elevated Serum Immunoreactive Insulin Level in Patients with Paravertebral Ligamentous Ossification: A Relationship to the Development of Ectopic Ossification

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ABSTRACT

Insulin has been shown to stimulate bone formation, and there is a high incidence of obesity and disturbance in the glucose metabolism of patients with paravertebral ligamentous ossification (PVLO). In an effort to clarify whether there is any alteration in insulin status in PVLO patients, and whether such changes play any role in the development of PVLO, glucose metabolism and serum insulin levels are examined in 11 PVLO patients and compared with 6 control patients of similar age and activities of daily living. More than half of the patients with PVLO exceed 110% of ideal body weight, and their fasting serum immunoreactive insulin (IRI) levels are significantly higher than those of control patients. In addition, there is a significant correlation between fasting IRI and % ideal body weight in PVLO patients. These results indicate that hyperinsulinism is present in many patients with PVLO, and that obesity further aggravates the hyperinsulinism in this disorder. Thus, it is suggested that hyperinsulinism is involved in the development or aggravation of ectopic ossification in PVLO patients. The relationship between hyperinsulinism and the other factors such as genetic and physical factors as well as the changes in calcium metabolism in the development of PVLO remains to be clarified.

Key words

Ectopic ossification-Paravertebral ligamentous ossification-Obesity-Hyperinsulinism

Introduction

Paravertebral ligamentous ossification (PVLO) is characterized by a progressive and ectopic ossification of paraspinal ligaments[1], and is one of the common causes of compression myelopathy among the elderly, especially in Japan and East Asia[2]. Although the exact mechanism of development of PVLO is yet uncertain, it is known that a high incidence of patients with vitamin D-resistant hypophosphatemic rickets/osteomalacia

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also suffer from PVLO[3]. In addition, we have previously demonstrated that PVLO is frequently seen in patients with hypoparathyroidism[4,5]. These findings raised the possibility that derangements in mineral metabolism may participate, at least in part, in the development and/or aggravation of PVLO. However, in subsequent studies in which mineral metabolism in PVLO patients was examined, only a small reduction in the intestinal calcium absorption was detected[5,6]. Therefore, although disturbances in mineral metabolism such as a deficiency in vitamin D action may be an aggravating factor[6], additional factor(s) must also be involved in the development of PVLO.

During the course of these studies, we and others[7] became aware of the fact that there is a high incidence of obesity and disturbance in glucose metabolism in patients with PVLO. Because insulin is required for the activation of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 by various stimuli[8-10], and because disturbances in mineral metabolism have been reported in insulin-deficient subjects and animals[11-13], there is a possibility that alterations in the insulin status may have a bearing on the development of PVLO. The present study was undertaken to examine in more detail possible abnormalities in glucose metabolism and insulin levels in PVLO patients. The results indicate that these patients exhibit higher incidence of obesity and elevated fasting immunoreactive insulin(IRI) levels than control subjects.

Materials and Methods

Twelve consecutive patients with PVLO complicated with compression myelopathy and admitted to University of Tokyo Hospital for surgical laminectomy (mean age 61 years, range 42 to 71 years), and six control patients with other vertebral disorders (mean age 62 years, range 50 to 70 years) were studied. Control patients had almost equal activities of daily living and age distribution as the PVLO patients. All the PVLO patients studied were male, reflecting the higher incidence of PVLO among the male population[2]. The diagnosis of PVLO was established by characteristic radiological findings such as a dense ossified strip along the margin of the vertebrae[2]. None of the PVLO or control patients had clinically overt diabetes mellitus, impaired renal function or any other endocrinological disturbance. Informed consent was obtained from all patients prior to the study.

Each patient was weighed, and percentile ideal body weight was calculated according to the following formula: %Ideal body weight (%IBW) = Body weight(kg)/(Height(cm)−100) ×0.9* or = Body weight(kg)/(Height(cm)−50) ×0.5** *Height more than 160 cm. **Height less than 160 cm. An oral 75 g glucose tolerance test was performed the morning after an overnight fast. Plasma glucose and serum IRI levels before and after the glucose load, and fasting blood glycosylated hemoglobin Alc concentration were measured. IRI was assayed by an enzyme linked immunoassay kit(Mochida Co., Tokyo, Japan), and hemoglobin Alc by a glycohemoglobin autoanalyzer (Toyo Soda HLC 723 GHb, Toyo Soda Manufacturing Co., Tokyo, Japan). Insulinogenic index was calculated as follows: Insulinogenic index = (IRI_{30} −fasting IRI)/(Plasma $glucose_{30}$−fasting plasma glucose); IRI_{30}, IRI 30 min after glucose load; Plasma glucose30, plasma glucose 30 min after glucose load. Statistical analyses of the data were performed by Student's t-test.

Results

As shown in **Table 1**, %IBW of all the control patients was within the normal limit and ranged between

Table 1. Body weight and parameters in glucose metabolism in patients with paravertebral ligamentous ossification (PVLO) and control patients.

	Patients with PVLO		Control
	Excess of weight	Normal weight	patients
Number of patients	6	5	6
%IBW	126±3.3[a]	103±1.6	102±2.5
Fasting plasma glucose (mg/dl)	93±3.6	83±8.3	77±6.1
Hemoglobin A_{1C}(%)	5.8±0.1	5.4±0.2	5.7±0.2
Fasting IRI (μU/ml)	24.0±4.3[b]	14.2±1.6[c]	8.0±1.1
Insulinogenc index	4.6±2.9	4.4±3.3	0.9±0.3

Data are means ± S.E. of the indicated number of patients.
[a]Singificantly different from the control ($p<0.001$).
[b]Significantly different from the control ($p<0.01$).
[c]Significantly different from the control ($p<0.02$).

91.2 and 108.7% (mean percentile 102%). In contrast, %IBW of 6 PVLO patients exceeded 110%. Therefore, the latter were divided into two groups: normal weight group whose %IBW ranged between 90 and 110%, and excessive weight group whose %IBW was over 110%. Fasting plasma glucose and blood glycosylated hemoglobin Alc concentrations were both within normal range in all the PVLO and control patients, and no significant difference in these parameters was observed among either group. Mean serum fasting IRI concentration, however, was significantly higher in both groups of PVLO patients compared to control patients. Although there was a tendency that the insulinogenic index was higher in both groups of PVLO patients compared to the control, no significant difference was found among any of the groups. **Figure.1** shows the relation ship between fasting serum IRI levels and %IBW in

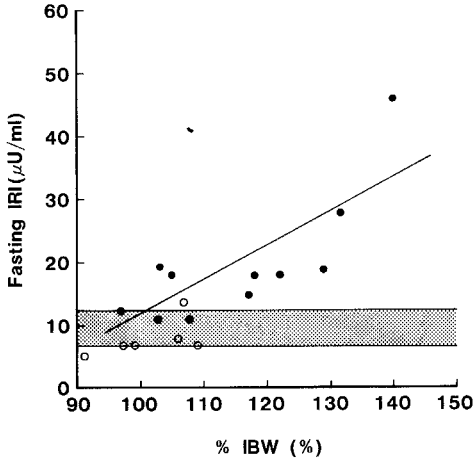

Figure.1 Relationship between %IBW and fasting serum IRI levels in PVLO (•–•) and control (o–o) patients. There is a significant correlation between these two parameters in PVLO patients ($r=0.79$, $p<0.025$). Dotted area represents normal range.

PVLO and control patients. There is a significant positive correlation between fasting serum IRI and %IBW in PVLO patients ($r=0.79$, $p<0.025$, **Fig.1**). However, only two patients with PVLO, one of normal weight and the other in the excessive weight group, exhibited impaired glucose tolerance after oral glucose load (data not shown).

Discussion

These studies demonstrate that more than a half of the patients with PVLO exceed 110% of IBW, and that fasting serum IRI concentrations are elevated in these patients in both normal and excessive weight groups. The reason for the elevated fasting IRI levels in normal weight PVLO patients with normal fasting glucose levels is not known at present. However, although fasting glucose levels are not significantly elevated in these patients, they tend to be higher in PVLO patients than in control subjects (**Table.1**). In addition, there is a significant correlation between fasting IRI and %IBW in PVLO patients (**Fig.1**). Thus, these individuals appear to have mild resistance to insulin, which may be the reason they exhibit higher fasting IRI and insulinogenic index than control subjects.

Insulin deficiency has been shown to be associated with reduced bone mass both in humans and animals[11, 12]. Furthermore, insulin replacement can reverse abnormalities in the bone and mineral metabolism[12, 14]. Direct effects of insulin on bone formation have also been reported, such as stimulation of the synthesis of collagen[15, 16] and stimulation of DNA synthesis of bone cells[17]. Thus, insulin may play a role in the promotion of ectopic ossification as well as normal bone formation. It has recently become increasingly evident that growth factors play an important part in the regulation of bone metabolism. Insulin-like growth factor-1 (IGF-1) is well known for its effect on bone formation[14]. Because insulin also exhibits affinity for IGF-I receptor, the effect of insulin on bone may be mediated through this receptor. If so, stimulation of bone formation or ectopic ossification can develop in association with hyperinsulinism in the face of the resistance to insulin in glucose metabolism. It is noteworthy that the incidence of diffuse idiopathic skeletal hyperostosis (DISH) is reported to be high in PVLO patients[18], and that the incidence of PVLO, especially ossification of the posterior longitudinal ligaments, in DISH is reported to be as high as 50%[19]. These disorders are both characterized by ossification of ligaments and/or tendons adjacent to bone and appear to be clinically similar, although DISH is common in the Western world whereas PVLO is com-

mon in Japan and East Asia. Further, patients with DISH also have a tendency toward obesity and hyperinsulinism[20]. Therefore, the present results as well as those previous studies are consistent with the possibility that hyperinsulinism is involved in the development or aggravation of ectopic ossification in PVLO as well as in DISH patients. Bell et al[21]. reported that obesity is associated with secondary hyperparathyroidism, an elevation in serum 1, 25-dihydroxyvitamin D level and a reduction in daily urinary calcium excretion. Although the authors suggest that the decrease in daily urinary calcium excretion is due to an enhanced renal tubular reabsorption of calcium, the simultaneous presence of secondary hyperparathyroidism would rather suggest that intestinal calcium absorption is reduced due to a decreased responsiveness to 1, 25-dihydroxyvitamin D. We previously demonstrated that there is a high in cidence of PVLO in patients with hypoparathyroidism, and that the development of PVLO is correlated with the duration of period without active vitamin D treatment[4]. In addition, our earlier observations suggest that there is a correlation between deficient actions of 1, 25-dihydroxyvitamin D and the development and aggravation of PVLO[6]. Thus, the decrease in 1, 25-dihydroxyvitamin D action in obese patients as indicated by the reduction in daily urinary calcium excretion may also act as an aggravating factor for PVLO. In contrast, there is also a possibility that genetic abnormalities may play a causative role in the development of PVLO, and that abnormalities in calcium metabolism or in insulin secretion may merely be aggravating factors. Nevertheless, the present results that PVLO patients have higher incidence of obesity and hyperinsulinism suggest that treatment and prevention of these two conditions may at least partially prevent the aggravation of PVLO.

In conclusion, fasting IRI levels are high in PVLO patients and more than half of these patients are of excessive weight. A significant positive correlation is also found between %IBW and fasting IRI levels in such patients. Because insulin has been shown to stimulate bone formation, the presence of hyperinsulinism in patients with PVLO may act to promote ligamentous ossification. However, further studies are needed to clarify the relationship between hyperinsulinism and genetic and physical factors as well as the changes in calcium metabolism in the development of PVLO.

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