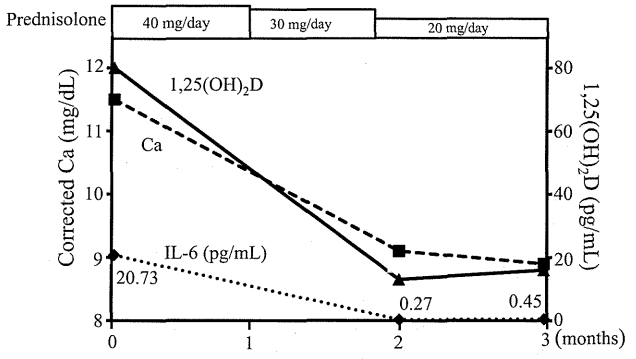

Fig. 2 The clinical course of the patient with MCD and hypercalcemia. Prednisolone treatment decreased the levels of $1,25(OH)_2D$, calcium and IL-6. The serum calcium concentration was corrected with serum albumin using Payne's formula [14]

Discussion

A few case reports have shown that some patients with MCD have hypercalcemia, although the frequency is unknown. It is known that IL-6, a proinflammatory cytokine, induces the expressions of osteoclastogenic factors, such as macrophage inhibitory protein 1 alpha, IL-3 and receptor activator of nuclear factor-kappa B ligand, and that the level of IL-6 is correlated with increased bone turnover [4, 5]. Because MCD is caused by the hyperproduction of IL-6, hypercalcemia was considered to occur because of activation of osteoclasts and increased bone turnover. Indeed, Washington et al. previously reported that a 25-year-old female with MCD had hypercalcemia caused by increased bone turnover mediated by cytokines such as IL-6-induced [6]. Although high bone turnover and bone lesions were not observed in the present case, it is possible that the treatments with low-dose prednisolone for AIHA and ITP, elcatonin and bisphosphonate might have affected bone turnover markers and the level of IL-6.

Recently, Donovan et al. analyzed 101 cases with $1,25(OH)_2D$-mediated hypercalcemia and reported that sarcoidosis was the most common etiology followed by hematological malignancies, infection, solid organ malignancies and other granulomatous diseases [7]. Although the immune/macrophage-related expression of 1-alpha-hydroxylase has been suggested [7–11], the frequency is unknown. A case of MCD with hypercalcemia was previously reported [6]; however, ectopic expression of 1-alpha-hydroxylate in macrophages/lymph nodes has not been reported in MCD thus far. Physiologically, $1,25(OH)_2D$ in the circulation is mainly derived from the kidneys by the action of PTH. However, of interest, we found that the level of $1,25(OH)_2D$ was increased in our case, although the int-PTH level was low and renal function was impaired. Because we considered ectopic 1-alpha-hydroxylase expression, immunohistological analysis was performed using a lymphadenopathy specimen and revealed the production of 1-alpha-hydroxylase in macrophages. Bone resorption markers were not increased because of treatments with elcatonin and bisphosphonate, suggesting that $1,25(OH)_2D$ excess might cause hypercalcemia by enhanced intestinal absorption of calcium, not increased bone resorption. Taken together, these findings suggest that hypercalcemia is caused by the ectopic production of 1-alpha-hydroxylase in activated macrophages in MCD. On the other hand, the levels of IL-6, Ca and $1,25(OH)_2D$ were simultaneously decreased during prednisolone treatment. These findings suggest that elevated IL-6 might be involved in the expression of $1,25(OH)_2D$, although the underlying mechanism is unclear. The clinical course supports our hypothesis that elevated active vitamin D produced by lymphadenopathy causes hypercalcemia in MCD.

Since hypercalcemia is rarely observed in patients with MCD, the characters involved in the occurrence of hypercalcemia in patients with MCD are not known. In our case, the patient previously had AIHA and ITP, which are reported sometimes to be accompanied by MCD through the augmentation of IL-6 [12, 13]. Therefore, the severity and comorbidity of MCD might be related to hypercalcemia. We therefore should accumulate further case reports and examine the association between hypercalcemia and background characteristics in MCD.

In conclusion, we herein presented a case of hypercalcemia caused by increasing active vitamin D due to the expression of 1-alpha-hydroxylase in macrophages in MCD. In addition, glucocorticoid treatment is effective for improving hypercalcemia in MCD patients.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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ORIGINAL RESEARCH

Renal Phosphate Reabsorption is Correlated with the Increase in Lumbar Bone Mineral Density in Patients Receiving Once-Weekly Teriparatide

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Abstract In order to assess the changes in serum calcium and phosphate and the changes in renal tubular phosphate reabsorption (TmP/GFR) and to evaluate the association between these indices and the increase in bone mineral density (BMD) with once-weekly intermittent administration of teriparatide (TPTD), the results from the teriparatide once-weekly efficacy research (TOWER) trial were re-analyzed. The TOWER trial studied postmenopausal women and older men with osteoporosis. Patients were randomly assigned to receive TPTD 56.5 μg or placebo for 72 weeks. Of these patients, the present study investigated those whose calcium and phosphate levels and lumbar BMD (L-BMD) were measured (TPTD group, $n = 153$ and Placebo group, $n = 137$). The TPTD group had significantly lower serum phosphate, calcium-phosphate product, and TmP/GFR at weeks 4, 24, 48, and 72 and urinary fractional calcium excretion (FECa) at weeks 12, 48, and 72 ($p < 0.05$). In the TPTD group, the serum phosphate and TmP/GFR during early treatment (4, and 12 weeks) showed a significant positive correlation with the percent change in L-BMD at weeks 48 and 72. Based on multivariate analysis corrected for age, BMI, and L-BMD at the start of treatment, serum phosphate and TmP/GFR at week 4 showed a significant correlation with the percent change in L-BMD. This study suggests that the L-BMD response to once-weekly long-term TPTD treatment is associated with circulating phosphate or with the status of its renal reabsorption. Preventing decrease in serum phosphate levels may be important in acquiring greater L-BMD with once-weekly TPTD.

Keywords Teriparatide · Phosphate · Reabsorption · Bone mineral density · Osteoporosis

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Introduction

The homeostasis of circulating calcium and phosphate plays an important role in bone mass regulation. Calcium homeostasis is primarily regulated by parathyroid hormone (PTH), which mediates calcium reabsorption at the renal distal tubule and calcium mobilization from the bone via bone resorption and also promotes calcium absorption from the intestinal tract by vitamin D mediated through vitamin D activation by PTH at the renal proximal tubule [1]. PTH

mobilizes phosphate from the bone through promoting bone resorption and promotes phosphate absorption from the intestinal tract via vitamin D activation [2, 3]. On the other hand, PTH is also known to suppress phosphate reabsorption at the renal proximal tubule and promote the secretion of FGF23, a phosphate diuretic hormone [4]. Collectively, PTH is known to suppress phosphate reabsorption in the kidneys and decrease the circulating phosphate concentration. Since calcium deficiency secondarily induces PTH oversecretion, PTH in turn promotes bone resorption and decreases circulating phosphate concentration, leading to decreased bone mass and bone mineral density (BMD) [5]. Moreover, phosphate deficiency blocks the formation of hydroxyapatite, which is a calcium phosphate crystal found locally in bone, leading to decreased BMD. On the other hand, although the secretions of PTH and FGF23 are stimulated in response to phosphate oversupply [6], excessive phosphate can cause tunica media thickening or vascular calcification when adequate compensation cannot be achieved [7] and is consequently known to be associated with the incidence of cardiovascular events or heart failure [8–10].

Teriparatide (TPTD) is an analog of PTH (1-34) with pharmacological actions similar to PTH. Its intermittent daily or once-weekly administration is known to increase BMD and significantly suppress fractures [11, 12].

When a single dose of TPTD 56.5 μg was administered, serum calcium increased transiently from 9.11 to 9.58 mg/dL around 4 to 6 h after the injection and subsequently returned to its baseline concentration until 24 h after the injection. At the same time, a decrease in urinary calcium excretion was observed at 4 h and again the decrease was transient. After TPTD administration, an increase in urinary phosphate excretion was observed at 2 and 6 h after the drug injection, but the increase was transient. Serum phosphate level was decreased transiently as a result, but subsequently returned to the level that was not statistically different from that of baseline value [13]. When patients receive TPTD 56.5 μg once-weekly repeatedly, serum calcium changes similarly, but without attenuation in its effects for 24 weeks [14]. On the other hand, the serum phosphate level just before TPTD administration gradually decreases compared to the level at the start of treatment. Whether these changes in calcium and phosphate during once-weekly intermittent TPTD treatment are associated with the increase in BMD has not been previously assessed.

Recently, the associations among changes in calcium and phosphate, changes in BMD, and changes in intima-media thickness (IMT) with daily TPTD treatment were investigated. The results showed that the changes in calcium and phosphate were not significantly correlated with BMD [15].

In the present study, to clarify whether the earlier changes in calcium and phosphate metabolism can predict the later change of BMD, the changes in serum calcium and phosphate, the changes in renal tubule phosphate reabsorption, and the association between these changes and the increase in BMD were evaluated in patients who received once-weekly TPTD.

Materials and Methods

TOWER Trial

Data from the TOWER trial, a randomized, controlled trial conducted in Japan with the objective of determining the effects of TPTD on suppressing bone fractures in postmenopausal women and men with osteoporosis, were used in the present analysis [12]. Patients were randomly assigned to receive once-weekly subcutaneous injections of TPTD 56.5 μg or placebo for 72 weeks. All patients received daily oral supplements of calcium 610 mg, vitamin D 400 IU, and magnesium 30 mg.

Clinical Laboratory Measurements

Blood and urine samples were collected prior to each TPTD treatment. Samples were analyzed collectively at a central laboratory. Adjusted serum calcium, serum phosphate, serum creatinine, urinary calcium, urinary phosphate, and urinary creatinine concentrations were measured at weeks 0, 4, 24, 48, and 72. At each time point, adjusted serum calcium-phosphate product, urinary fractional calcium excretion (FECa), and the phosphate reabsorption index TmP/GFR were calculated. Equations for FECa and TmP/GFR are as follows:

FECa (%) = (Urinary calcium × Serum creatinine) × 100/(Urinary creatinine × Serum calcium)

TmP/GFR = Serum phosphate × (1 − (Urinary phosphate × Serum creatinine)/(Serum phosphate × Urinary creatinine))

BMD Measurement

Lumbar (L)-BMD was measured at each medical institution at weeks 0, 24, 48, and 72, and DXA data of the L2-4 area were determined using two types of instruments [QDR (Hologic, Bedford, MA) and DPX (GE Healthcare, Fairfield, CT)]. DXA data were re-analyzed collectively at a central laboratory and measured by a specialist. Percent changes between late treatment (weeks 48 and 72) and pretreatment levels were calculated.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD). Adjusted serum calcium, serum phosphate, serum calcium-phosphate product, FECa, and TmP/GFR were compared between groups for each time point (*t*-test). The associations between these variables during early treatment (weeks 4 and 12) and the percent change in L-BMD during late treatment (weeks 48 and 72) were evaluated using Pearson's correlation coefficient. Variables that showed significant correlations with L-BMD were subjected to multivariate analysis using age, BMI, and initial L-BMD as factors for adjustment. Additionally, significant explanatory variables were split at the median of the TPTD group into high and low groups, and the difference in the actual percent changes in L-BMD was compared with the *t*-test between the two groups for each variable. $p < 0.05$ was considered significant.

Results

Of the 578 patients who received randomized treatment in the TOWER trial, those whose clinical laboratory values of calcium and phosphate, as well as L-BMD, were measured (TPTD group, $n = 153$; Placebo group, $n = 137$) were investigated. The patient characteristics of each group are shown in Table 1. Significant differences were not evident between the groups in any of the parameters.

L-BMD percent changes during late treatment in the TPTD group and Placebo group were 5.8 ± 4.6 % ($n = 113$) and 0.6 ± 3.8 % ($n = 138$) at 48 weeks and 6.7 ± 5.3 % ($n = 107$) and 0.3 ± 4.5 % ($n = 130$) at 72 weeks, respectively, showing significant differences between the groups at both time points ($p < 0.001$).

Adjusted serum calcium, phosphate, calcium-phosphate product, FECa, and TmP/GFR at each time point are shown in Fig. 1. Serum calcium was not significantly different between the groups. Serum phosphate, calcium-phosphate product, and TmP/GFR were significantly lower in the TPTD group at weeks 4, 24, 48, and 72 ($p < 0.05$). FECa was significantly lower in the TPTD group at weeks 12, 48, and 72 ($p < 0.05$).

Table 2 shows the correlation between adjusted serum calcium, phosphate, calcium-phosphate product, FECa, and TmP/GFR in the TPTD group during early treatment (weeks 4 and 12) and the percent change of L-BMD during late treatment (weeks 48 and 72). Serum phosphate and TmP/GFR at both 4 and 12 weeks showed a significant positive correlation with the percent change in L-BMD at both 48 and 72 weeks ($p < 0.05$).

Table 3 shows the results of the multivariate analysis using serum phosphate and TmP/GFR, which are variables that showed significant differences during early treatment (week 4). Based on the analysis adjusted for age, BMI, and initial L-BMD, serum phosphate and TmP/GFR at week 4 showed a significant association with the percent change of L-BMD ($p < 0.05$). Serum phosphate and TmP/GFR at week 4 were split at the median (3.5 and 3.16 mg/dL, respectively) into high and low groups, and the percent changes in L-BMD at 72 weeks were compared between these groups (Fig. 2). Greater L-BMD was observed in the serum phosphate ≥3.5 mg/dL group, though the difference was not significant, and significantly greater L-BMD was observed in the TmP/GFR ≥3.16 mg/dL group ($p = 0.032$).

Discussion

In the present study, the changes in calcium, phosphate, calcium excretion, and phosphate reabsorption were examined in patients who received once-weekly long-term TPTD treatment. With TPTD, serum phosphate and calcium-phosphate product decreased significantly. Moreover, the calcium excretion index FECa and the phosphate reabsorption index TmP/GFR also decreased. The associations between these decreases and the percent change in L-BMD were also examined during late TPTD treatment to

Table 1 Baseline characteristics

Item	Placebo ($n = 153$)		TPTD ($n = 137$)		p
	Mean	SD	Mean	SD	
Age (years)	74.9	5.9	74.2	5.4	0.348
BMI (kg/m^2)	23.0	3.2	22.9	3.1	0.823
Adjusted serum calcium (mg/dL)	9.6	0.4	9.5	0.4	0.237
Serum phosphate (mg/dL)	3.6	0.4	3.6	0.5	0.671
Adjusted serum calcium × phosphate	34.6	4.9	34.2	4.7	0.459
FECa (%)	1.3	0.8	1.3	0.8	0.520
TmP/GFR (mg/dL)	3.3	0.5	3.2	0.4	0.553
L-BMD (g/cm^2)	0.72	0.12	0.71	0.12	0.312

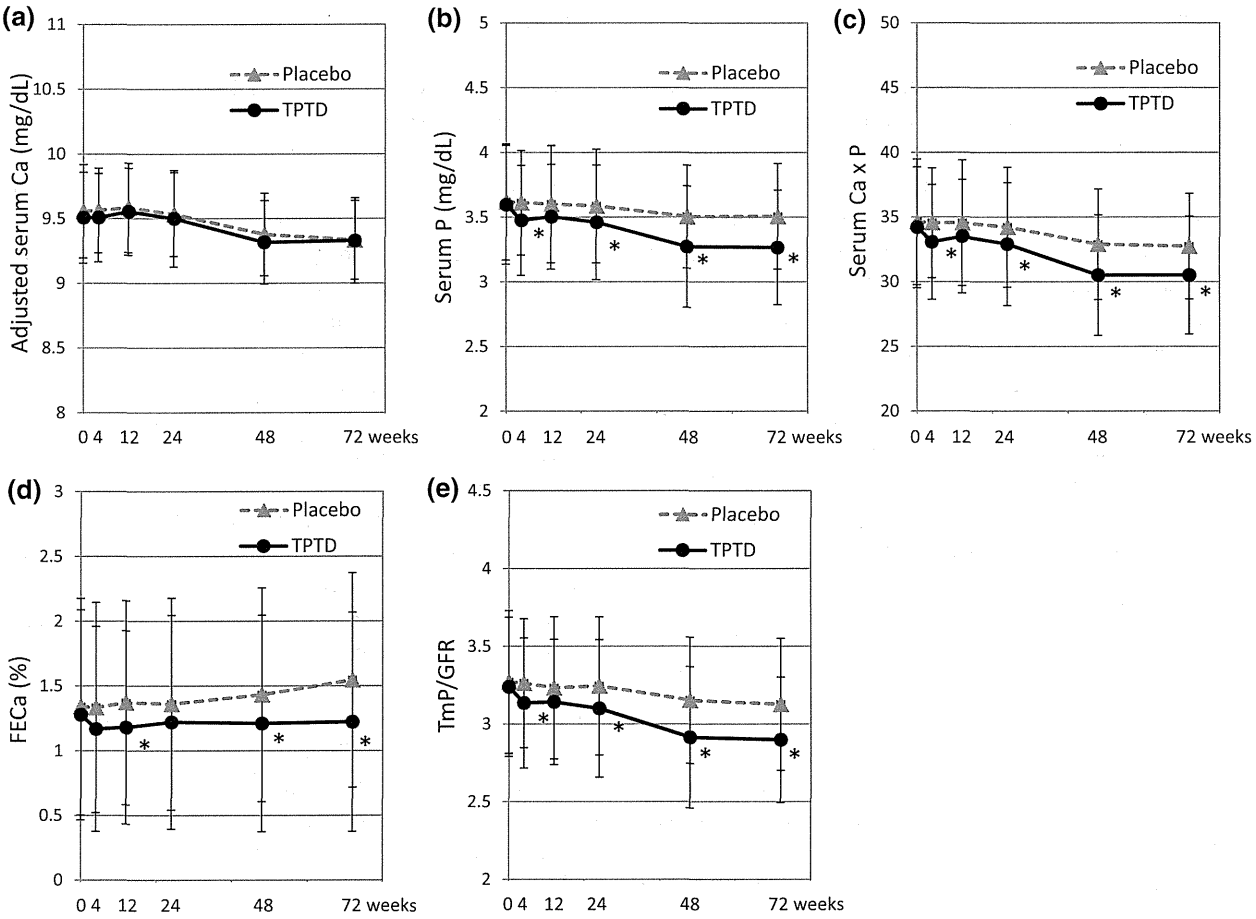

Fig. 1 Changes of calcium, phosphate, and the reabsorption rate. **a** adjusted serum calcium, **b** serum phosphate **c** serum calcium × phosphate, **d** urinary fractional calcium excretion (FECa) and **e** phosphate reabsorption index (TmP/GFR). *TPTD* teriparatide. * $p < 0.05$, values are mean ± SD

Table 2 Correlations of calcium and phosphate with the change in L-BMD

Parameter	Weeks	Change in L-BMD at 48 weeks		Change in L-BMD at 72 weeks	
		R	*p*	R	*p*
Adjusted serum calcium	4	−0.114	0.230	0.026	0.792
	12	−0.134	0.159	−0.059	0.550
Serum phosphate	4	0.215	0.022	0.205	0.034
	12	0.233	0.013	0.218	0.024
Adjusted serum calcium × phosphate	4	0.163	0.084	0.186	0.055
	12	0.162	0.087	0.169	0.082
FECa	4	−0.010	0.920	0.001	0.991
	12	−0.015	0.877	−0.037	0.705
TmP/GFR	4	0.231	0.014	0.228	0.019
	12	0.288	0.002	0.312	0.001

demonstrate that Tmp/GFR was positively correlated with the percent increase in L-BMD. These results indicate that the smaller the decrease in renal tubule phosphate reabsorption with once-weekly TPTD treatment, the better it is for increasing BMD. These were the first observations indicating the clinical significance of adequate phosphate response to TPTD administration for more efficient acquisition of BMD during once-weekly TPTD treatment.

Table 3 Multiple regression analysis for change in L-BMD at 72 weeks

Model	Item	Estimate	SE	*p*	R^2
1	Age	−0.01	0.09	0.890	0.090
	BMI	0.29	0.17	0.091	
	L-BMD at 0 weeks	−0.10	0.05	0.041	
	Serum phosphate at 4 weeks	2.46	1.21	0.044	
2	Age	−0.03	0.09	0.783	0.094
	BMI	0.29	0.17	0.089	
	L-BMD at 0 weeks	−0.09	0.05	0.068	
	TmP/GFR at 4 weeks	2.63	1.21	0.032	

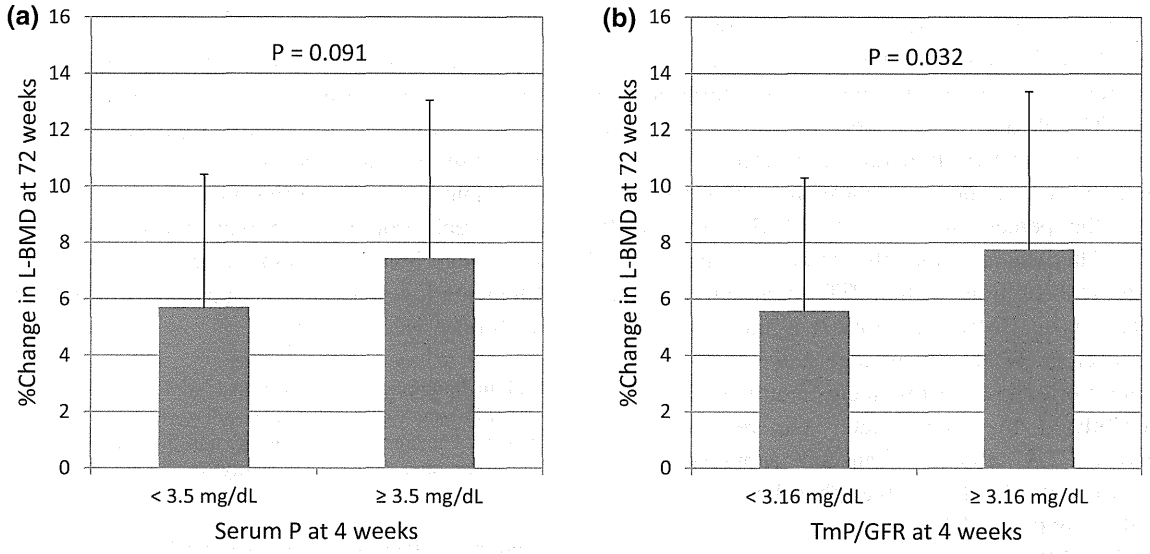

Fig. 2 Differences in changes of L-BMD by serum phosphate and TmP/GFR category. **a** serum phosphate and L-BMD and **b** TmP/GFR and L-BMD

In addition, they suggest the clinical importance of monitoring serum phosphate levels during TPTD therapy.

When TPTD is given, there is a transient elevation in the serum calcium concentration and a transient decrease in the phosphate concentration, both of which return to their respective baseline levels by the subsequent TPTD treatment [13]. However, the present results suggest that the decrease in renal phosphate reabsorption initiated by TPTD administration lasts for a long time in quite a few of subjects. Given that the biological actions of exogenous PTH after a single TPTD injection do not continue over a day because circulating levels of TPTD returned to basal value until 7 h after injection [13, 14], the decrease in serum phosphate is possibly due to the decrease in Tmp/GFR that might be caused by some intrinsic mechanisms, such as endogenous PTH, FGF23, and vitamin D actions that regulate phosphate metabolism. For example, exogenously administered TPTD has been shown to increase the circulating level of FGF23 [16], which could inhibit renal phosphate reabsorption and vitamin D activation. Thus, once-weekly TPTD administration might decrease serum phosphate levels via the stimulation of FGF23 when vitamin D actions are insufficient to prevent its decrease, for instance, in the presence of vitamin D insufficiency/deficiency. Although mean values of serum endogenous PTH were suppressed by TPTD administration until 6 days [13], endogenous PTH levels might also be dependent on vitamin D sufficiency. Then, another possibility is that relatively lower serum phosphate levels might be observed in subjects with relatively higher endogenous PTH levels in the presence of vitamin D insufficiency/deficiency.

With regards to TPTD's effects on bone, it is known that bone formation is promoted via TPTD's effects on the stimulation of osteoblast progenitor proliferation [17]. Another effect of TPTD on bone is the promotion of bone resorption mediated through RANKL expression stimulation [18]. The primary effects of TPTD from the perspective of calcium and phosphate metabolism are the promotion of bone resorption and renal calcium reabsorption and the suppression of renal phosphate reabsorption.

TPTD, therefore, could have dual effects, regulation of calcium and phosphate metabolism via its physiological actions on bone and kidney and bone formation via its pharmacological actions on bone-forming cells. Therefore, when primarily considering bone formation, because appropriate levels of calcium and phosphate are necessary for the mineralization of the bone matrix, the decrease in serum phosphate concentration is postulated to be unfavorable in bone mineralization, resulting in less BMD acquisition. Indeed, osteomalacia caused by decreased bone mineralization is sometimes observed in patients with severe primary hyperparathyroidism or in patients with secondary hyperparathyroidism undergoing dialysis [19].

Since renal tubule phosphate reabsorption decreased with TPTD administration in the present study, a significant decrease in serum phosphate concentration was observed. The degree of this decrease might affect the extent of bone matrix mineralization reflecting BMD, because there was a positive correlation between Tmp/GFR and the percent increase in L-BMD with TPTD treatment. This suggests that the greater the decrease of phosphate reabsorption with TPTD treatment, the less beneficial it is to BMD elevation. It is unlikely that the direct effects of TPTD given once a week persist until immediately prior to the subsequent treatment. Therefore, it is postulated that the greater the re-elevation of endogenous PTH after its transient suppression with TPTD treatment, the lower the phosphate reabsorption immediately before TPTD treatment and the less the increase in BMD. Otherwise, once-weekly TPTD could repeatedly stimulate the secretion of FGF23 that inhibits renal phosphate reabsorption and vitamin D activation and might decrease serum phosphate levels via the stimulation of FGF23, when vitamin D stores are insufficient due to vitamin D insufficiency/deficiency.

In general, the factor that is considered to most strongly affect circulating PTH levels in individuals with normal renal function without abnormal parathyroid function is vitamin D status [20, 21]. This signifies that, since circulating PTH increases in response to vitamin D deficiency or insufficiency, sufficient vitamin D levels appear to be necessary to maintain PTH at a physiologically stable state.

Our findings suggest two distinct biological functions of TPTD and PTH, bone formation promotion and calcium-phosphate metabolism regulation, and that both of them act independently from one another. In addition, it is possible from the perspective of BMD elevation that a sufficient vitamin D level is necessary to suppress the promotion of endogenous PTH secretion and to minimize the decrease in serum phosphate concentration during TPTD treatment. The present results suggest that further increases in BMD may be attained by more vitamin D supplementation when there is a marked decrease in serum phosphate concentration during TPTD treatment. Alternatively, larger and/or longer suppression of endogenous PTH by TPTD might be involved in greater BMD acquisition along with less decrease in serum phosphate irrespective of vitamin D sufficiency.

There are several limitations to this study. First, this study did not measure the endogenous concentration of PTH. It is therefore not clear whether the present results are a direct effect of TPTD or an indirect effect mediated via endogenous PTH. Second, 25-hydroxy vitamin D concentration before TPTD treatment was not measured, and the state of vitamin D sufficiency was, therefore, unknown. Moreover, while patients received native vitamin D supplementation, the amount was relatively low at 400 IU/day, and whether this amount adequately improved vitamin D deficiency or insufficiency is not known.

In summary, this study suggests that the L-BMD response to once-weekly long-term TPTD treatment is associated with circulating phosphate and the status of its renal reabsorption. To prevent the decrease in the serum phosphate level, for example, with ample vitamin D supplementation, may be important in acquiring greater BMD with once-weekly TPTD.

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Author Contributions Guarantor: YT. Study concept and design: YT, TK. Statistical analysis: TK. Drafting of the manuscript: YT, TK. Data interpretation and critical revision of the manuscript for important intellectual content, writing of the report, and approval of the final version: YT, TK, TS, MS, TN.

Compliance with Ethical Standards

Conflict of interest YT has received research grants and/or consulting fees from Eli Lilly Japan, Chugai Pharmaceutical, Teijin Pharma, Asahi Kasei Pharma, and Daiichi-Sankyo. TK is an employee of Asahi Kasei Pharma Corporation. TS has received consulting fees from Asahi Kasei Pharma and research grants from Eli Lilly Japan, Taisho-Toyama Pharmaceutical, Chugai Pharmaceutical, Daiichi-Sankyo, and Ono Pharmaceutical. MS has received consulting fees from Teijin Pharma, MSD, and Asahi Kasei Pharma and received lecture fees from Chugai Pharmaceutical, Ono Pharmaceutical, Astellas, Pfizer, Daiichi-Sankyo, Eisai, and Eli Lilly Japan. TN has received research grants and/or consulting fees from Asahi Kasei Pharma, Merck Sharp & Dohme, Daiichi-Sankyo, Eli Lilly Japan, Pfizer, Chugai Pharmaceutical, AMGEN, and Taisho-Toyama Pharmaceutical.

Ethical Approval The protocol of the original TOWER trial was approved by the institutional review boards at each participating institution, and the trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice.

Informed consent Written informed consent was obtained from all patients.

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[特集1] 日常臨床に潜む甲状腺機能異常の最近の話題

指定難病となった甲状腺ホルモン不応症

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Key Word
◉甲状腺ホルモン不応症（syndrome of resistance to thyroid hormone：RTH），◉TSH不適切分泌症候群（syndrome of inappropriate secretion of TSH：SITSH），◉指定難病（designated rare/intractable diseases）

要旨

2015年1月より甲状腺ホルモン不応症（syndrome of resistance to thyroid hormone：RTH）が新たに指定難病に認定され，重症度分類で中等度以上に相当する症例が医療費助成の対象となった。それに伴い，対象症例を正確に診断して助成することを目的として，RTHの診断アルゴリズムをもとに診断基準が策定された。RTHはBasedow病と間違えられて不必要な治療をされてしまうこともあり，TSH不適切分泌症候群（syndrome of inappropriate secretion of TSH：SITSH）と通常の甲状腺中毒症の鑑別が重要である。また，SITSH症例の鑑別診断においては，「真のSITSH」か否かという点と，TSH産生下垂体腫瘍とRTHの鑑別が鍵となる。診断基準，重症度分類，診断アルゴリズムとも，よりよいものを目指して現在も改良が進められている。

はじめに

2015年1月から開始された厚生労働省指定難病第1次実施分として110疾患が選定され，甲状腺ホルモン不応症（syndrome of resistance to thyroid hormone：RTH）が新たに認定された。そこで本稿では，はじめに指定難病について大まかなことを述べ，さらに，甲状腺ホルモン不応症について，指定難病の認定に必要な診断基準，重症度分類の制定や，それらのもととなる診断アルゴリズムを中心に概説する。

指定難病とは

指定難病という言葉は，2014年5月に成立し，2015年1月1日に施行となった「難病の患者に対する医療等に関する法律」という法律のなかで定められた。この法律は，難病患者に対する医療助成費の財源を確保するとともに，対象疾患を拡大し助成が行き渡ることを目的として制定された。「難病」の定義としては，①発病の機構が明らかでなく，②治療方法が確立していない，③希少な疾患であって，④長期の療養を必要とするもの，という4つの条件が挙げられているが，「指定難病」にはさらに，⑤患者数がわが国において一定の人数（人口の約0.1％程度）に達しないこと，⑥客観的な診断基準（またはそれに準ずるもの）が成立していること，という2条件を満たすことが必要になっている。2015年1月1日より110疾患が指定になり，7月からはさらに306疾患に拡大されている。

指定難病の新規診断は難病指定医のみが行うこととなった。難病指定医の要件としては，①難病の診断または治療に5年以上従事した経験があり，申請時点において関係学会の専門医の資格を有していること，または，②難病の診断または治療に5年以上従事した経験があり，一定の研修を修了していること，が必要とされている。難病指定医は，各疾患に定められた診断基準および重症度分類に従って，診断書に相当する臨床個人調査票を作成して登録し，それに基づいて各都道府県が助成に関する判定を行うしくみになっている。

これらの制度の詳細については，難病情報センターのウェブサイト（http://www.nanbyou.or.jp）を参照されたい。各指定難病の診断基準，重症度分類，臨床個人調査票も同サイト内から入手可能となっている。

RTHの概要

RTHは，甲状腺ホルモンに対する標的臓器の反応性が減弱している家族性症候群として，Refetoffらによって1967年に報告された[1]。1988年には，RTH患者において初めて*TR*β遺伝子に変異が同定された[2]。現在ではRTH家系の約85％に*TR*β遺伝子変異を認めることがわかっており，RTHはTRβの異常症と同義と考えられるようになっている[3]。変異TRβは正常なTRβおよびTRαの機能を阻害するドミナントネガティブ作用を有するため，本症は例外的な1家系(*TR*β遺伝子の大部分が欠失している)[4]を除いて，すべて常染色体性優性遺伝形式をとる。約15％の家系における原因遺伝子は明らかでないが，*TR*β遺伝子変異を伴う家系と臨床症状の区別がつかないことから，何らかの原因でTRβの機能が障害されているものと考えられ，nonTR-RTHと呼ばれている。

正確な発症頻度は明らかではないが，FT_4とTSHを指標としたスクリーニングの結果，*TR*β遺伝子変異を伴うRTHの発症頻度は約40,000人に1人と推定されている[5][6]。しかし，日本甲状腺学会が2009年に把握したRTH症例はわずかに98例(71家系)であり，日本ではいまだ多くのRTH症例が診断されないままになっていると考えられる。

RTH患者では，ネガティブフィードバック機構の障害のため，TSHの抑制を伴わない血中サイロキシン(T_4)，トリヨードサイロニン(T_3)の高値〔TSH不適切分泌症候群(syndrome of inappropriate secretion of TSH：SITSH)〕を呈する。下垂体からTSHが過剰分泌される結果，甲状腺は機能亢進状態となり多くの例で腫大する。TRβの機能異常が原因であるため，TRβの発現が強い肝臓や下垂体では甲状腺ホルモンに対する応答性の低下が認められる。一方，TRαの発現が多い心臓では，甲状腺ホルモン作用の障害の程度が少ないため，逆に甲状腺ホルモン過剰状態の影響を受けやすくなる。甲状腺ホルモン作用の減弱が甲状腺ホルモンの増加により代償された状態となっているため，多くの症例では甲状腺腫と軽度の頻脈程度の症状で治療を必要としない。しかし，甲状腺中毒症症状が強く注意欠陥/多動性障害や著しい頻脈を示す患者もまれではない[3]。これらの症状に対し，β遮断薬による対症療法が有効であることが多いが，この効果が十分でない場合は治療に難渋する。逆に受容体異常の程度が特に強いと，TRαとTRβ双方のはたらきを抑えてしまうため，先天性甲状腺機能低下症の症状である知能発達遅延や低身長，難聴といった障害を伴う[1]。このような症例では，通常の甲状腺機能低下症の患者と異なり血液中の甲状腺ホルモン濃度は上昇しているが，甲状腺ホルモン薬の投与により甲状腺機能低下による症状が緩和される。

ほとんどの症例では，予後は健常人と変わらない。頻脈から心房細動のため若年で脳梗塞を起こした報告もあるが[7]，その頻度は明らかではない。また，患者が変異をもたない児を妊娠した場合，甲状腺中毒症により低出生体重児となることがある[8]。

RTHの正しい診断に向けて

RTH診療における最大の問題は，甲状腺ホルモン値が高く甲状腺がびまん性に腫大するため，Basedow病と誤診されて不必要な治療が行われることがあるという点である。TSHが低値となる甲状腺中毒症とSITSHをきちんと見分けることが重要である。

SITSHを呈する症例の鑑別診断の手順として，**図1**にRTH診断のためのアルゴリズムを示した。このアルゴリズムでは，「真のSITSH」か否かという点と，TSH産生下垂体腫瘍とRTHの鑑別を主眼に置いている。日本甲状腺学会の研究班では，本アルゴリズムを最初に制定し，それをもとに診断基準(第1次案)と重症度分類を策定した(**表1**，**2**)。重症度分類で中等度以上に該当する症例が助成の対象となる。アルゴリズム，診断基準，重症度分類とも，よりよいものを目指してさらに検討を進めている。

1回の血液検査でSITSHの所見が得られた場合も，その80％程度は以下に示すような理由により「見かけ上のSITSH」を呈している[9]。まず，抗T_4抗体やヒト抗マウス抗体をもつ症例では，これらの抗体によりT_4やTSHの測定系が干渉を受けることがある。次に，TSHの変動はT_4の変動に遅れるため，破壊性甲状腺炎やBasedow病の初期に，TSHの抑制がT_4の上昇に一時的に追いついていない場合がある。また，甲状腺機能低下症に対してT_4製剤による補充療法を行っている場合に，T_4が高値であるがTSHやT_3は正常範囲になることがある。さらに，後述する家族性異常アルブミン性高サイロキシン血症でも見かけ上のSITSHを呈する。「真の」あるいは「確からしい」SITSHであることを示すために，再検査を1ヵ月後以降に，さらに3ヵ月後に行い，これら再検査の際，可能なら検査方法(ホルモンの測定系)を変えて検査することが推奨される。

家族性異常アルブミン性高サイロキシン血症(familial dysalbuminemic hyperthyroxinemia：FDH)は，アルブミン遺伝子の変異によりアルブミンのT_4結合能が上昇する疾患である[10]。総T_4高値に対してFT_4は正常～軽度高値，TSHは正常で臨床的に甲状腺機能異常による症状を認めない。報告例では，アルブミン遺伝子のR218部分にあたる一塩基変異が原因

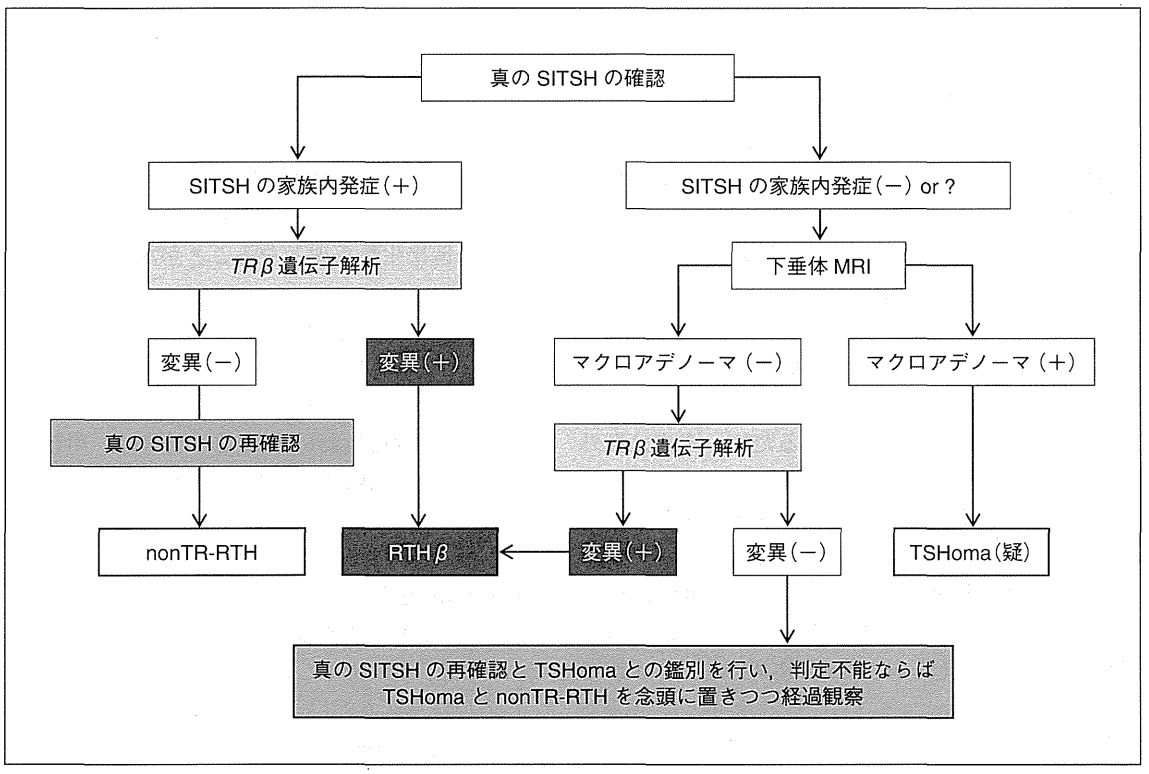

図1　RTH診断のためのアルゴリズム
日本甲状腺学会による診断のためのアルゴリズム。特に，TSH産生下垂体腫瘍(TSHoma)との鑑別に重点が置かれている。

の症例が多い。FT_4とTSHの値によって真のSITSHと鑑別することは困難であることが多く，アルブミン遺伝子変異検索をアルゴリズムに追加するべきか検討中である。

TSH産生下垂体腫瘍(TSHoma)症例では，画像検査で下垂体腫瘍を認めることが多い。また，TSHomaの家族内発症はきわめてまれであるため，家族歴の聴取が重要であるが，RTHにも家族歴がない孤発例があるので注意を要する。参考所見として，血中αサブユニットの高値やTRH負荷試験に対するTSHの無反応～低反応を示す例が多い。TSHomaも指定難病(下垂体性TSH分泌亢進症)に相当し，別途に診断の手引きがある。画像検査で明らかな下垂体腫瘍(マクロアデノーマ)を認めない症例ではnonTR-RTHと鑑別が困難であり，RTH診断基準制定における最大の検討課題となっている。現状のアルゴリズムでは，判定不能ならばTSHomaとnonTR-RTHを念頭に置きつつ経過観察となっているが，2つの指定難病の間で鑑別がつかず，どちらの助成も受けられないという事態は極力避けねばならない。

RTHの診断アルゴリズムでは，*TR*β遺伝子診断が大きな役割を果たしている。しかし，コマーシャルベースで行えるわけではなく，研究の一環として行われているのが現状である。遺伝子を扱ううえでの倫理上の問題や，遺伝子診断に伴って発生する責任など，今後解決するべき問題は多い。

また，近年，甲状腺ホルモンに対する感受性が低下する類縁疾患が報告されている。*TR*α遺伝子異常症では発達障害を認め，T_3およびTSH正常，T_4軽度低値で甲状腺ホルモンに対する反応性が低下していた[11]。また，甲状腺ホルモンのトランスポーターの一つであるmonocarboxylate transporter 8(MCT8)の異常症では，精神発達遅延や神経症状が強く，T_3高値，T_4低値，TSH正常～軽度高値を示す[12)13)]。脱ヨード酵素などの合成にかかわるselenocysteine insertion-sequence binding protein 2(SBP2)の異常症では，成長障害や精神発達遅滞を認め，T_3低値，T_4高値，TSH正常～軽度高値を示す[14]。これらの疾患ではSITSHを呈さないため，TRβ機能異常症としてのRTHと臨床的に鑑別できると考えられる。

おわりに

指定難病という制度に伴い，RTHを正確に診断することの重要性を述べてきたが，2015年1月制定の110疾患のなかにも甲状腺が関与している疾患が多数見受けられる。直接関連があるものはRTHの他，下垂体性ADH分泌異常症，下垂体性TSH分泌亢進症，下垂体性PRL分泌亢進症，クッシング病，下垂体性ゴナドトロピン分泌亢進症，下垂体性成長ホルモン分泌亢進症，下垂体前葉機能低下症といったTSH

表1　甲状腺ホルモン不応症診断基準(第1次案)

Ⅰ. 主要症候
①大部分の代謝状態は正常で臨床症状はない(全身型)。
しかし，甲状腺機能低下症あるいは亢進症の症状のいずれもとり得る。
さらに，同一症例にこれらの症状が混在することがある。
亢進症状の強い症例を下垂型としてきた。
②軽度のびまん性甲状腺腫大を認めることが多い。
③血中の甲状腺ホルモン濃度と全身の代謝状態が合致しない*1。

Ⅱ. 検査所見
①血中甲状腺ホルモン(特に遊離T_4値)が高値にもかかわらず，血中TSHは基準値内～軽度高値を示すsyndrome of inappropriate secretion of TSH(SITSH)が持続する*2。
②甲状腺ホルモン薬投与による反応が乏しい。
③甲状腺ホルモン受容体β遺伝子に変異を認める。

Ⅲ. 参考事項
①TRH試験により血中TSHは正常反応を示す。
甲状腺ホルモン薬を投与した際のTSHの抑制が不十分。
②血中αサブユニットあるいはαサブユニット/TSHモル比は正常。
③血縁者に発生する。

Ⅳ. 除外項目
TSH産生腫瘍やアルブミン遺伝子異常による家族性異アルブミン性高T_4血症との鑑別を必要とする。

[診断の基準]
確実例：ⅠとⅡの①，③を満たす症例。
疑診例：ⅠとⅡの①を満たす症例。
＊1：参考所見としてSHBG，ALP，フェリチン，CK，尿中デオキシピリジノリンなど。
＊2：測定系や測定時期を変更し，真のSITSHであるか確認する。

遺伝子診断について
*TR*β遺伝子解析の結果，変異があり以下の3つのいずれかの条件を満たせばRTHの診断は確定する。
①第1度近親者にSITSH症例が存在する。
②*TR*β遺伝子変異がRTH症例において既報の変異である。
③これまでに報告のない新規変異であるが，その変異がRTHにおいて変異が収束する3つのクラスター上に位置する(**図1**)。
④(参考)以上のいずれにも該当しないが，*in vitro*でTRβの機能異常が確認された変異である。

表2　甲状腺ホルモン不応症重症度分類(案)

診断基準の主に主要症候によって重症度分類される。
・軽症　：SITSH・甲状腺の軽度肥大以外の症状を示さず，日常生活に支障がない。
・中等度：頻脈による動悸や易被刺激性などを示し，日常生活に支障がある。
・重症　：著しい頻脈や心房細動，注意欠陥/多動性障害，精神発達遅滞・成長障害など，日常生活に著しい支障がある。

重症度にかかわらず，患者が出産した場合，児に遺伝する可能性が50%である。また，児が変異*TR*β遺伝子をもたない場合，低体重となる可能性があるなど支障がある。

※なお，症状の程度が上記の重症度分類などで一定以上に該当しないものであるが，高額な医療を継続することが必要な者については，医療費助成の対象とする。

分泌異常を来しうる下垂体疾患が挙げられる。診断において甲状腺の所見が重要である疾患には，ミトコンドリア病，全身性アミロイドーシス，クロウ・深瀬症候群がある。混合性結合組織病，シェーグレン症候群，原発性胆汁性肝硬変，自己免疫性肝炎については慢性甲状腺炎の合併が明記されている。さらに，診断のために甲状腺疾患を除外するべき疾患に，重症筋無力症，脊髄小脳変性症，家族性高コレステロール血症，慢性特発性偽性腸閉塞症が該当する。加えて，7月に追加選定となる疾患にも甲状腺に関連するものが多数含まれており，甲状腺疾患に携わる者にとって指定難病という制度は想像以上にかかわりが深いものと

考えられる。

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くる病・骨軟化症の診断マニュアル

【診断指針】

●くる病

大項目

a) 単純X線像でのくる病変化(骨幹端の杯状陥凹、または骨端線の拡大や毛ばだち)

b) 高アルカリホスファターゼ血症*

小項目

c) 低リン血症*、または低カルシウム血症*

d) 臨床症状

O脚・X脚などの骨変形、脊柱の弯曲、頭蓋癆、大泉門の開離、肋骨念珠、関節腫脹のいずれか

*年齢に応じた基準値を用いて判断する。

1) くる病

大項目2つと小項目の2つをみたすもの

2) くる病の疑い

大項目2つと小項目の2つのうち1つをみたすもの

●骨軟化症**

大項目

a) 低リン血症、または低カルシウム血症

b) 高骨型アルカリホスファターゼ血症

小項目

c) 臨床症状

筋力低下、または骨痛

d) 骨密度

若年成人平均値(YAM)の80%未満

e) 画像所見

骨シンチグラフィーでの肋軟骨などへの多発取り込み、または単純X線像でのLooser's zone

1) 骨軟化症

大項目2つと小項目の3つをみたすもの

2) 骨軟化症の疑い

大項目2つと小項目の2つをみたすもの

除外すべき疾患

癌の多発骨転移、腎性骨異栄養症、原発性副甲状腺機能亢進症

**くる病として発症した症例は、くる病の診断指針に準じる。

○骨石灰化障害を惹起する薬剤使用例では、くる病、骨軟化症いずれにおいても、低リン血症、または低カルシウム血症の存在を除いて判断する。

解説

【定義】

くる病、骨軟化症は、骨石灰化障害を特徴とする疾患である。このうち、成長軟骨帯閉鎖以前に発症するものを、くる病と呼ぶ。

【症候】

くる病では、成長障害、O脚・X脚などの骨変形、脊柱の弯曲、頭蓋癆、大泉門の開離、肋骨念珠、関節腫脹が認められることがある。骨軟化症では、骨痛や筋力低下に加え、胸郭の変形(鳩胸)、脊柱の変形、偽骨折(Looser’s zone)が生じることがある。

【検査所見】

単純骨X線でのくる病変化には、骨幹端の杯状陥凹、骨端線の拡大や毛ばだちがある(図1)。低石灰化領域を示すLooser’s zoneは、骨軟化症に特異的である(図2)。二重エネルギーX線吸収測定法などによる骨密度の測定では、骨中のカルシウム含量が測定される。従って骨軟化症では、骨密度の低下が認められる。このため骨密度の低下が認められる場合には、骨粗鬆症の診断の前に骨軟化症の可能性を考慮する必要がある。骨軟化症患者では、骨シンチグラフィーで肋軟骨への数珠状の取り込みなど、多発性の取り込みが認められることが多い(図3)。骨軟化症患者の生化学所見では、高骨型アルカリホスファターゼ血症が特徴的であり、一部を除いて慢性の低リン血症も認められる。一方くる病患者では、低リン血症ではなく低カルシウム血症が主な異常となる場合がある。

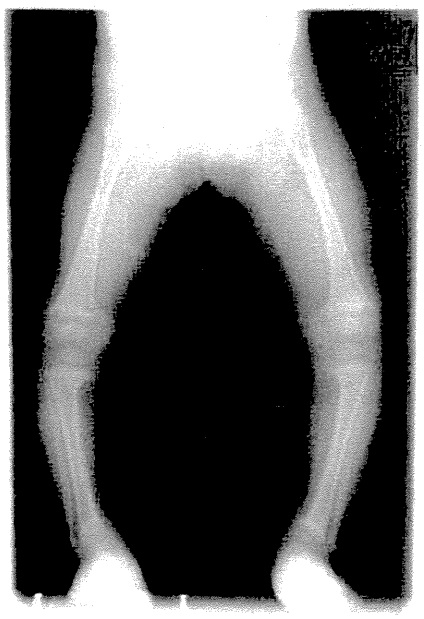

図1. 単純X線でのくる病所見

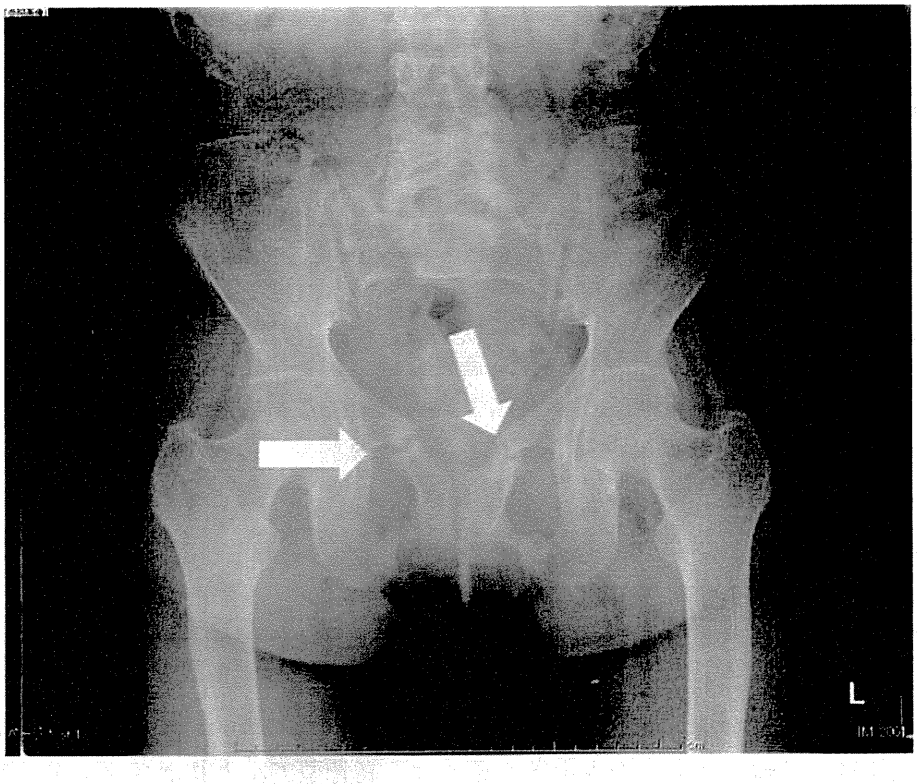

図 2. Looser' s zone

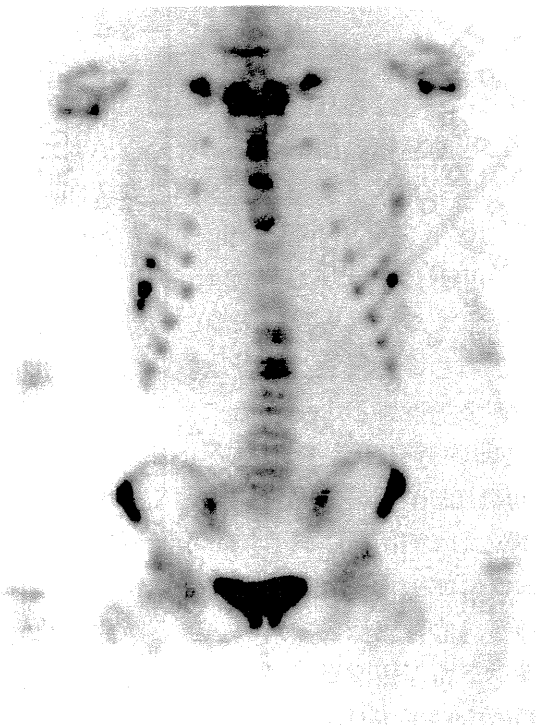

図 3. 骨軟化症患者に認められる骨シンチグラフィーでの多発取り込み