

REVIEW

# Saccharated Ferric Oxide-Induced Osteomalacia in Japan: Iron-Induced Osteopathy Due to Nephropathy

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## Introduction

Adult-onset hypophosphatemic osteomalacia is very rare in well-developed countries [1]. The most likely diagnosis of such patients, if their diet contains enough vitamin D, is oncogenic or iatrogenic osteomalacia [2, 3].

Saccharated ferric oxide (SFO;  $[\text{Fe}(\text{OH})_3]_m [\text{C}_{12}\text{H}_{22}\text{O}_{11}]_n$ ) is an intravenous preparation indicated for patients with iron-deficiency anemia [4, 5]. Since its introduction into the medical market in 1961, SFO has been used widely in Japan for iron-deficiency anemia. SFO is prepared by coating ferric iron with polysaccharide to reduce the irritancy and toxicity of iron. After intravenous administration, the colloidal iron is incorporated immediately into the reticuloendothelial system of the liver and spleen, where the iron is sequestered and stored as ferritin and hemosiderin. Some iron is released from the iron store, binds tightly to transferrin and circulates in the blood stream, and is taken up by erythroid cells in the bone marrow, leading to stimulation of erythropoiesis and improvement of iron-deficiency anemia [4, 6]. One vial of SFO contains 40 mg iron, almost equivalent to the daily flow of iron through the peripheral blood [6]. In view of the fact that the male and female body content of iron is 50 and 37 mg/kg, respectively [6], 10 to 20 vials would be usually sufficient to treat a patient with moderate anemia. However, over 7 million vials were consumed per

year 1990, suggesting excessive administration to some patients. Indeed, unexpected adverse effects developed in a few patients who received excessive SFO for prolonged periods.

The first two cases of SFO-induced osteomalacia were reported by Okada *et al.* in 1982 [7] and over 10 patients have been reported, mostly in Japanese journals [8–14] (Table 1). Most of these cases were reported not by the physicians who administered SFO, but by those who stopped the medication. The clinical data presented in some case reports are not those obtained during SFO administration but those after withdrawal of SFO (Tables 1–4). Therefore, the pathogenesis of SFO-induced osteomalacia was not elucidated fully. Furthermore, only brief histomorphological details have been reported [8, 9]. In order to stimulate interest in this iatrogenic osteomalacia, we have reviewed its clinical features, histopathology of skeletal tissue, and pathogenesis. Furthermore, we have discussed why this peculiar type of iatrogenic osteomalacia has, so far, been reported only in our country.

## Clinical Features

Patients with SFO-induced osteomalacia have chronic, intractable iron-deficiency anemia due to various disorders, such as nonspecific multiple ulcers of the intestine, and chronic hepatitis C with liver cirrhosis [7, 14]. In some patients, no suitable reason for SFO administration could be found, suggesting inappropriate administration (Table 1, 2). Most of the patients were in their fifth to seventh decades of life and the male to female ratio was 1 to 10. At the time of diagnosis, their serum iron levels were high, and the total iron-binding capacity

Received: November 10, 1997

Accepted: April 6, 1998

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**Table 1.** Characteristics of reported patients with SFO-induced osteomalacia

Patient	Daily dose (duration)	Total dose	Diagnosis [Reference]
1. F (46)	80 mg (3 years)	7.2 g	Multiple ulcers of small intestine [7]
2. F (37)	40 mg (9 years)	ND	Multiple ulcers of small intestine [7]
3. F (61)	40 mg (3 years)	40 g	Anemia, rheumatoid arthritis? [8]
4. F (58)	80 mg (2.5 years)	29 g	Iron-deficiency anemia [9]
5. F (55)	ND	ND	Short intestine syndrome [10]
6. F (61)	ND (1.9 years)	ND	Iron-deficiency anemia [10]
7. F (51)	ND (6 months)	ND	Iron-deficiency anemia [10]
8. F (47)	20 mg (4 years)	20 g	Iron-deficiency anemia [11]
9. F (60)	ND (2.5 years)	12 g	Iron-deficiency anemia [12]
10. F (58)	ND (1 year)	ND	Anemia [13]
11. M (60)	5 years	25 g	Anemia, liver cirrhosis [14]

ND: not described. SFO, saccharated ferric oxide.

**Table 2.** Clinical data of patients with SFO-induced osteomalacia (1)

	Hb (g/dl)	RBC (10 <sup>4</sup> /mm <sup>3</sup> )	Ht (%)	WBC (/mm <sup>3</sup> )	Serum Fe (μg/dl)	TIBC (μg/dl)	ferritin (ng/ml)
Patient 1	10.2	331	33	4,300	38	285	—
2	—	—	—	—	—	—	—
3	12.8	382	38	4,000	191	211	5,440
4	11.5	357	36	5,400	175	185	—
5	6.4	330	—	3,000	—	—	—
6	10.8	349	—	3,500	—	—	—
7	10.5	320	—	7,300	—	—	—
8	11.1	322	32.8	5,440	93	276	993
9	11.8	368	36	5,000	181	203	2043
10	10.5	—	—	—	168	—	4050
11	12.3	361	37.9	3,200	181	181	1370

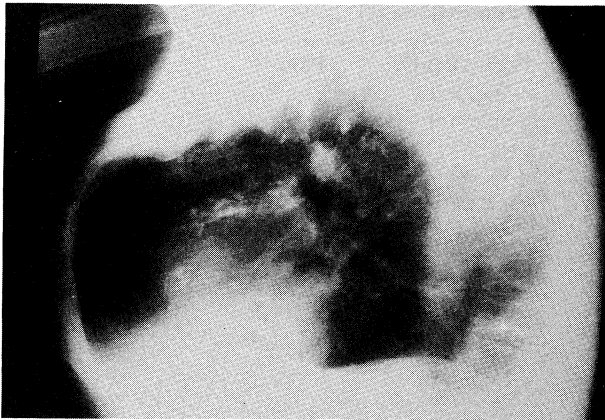
SFO, saccharated ferric oxide; TIBC, total iron-binding capacity.

(TIBC) was virtually saturated [14], suggesting that serum iron levels would have exceeded the TIBC during the SFO infusion, as reported in patients with acute iron poisoning [15]. In keeping with these data, their serum ferritin levels were considerably elevated, reflecting the increased iron deposition. In one patient, injection of desferioxamine increased the urinary excretion of iron markedly [8].

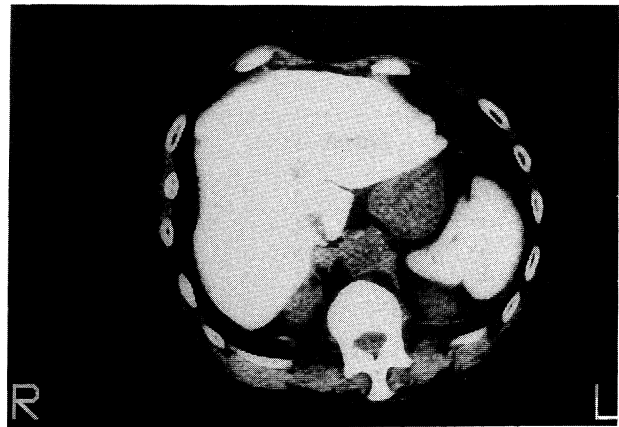
The clinical and radiographic features of SFO-induced osteomalacia do not differ from those of osteomalacia in general, although symptoms of general debility may be more marked in patients with advanced disease. All patients complained of generalized bone pains in the shoulders, thorax, back, hips, and knees, which gradually worsened after receiving intravenous injections of SFO. The bone pains worsened over a few years until SFO

was discontinued, they were so severe that the patients could walk only with crutches, and some patients were confined to bed due to severe pains. The most severely affected patient, who received SFO every day for 3 years, had body length shortening by 14 cm, accompanied by marked kyphosis and barrel-shaped thorax and abdomen [8] (Fig. 1). Consistent with characteristic findings in patients with hemochromatosis [16], a computed tomographic (CT) scan of the abdomen revealed greatly increased CT number for the liver and spleen, whereas that of the kidney was only slightly increased [8] (Fig. 2). In all patients, the skin was darkened, suggesting secondary hemochromatosis [9].

Most of the reported patients had normal renal function (Table 3). Their serum BUN and creatinine levels were normal, they had almost normal or



**Fig. 1.** Chest X-ray film of a patient with SFO-induced osteomalacia. A 61-year-old woman had been injected with SFO (40 mg every day) for 3 years (Patient 3) [8].



**Fig. 2.** CT scan of the abdomen of a patient with SFO-induced osteomalacia. The same patient as in Fig. 1. Note the metallic density of the liver and spleen, suggesting hemosiderosis. Her barrel-shaped thorax and abdomen due to kyphosis are remarkable.

**Table 3.** Clinical data of patients with SFO-induced osteomalacia (2)

	Serum							Urine				
	TP (g/dl)	Alb (g/dl)	Ca (mg/dl)	P (mg/dl)	Al-P (U/l)	BUN (mg/dl)	Cr (mg/dl)	Prot	Gl	Ca (mg/day)	P (mg/day)	TRP (%)
Patient												
1	6.7	3.7	8.9	1.0	182	12	0.6	(-)	(-)	112	476	63%
2	4.2	2.3	-	1.0	-	-	-	-	-	-	-	-
3	6.6*	-	8.9*	3.6*	53*	9*	0.9*	(-)	(-)	-	-	-
4	6.8	4.2	9.6	2.0	24.7 <sup>#</sup>	15	0.9	-	-	100	100	-
5	-	-	8.2	1.6	40 <sup>#</sup>	6	0.7	-	-	-	-	52%
6	-	-	8.1	1.9	155	18	0.7	-	-	-	-	78.5%
7	-	-	7.4	1.9	39.7 <sup>#</sup>	17	1.0	-	-	-	-	-
8	6.9	4.0	8.0	1.5	18.7 <sup>#</sup>	17	0.6	(-)	(-)	66	318	80%
9	-	-	8.4	1.1	41.4 <sup>#</sup>	-	-	(-)	(-)	-	-	-
10	-	-	-	1.4	977	-	-	-	-	-	-	72.5%
11	8.1	3.6	8.0	0.5	945	18	1.0	(+)	(++)	40	290	-

\*Samples were taken after SFO was discontinued. <sup>#</sup>KA unit. SFO, saccharated ferric oxide; TRP, tubular reabsorption of phosphate.

slightly reduced creatinine clearance. Although proteinuria was negative, increased urinary excretion of  $\beta_2$ -microglobulin and N-acetyl- $\beta$ -D-glucosaminidase were detected [11], indicating that proteinuria was not of glomerular, but tubular, origin [17]. Despite marked hypophosphatemia, urinary excretion of phosphate was inappropriately high, suggesting that renal tubular reabsorption of phosphate (TRP) was impaired (Table 3). The impaired %TRP gradually improved after stopping the medication. Liver function was normal except

in one patient with chronic hepatitis C and liver cirrhosis [14]. Alkaline phosphatase (Al-P) activity of bone origin was increased in all patients (Table 3).

Serum calcium was normal or slightly decreased, with slightly increased intact PTH (Table 4). Serum 25-OHD was normal or slightly decreased, whereas serum 1,25-(OH) $_2$ D was decreased to undetectable levels during SFO administration [14]. Active vitamin D gradually increased after discontinuation of SFO [14], which accounts for the normal serum

**Table 4.** Clinical data of patients with SFO-induced osteomalacia (3)

	25-OHD (ng/ml)	1,25-(OH) <sub>2</sub> D (pg/ml)	24,25-(OH) <sub>2</sub> D (ng/ml)	PTH
Patient 1	47.0 <sup>†</sup>	—	—	0.49 ng/ml <sup>#</sup>
2	—	—	—	—
3	6*	39*	0.44*	0.44 ng/ml <sup>##</sup>
4	8.0	18	1.1	0.38 ng/ml <sup>#</sup>
5	—	—	—	<0.6 ng/ml <sup>#</sup>
6	—	—	—	<0.6 ng/ml <sup>#</sup>
7	—	—	—	<0.6 ng/ml <sup>#</sup>
8	4.0*	55*	1.1*	0.2 ng/ml <sup>##</sup>
9	Normal*	Normal*	Normal*	—
10	—	—	—	—
11	4.6	<7.5	0.35	74 pg/ml <sup>##</sup>
Normal range	10–30	30–70	0.5–1.5	23–73 <sup>##</sup>

<sup>†</sup>Samples were taken during vitamin D<sub>2</sub> supplementation. \*Samples were taken after SFO was discontinued. # PTH determined by RIA specific for the C-terminal region of PTH. ## Intact PTH determined by immunoradiometric assay (IRMA). SFO, saccharated ferric oxide.

1,25-(OH)<sub>2</sub>D levels reported in several cases [8, 9, 11]. This was demonstrated clearly in a patient treated with vitamin D<sub>2</sub> at a daily dose of 1000 U (Fig. 3). One week and three months after discontinuation of SFO, the serum levels of 25-OHD<sub>2</sub> and 1,25-(OH)<sub>2</sub>D<sub>2</sub>, respectively, increased, suggesting that 25-hydroxylase in the liver remains intact and the impairment of renal 1 $\alpha$ -hydroxylase activity is reversible [14]. Several patients were prescribed vitamin D (dihydroxycholesterol, D<sub>2</sub>, 1 $\alpha$ -OHD<sub>3</sub>), whilst receiving SFO, but their bone pains did not improve, until the iron infusion was discontinued. As expected, the bone deformities of the most severely affected patient were permanent [8].

### Histomorphology of Skeletal Tissue

Examination of a bone marrow biopsy specimen of a patient revealed numerous blue deposits of iron, suggesting that the iron-transferrin complex had been taken up into the erythroid marrow cells and reticuloendothelial cells, where iron is stored as aggregated ferritin (hemosiderin) [9, 10, 13] (Fig. 4). Liver biopsy samples of two patients revealed abundant hemosiderin deposits in the Kupffer cells and hepatocytes [10, 13], as reported in patients with iron overload [18]. These findings are compatible with greatly increased CT numbers for

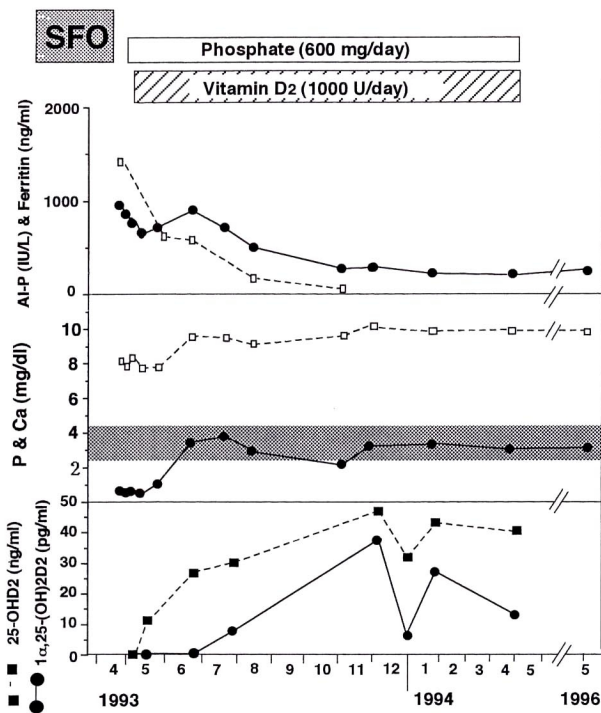
the liver and spleen [8] (Fig. 2). A kidney biopsy specimen from one patient [12] revealed a small amount of iron deposited in the proximal renal tubules.

Bone biopsy was performed in five patients [8–11], all of whom showed marked hyperostoidosis with little double labeling band of tetracycline (Fig. 5). Furthermore, iron deposits were identified in the calcification front and in osteoblasts in the iliac bone (Fig. 6). These findings are compatible with the experimental findings of Huser *et al.* [19] and De Verejoul *et al.* [20] that injection of a large amount of iron into mice and pigs, respectively, resulted in linear deposition of iron at the edges of the trabecular surfaces and osteoid/mineralized bone interface, as well as deposition in osteoblasts and marrow macrophages. Similar findings were reported in patients with thalassemia major who had received massive blood transfusions since childhood [21–23].

### Pathophysiology of SFO-Induced Osteomalacia

In general, osteomalacia develops when serum levels of calcium, phosphorus or 1,25-(OH)<sub>2</sub>D are decreased or osteoblasts are unable to produce alkaline phosphatase and bone matrix proteins [1]. As the serum levels of phosphorus and 1,25-(OH)<sub>2</sub>D

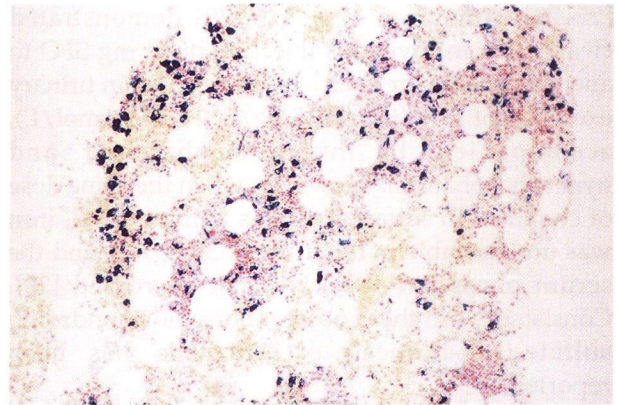




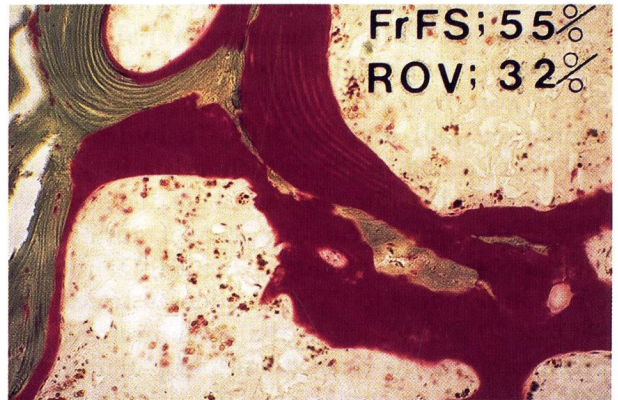
**Fig. 3.** The clinical course of a patient with saccharated ferric oxide (SFO)-induced osteomalacia. A 60-year-old man with liver cirrhosis who had been receiving SFO intravenously for 5 years developed severe bone pains. Injection of SFO was discontinued in April, 1993, and vitamin D<sub>2</sub> and phosphate were prescribed. His serum 25-OHD<sub>2</sub> level increased immediately, whereas that of serum 1,25-(OH)<sub>2</sub>D<sub>2</sub> increased after 3 months, accompanied by gradual improvement of all his clinical manifestations. Upper panel: ●, Al-P (IU/L); □, ferritin (ng/ml), middle panel: ●, P (mg/dl); □, Ca (mg/dl), lower panel: ■, 25-OHD<sub>2</sub> (ng/ml); ●, 1,25-(OH)<sub>2</sub>D<sub>2</sub> (pg/ml). (Reproduced from Ref. 14, with permission of the publisher).

in patients with SFO-induced osteomalacia were markedly decreased to levels low enough to impair bone formation, it is very reasonable that hypophosphatemic, active vitamin D-deficient osteomalacia developed as a result of excessive and prolonged administration of SFO to patients with chronic anemia.

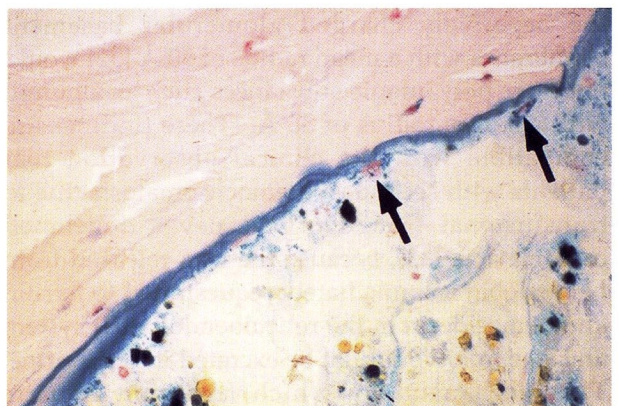
In contrast to negatively charged chondroitin sulfate-iron with a particle diameter of 100 Å (Brutal, Dainippon Pharmaceutical Co., Osaka, Japan) [24], SFO with a particle diameter of 20–50 Å and neutrally charged saccharide [25] filters easily through the negatively charged glomerular basement membrane, and is excreted into the urine



**Fig. 4.** Bone marrow biopsy specimen of a patient with saccharated ferric oxide (SFO)-induced osteomalacia. Iron deposits are abundant in bone marrow cells of the iliac bone in patient 3 (Prussian blue staining).



**Fig. 5.** Bone biopsy specimen of a patient with saccharated ferric oxide (SFO)-induced osteomalacia. Marked osteoid tissue in the trabecular bone of the ilium in patient 3 (Goldner staining). ROV, Rate of osteoid volume; FFS, Fractional ferric staining.



**Fig. 6.** Iron deposition in the calcification front. Prussian blue staining revealed iron deposition in the calcification front of the iliac bone of patient 3. Iron deposits were also found in osteoblasts (arrows).

[25–29]. Imamura *et al.* [26, 29] demonstrated clearly that intravenous injection of 40 mg SFO to anemic patients for over 14 days resulted in urinary excretion of iron (635–6215  $\mu\text{g/L}$ ; 11–111  $\mu\text{mol/L}$ ), accompanied by hypophosphatemia and hyperphosphaturia. However, when the same dose of chondroitin sulfate-iron was administered, iron was undetectable in the urine ( $< 50 \mu\text{g/L}$ ), and the serum phosphate level was not decreased [26]. Consistent with these observations, no chondroitin sulfate-iron-induced osteomalacia has been reported.

An electron-microscopic study in rats revealed that the filtered SFO particles were taken up by pinocytosis into the proximal renal tubules [25]. The apical vesicles containing iron particles then fused with lysosomes, which were later broken down, scattering the particles in the cytoplasm and mitochondria [25]. Therefore, renal tubular reabsorption of phosphate, which is controlled by Na-Pi cotransporter (NPT2) on the luminal membrane [30] and 25-OHD<sub>3</sub>-1 $\alpha$ -hydroxylase, which is located in the mitochondria [31], were both impaired, leading to phosphate diabetes. We developed a primary culture system of murine renal tubular cells, which produce 1,25-(OH)<sub>2</sub>D<sub>3</sub> from 25-OHD<sub>3</sub> in response to PTH, and demonstrated that SFO, at 30  $\mu\text{M}$ , which is attainable in urine and presumably in the renal tubules of patients with SFO-induced osteomalacia [26], impaired 1 $\alpha$ -hydroxylase activity directly [14].

In contrast to SFO, iron bound to transferrin (stokes radius, 40 Å) [39], ferritin (stokes radius, 61 Å) [32] or chondroitin sulfate (stokes radius, 100 Å) [24] is not excreted into the urine, because the negatively charged glomerular basement membranes with a mean radius of 50 Å [32] would not filter polyanionic substances such as albumin with a stokes radius of 36 Å. These findings are compatible with the clinical observation that patients with secondary hemochromatosis due to transfusional iron overload never developed osteomalacia [33], because the iron released from hemoglobin is immediately sequestered to ferritin and hemosiderin in the reticuloendothelial system and free iron would not be excreted into the urine. The mechanism by which free iron impairs proximal renal tubular functions, particularly renal reabsorption of phosphate and 1 $\alpha$ -hydroxylase, remains to be elucidated. In rats with nephrotic

syndrome, free iron released from transferrin in acidic renal tubular fluid elicits tubulointerstitial injury by catalysing hydroxyl radical ( $\cdot\text{OH}$ ) formation [34]. It is well known that cytoplasmic P450 oxidases, xanthin oxidase, and prostaglandin endoperoxidases can synthesize free radicals in the proximal renal tubules, the levels of which are enhanced in the presence of iron [35–38]. Very recently, cDNA for 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase was cloned, and the deduced amino acid sequence of this cDNA has substantial homology with members of mitochondrial P450 family [39]. Therefore, it is highly likely that free iron in the renal tubules released from colloidal iron damages renal tubular function by peroxidation-related mechanisms, leading to damage to phosphate transporters in the renal tubular cells and inactivation of the mitochondrial enzymes.

In addition to its detrimental effects on renal tubules, SFO, at concentrations (3  $\mu\text{M}$ ) probably attainable in serum when excessive doses are administered intravenously, was found to inhibit bone formation directly [14]. However, no osteomalacic lesion was found when fetal mouse bones were cultured in medium sufficiently supplemented with calcium and phosphate despite the high concentrations of SFO [14]. Iron in peripheral blood is usually bound tightly to transferrin, and hardly any free iron is present in the blood [35, 40]. However, when iron is injected repeatedly to the extent that the iron-binding capacity is saturated, free iron is deposited on the calcification front in skeletal tissue, as demonstrated in experimental animal models [19, 20].

It should be pointed out that SFO is used not only in Japan but also in the other countries, such as Australia, Ireland and England [4]. However, so far, the iatrogenic osteomalacia has been reported only in our country [4, 41], where the extremely socialized health insurance system pays for all the medicines used for patients piecemeal [42]. Once a new drug is approved by the Ministry of Public Welfare, a physician can use it at will, because the health insurance system is based on the assumption that every physician prescribes medicine at an appropriate dose for an appropriate period for appropriate diseases. Unfortunately, a few physicians, who do not understand ferrokinetics, have used SFO arbitrarily or even abusively,

without knowing its adverse effects.

### Diagnosis and Treatment of SFO-Induced Osteomalacia

SFO-induced osteomalacia is characterized by generalized bone pains accompanied by hypophosphatemia, phosphaturia, and decreased serum levels of 1,25-(OH)<sub>2</sub>D, resembling to some extent oncogenic osteomalacia in which an unidentified humoral factor(s), called phosphatonin, inhibits renal tubular reabsorption of phosphate and 1 $\alpha$ -hydroxylase by unknown mechanisms [30]. However, if a physician knows that excessive administration of SFO may cause hypophosphatemic osteomalacia with renal phosphate wasting, a snap diagnosis can be made [14]. Bone biopsy is recommended, but is not mandatory in establishing the diagnosis [43].

Once SFO-induced osteomalacia has been diagnosed, simply discontinuing SFO without any medication is enough for recovery [11]. In one patient, the serum phosphate level normalized 12 days after stopping SFO infusion, followed by gradual improvement of bone pains [11], whereas it took 3 months for the 1 $\alpha$ -hydroxylase activity to recover in a patient with a prolonged history of SFO-induced osteomalacia [14]. If hypophosphatemia and bone pains are severe, oral phosphate and vitamin D supplementation is recommended. Fortunately, the renal tubular dysfunction and the osteomalacia were reversible in all the reported patients, whereas the bone deformities were permanent in the most severely affected patient [8].

### Summary

Saccharated ferric oxide (SFO)-induced osteomalacia develops when excessive SFO

infusions are administered to patients with anemia for prolonged periods for a few years. The small particles and almost neutral saccharide of SFO filter through the glomerular tufts into the renal tubules, resulting in impairment of proximal renal tubular function, particularly renal reabsorption of phosphate and 1 $\alpha$ -hydroxylase activity, resulting in decreased serum levels of phosphorus and active vitamin D, both of which lead to development of hypophosphatemic osteomalacia. Furthermore, SFO, at concentrations attainable in serum, exacerbates the osteomalacia by inhibiting bone formation directly. In contrast to itai-itai disease, another iatrogenic osteomalacia due to cadmium nephropathy [44], the proximal renal tubular function impairment induced by SFO is reversible simply by discontinuing the nephrotoxin, which is followed by improvement of all the clinical manifestations, except bone deformities.

So far, SFO-induced osteomalacia, that is, SFO-induced osteopathy due to nephropathy, has been reported only in Japan, probably due to the lax surveillance system of the health insurance scheme. All physicians who prescribe SFO should be aware of its severe adverse effects. We hope that such iatrogenic osteomalacia caused by abusive infusion of SFO will never again be reported in our country.

### Acknowledgments

We thank Prof. Hiroshi Demura for his critical review of the manuscript. We also thank Dr. Akira Yamaguchi (Tokyo Metropolitan Institute of Geriatrics, Tokyo, present address; Department of Oral Pathology, School of Dentistry, Showa University, Tokyo) for providing us with histological data. We are very grateful to Yoshitomi and Dainippon Pharmaceutical Co. (Osaka) for providing us with valuable information. This study was supported by Grants-in-Aid from the Research Society for Metabolic Bone Diseases.

### References

1. Goldring SR, Krane SM, Avioli LV (1995) Disorders of calcification: Osteomalacia and rickets. In: DeGroot LJ (ed) *Endocrinology*. 3rd ed, Philadelphia, W. B. Saunders, vol. 2: 1204–1227.
2. Bikle DD (1996) Drug-induced osteomalacia. In: Favus MJ (ed) *Primers on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 3rd ed, Lippencott-Raven, New York, 333–337.



3. Drezner MK (1996) Tumor-induced rickets and osteomalacia. In: Favus MJ (ed) *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 3rd ed, Lippencott-Raven, New York, 319–325.
4. Drug Interview Form, Fesin (Nippon Hyoujun Shouhin Bunrui Bango 873222), Yoshitomi Pharmaceutical Co, Osaka, Japan, revised in June 1996.
5. Sakae F, Kobayashi K (1956) Effects of saccharated ferric oxide on patients with iron-deficiency anemia: effect on serum iron. *Shinyaku to Rinshou* 5: 389–395 (In Japanese).
6. Hillman RS (1996) Drugs effective in iron-deficiency and other hypochromic anemias. In: Hardman JG, Limbird LE, Morinoff PB, Rubbon RW, Gilman AG (eds) *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 9th ed, McGraw-Hill, New York, 1317–1325.
7. Okada M, Imamura K, Fuchigami T, Omae T, Iida M, Nanishi F, Murakami M, Ohgushi H, Yao T, Fujita K, Ogawa K (1982) Osteomalacia caused by intravenous administration of saccharated ferric oxide for treatment of iron-deficiency anemia associated with nonspecific multiple ulcers of the small intestine: Report of two cases. *Jpn J Intern Med* 71: 1566–1572 (In Japanese).
8. Shiraki M (1986) Osteomalacia induced by iron and aluminum. Review and cases. *Nippon-Rinsho* 44: 2493–2498 (In Japanese).
9. Sasaki S, Harada M, Ueno Y, Shima Y (1987) A case of osteomalacia due to secondary hemochromatosis. *Seikei-geka* 38: 393–397 (In Japanese).
10. Kuranobu K, Yamamoto K, Kishimoto H, Ogino H (1990) Three cases of osteomalacia caused by intravenous administration of saccharated ferric oxide. *Seikeigeka to Saigaigeka* 38: 1182–1185 (In Japanese).
11. Mizumoto H, Ikota A, Mashio Y, Tsuji S, Takahashi H (1990) A case of osteomalacia caused by intravenous administration of saccharated ferric oxide. *Naika* 65: 593–596 (In Japanese).
12. Mizutani Y, Tsukada T, Shimomura A, Kobayashi M, Shido T (1991) A case of osteomalacia induced by saccharated ferric oxide. *Naika* 68: 1187–1189 (In Japanese).
13. Suzuki A, Ohike H, Matsuoka Y, Irimajiri S (1993) Iatrogenic osteomalacia caused by intravenous administration of saccharated ferric oxide. *Am J Hematol* 43: 75–76.
14. Sato K, Nohtomi K, Demura H, Takeuchi A, Kobayashi T, Kazama J, Ozawa H (1997) Saccharated ferric oxide (SFO)-induced osteomalacia: In vitro inhibition by SFO of bone formation and 1,25-dihydroxy-vitamin D production in renal tubules. *Bone* 21: 57–64.
15. Banner W, Tong TG (1986) Iron poisoning. *Pediatr Clin North Am* 33: 393–409.
16. Howard JM, Ghent CN, Carey LS, Planagan PR, Valberg LS (1983) Diagnostic efficacy of hepatic computed tomography in the detection of body iron overload. *Gastroenterology* 84: 209–215.
17. Gonick HC (1995) Nephropathy of heavy metal intoxication. In: Massry SG, Glasscock RJ (eds) *Textbook of Nephrology*. 3rd ed, Wilkins, Baltimore, 947–963.
18. Iancu TC, Shiloh H (1994) Morphologic observations in iron overload: An update. *Adv Exp Med Biol* 356: 255–265.
19. Huser HJ, Eichenberger P, Cottier H (1971) Incorporation of iron into osteoid tissue and bone. *Schweiz Med Wschr* 101: 1815.
20. De Verejoul MC, Pointillart A, Golnzer CC, Morieux C, Bielakoff J, Modrowski D, Miravet L (1984) Effects of iron overload on bone remodeling in pigs. *Am J Pathol* 116: 377–384.
21. De Verejoul MC, Girot R, Gueris J, Cancela L, Bang S, Bielakoff J, Mautalen C, Goldberg D, Miravet L (1982) Calcium phosphate metabolism and bone disease in patients with homozygous thalassemia. *J Clin Endocrinol Metab* 54: 276–281.
22. Gratwick GM, Bullough PG, Bohne WHO, Markenson AL, Peterson CM (1978) Thalassemic osteoarthropathy. *Ann Intern Med* 88: 494–501.
23. Rioja L, Girot R, Garabédian M, Cournot-Witmer G (1990) Bone disease in children with homozygous  $\beta$ -thalassemia. *Bone & Mineral* 8: 69–86.
24. Wakisaka K, Kariyone S (1964) Studies on reticuloendothelial function using colloid-iron and heat-treated erythrocytes. *Nippon Mounaikei Gakkai Zasshi* 4: 32–46 (In Japanese).
25. Tanaka S (1964) An electron-microscopic study on the filtration and resorption of saccharated ferric oxide of the rat kidney. *Nippon Jinzou Gakkai-shi* 7: 347–360 (In Japanese).
26. Imamura K, Okada M, Fuchigami T, Iida M, Omae T (1982) Effect of intravenous administration of iron preparation on hypophosphatemia—the second report. *Igaku-no-Ayumi* 121: 413–414 (In Japanese).
27. Nakanishi T (1991) Studies on the pathogenesis of iron-deficiency anemia. Urinary excretion of iron in clinical and experimental experiments. *Okayama Igakukai Zasshi* 103: 803–811 (In Japanese).
28. Nakanishi Y, Kukita K, Yoshimura Y, Ose S (1966) Studies on iron-chondroitin-sulfate colloid for intravenous injection. I. Relations between physicochemical and pharmacological properties. *Yakugaku-Zasshi* 86: 46–50 (In Japanese with English abstract).
29. Okada M, Imamura K, Iida M, Fuchigami T, Omae T (1983) Hypophosphatemia induced by intravenous administration of saccharated iron oxide. *Klin Wschr* 61: 99–102.
30. Drezner MK (1996) Phosphorus homeostasis and



- related disorders. In: Bilezikian JP, Raisz LG, Rodan GA (eds) *Principles of Bone Biology*. Academic Press, San Diego, 263–276.
31. Feldman D, Malloy P, Gross C (1996) Vitamin D: metabolism and action. In: Marcus R, Feldman D, Kelsey J (eds) *Osteoporosis*. Academic Press, San Diego, 205–235.
  32. Myers BD (1995) Determinants of the glomerular filtration of macromolecules. In: Massry SG, Glasscock RJ (eds) *Massry & Glasscock's Textbook of Nephrology*. 3rd ed, Williams & Wilkins, Baltimore, 60–65.
  33. Edwards CQ (1993) Hemochromatosis and other iron storage disorders. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds) *Wintrobe's Clinical Hematology*. 9th ed, Lea & Febiger, Philadelphia, 1: 872–884.
  34. Alfrey AC (1992) Toxicity of tubule fluid iron in the nephrotic syndrome. *Am J Physiol* 263: F637–F641.
  35. Britton RS, Ramm GA, Olynyk J, Singh R, O'Neill R, Bacon BR (1994) Pathophysiology of iron toxicity. *Adv Exp Med Biol* 356: 239–253.
  36. Burkitt MJ, Mason RP (1991) Direct evidence for in vivo hydroxyl-radical generation in experimental iron overload: An ESR spin-trapping investigation. *Proc Natl Acad Sci USA* 88: 8440–8444.
  37. Koppenol WH (1994) Chemistry of iron and copper in radical reactions. In: Rice-Evance CA, Burden RH (eds) *Free Radical Damage and its Control*. Elsevier Science BV, 3–24.
  38. Lauffer RB (1992) Iron, aging, and human disease: Historical background and new hypotheses. In: Lauffer RB (ed) *Iron and Human Disease*. CRC Press, Boca Raton, 1–20.
  39. Kitanaka S, Takeyama K, Murayama A, Sato T, Okumura K, Nogami M, Hasegawa Y, Niimi H, Yanagisawa J, Tanaka T, Kato S (1998) Inactivating mutations in the 25-hydroxyvitamin D<sub>3</sub> 1 $\alpha$ -hydroxylase gene in patients with pseudovitamin D-deficiency rickets. *N Engl J Med* 338: 653–661.
  40. Aisen P (1980) Iron transport and storage proteins. *Ann Rev Biochem* 49: 357–394.
  41. Burns DL, Mascioli EA, Bistrian BR (1995) Parenteral iron dextran therapy: A review. *Nutrition* 11: 163–168.
  42. Cambell JC, Ikegami N (1998) *The Art of Balance in Healthy Policy: Maintaining Japan's Low-Cost, Egalitarian System*. Cambridge University Press, Cambridge, UK.
  43. Bingham C, Fitzpatrick LA (1993) Noninvasive testing in the diagnosis of osteomalacia. *Am J Med* 95: 519–523.
  44. Wedeen RP (1997) Nephrotoxicity secondary to environmental agents and heavy metals. In: Schrier RW, Gottschalk CW (eds) *Diseases of the Kidney*. 6th ed, Little Brown & Co., Boston, 1231–1247.