PATIENT

Initials for the patient's name: H.S. Nationality: Japanese
Sex: female, Place of birth: Tokyo Birth date: January 17, 1940,
Birth weight: 2,750g (Full term)
She had blue sclera and teleangiectasia at both cheeks. She had no other recognizable abnormality.
Family history Her maternal grand-mother was told by her doctor that she had an advanced osteoporosis at age 70, although she did not sustain any bone fracture. She died of a subarachnoid hemorrhage at age 83. Meanwhile, her mother, director of an obstetrician clinic, sustained a thoracic vertebral compression fracture and put on a corset since she was in her 60's. When she was 69 years old, she stumbled in trying to get out of a car. Then, she sustained a right femoral neck fracture. She was hospitalized at Tokai University Hospital, where she was operated on. Her post-operational course was uneventful. However, she did not show any enthusiasm to undergo rehabilitation to restart walking. She remained bedridden, developing a string of cerebral infarctions. She expired at the age 73.

Patient's osteoporosis-related history

In December 1952, when she was a junior high school freshman, she went on a skiing trip with a group of her classmates led by her school teacher to the Akakura Onsen skiing resort at Mt. Akakura in Myoko, Niigata Prefecture. She ascended the skiing slope to its top and then started to descend it down. For an unknown reason, she veered to the left, losing her balance and falling sideways. She sustained a fracture of her right tibia. The type of her fracture was what osteopathic physicians in Japan called a wakatake kossetsu [a sort of greenstick fracture similar to those seen when "wakatake (young bamboo)" branches are bent excessively] This is a type of fractures seen often among children. She did not undergo an orthopedic incision surgery to fix the fractured site, but was admitted for three months into Tokyo's Nagura Clinic, which was then the most famous osteopathic clinic in Kitasenjyu, Adachi Ward.
She preferred the clinic's classic massage and plaster-based treatments to an open surgery which she feared would leave a keloid-type scar on her leg. She had been taking ballet lessons at the Baku Ishii Ballet Studio at Tokyo's Jiyugaoka, ever since she was 8 years old, dreaming of becoming a

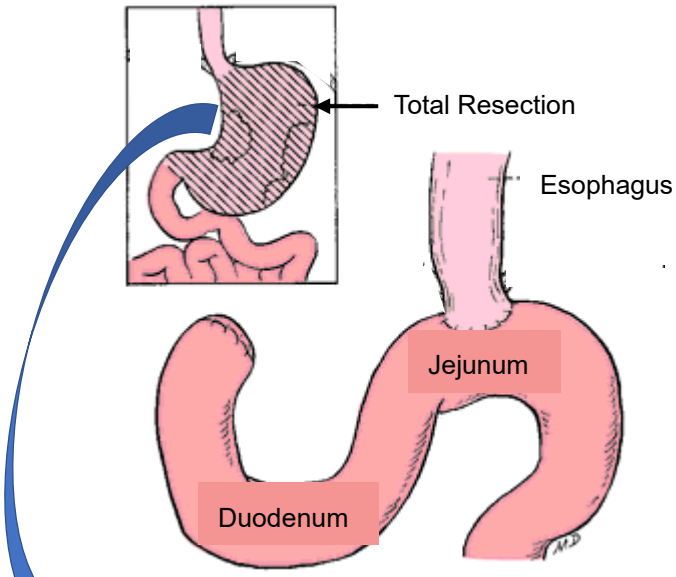
professional ballerina someday. Still, the orthopedic surgeon at the skiing resort's hospital terrified the would-be prima donna by telling her unreservedly that he would surgically open up her lower limb and connect the ends of the fractured tibia with wires, keeping the lower limb suspended from a rack mounted on her bed with a separate set of wires, so that the now-connected edges may be firmly joined through a natural ossification process.

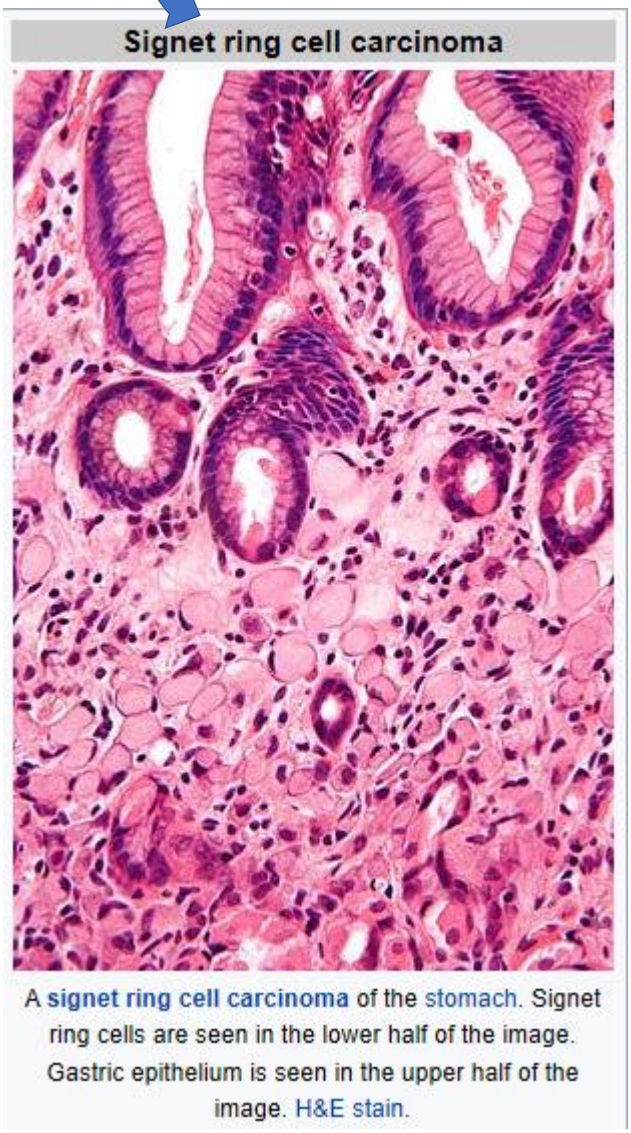
During the subsequent three-month hospitalization at the Tokyo clinic to which the frightened teenager "fled," osteopathic physicians daily gave her a massage, covering her right leg with a dark-black viscous oily substance as if a carpenter plastered a wall. The cast-like substance, also replaced daily, was soft for a short space of time, but speedily stiffened. Even after she was discharged from the clinic and returned home in early March, the physicians made her broken leg stay immobilized with a cast for a few more weeks. She returned to school the following month.

Figure 17. A 12-year-old patient photographed at Mt. Takao in the outskirts of Tokyo. The picture was taken in October 1952, two months before her tibia fracture on the Mt. Akakura skiing slope

After graduating from Keio University and working as a medical researcher on molecular biology in the United States, she returned to Japan, undergoing a periodic upper gastrointestinal checkup with barium-based contrast radiography every year until 1999. No abnormality was found in the 1999 check. But when she was examined with an endoscope for the first time in her life in March 2000 at Tokai University Tokyo Hospital, Dr. Jun Aoki detected a carcinoma measuring about 2 cm in diameter at the lesser curvature of her stomach. Then, a total gastrectomy was performed by Dr. Hiroyasu Makuuchi at the university's another hospital in Kanagawa Prefecture on April 4, 2000. This was done after a pathological check revealed the presence of signet-ring cell carcinoma with a peritoneal dissemination. Metastases to several lymph nodes around the stomach were also detected. The nodes were also removed. Her postoperative course was uneventful. In December 2007, however, an intramucosal esophageal cancer was endoscopically found by Dr. Aoki. Then the cancer was surgically removed under an endoscopic observation by Dr. Makuuchi.

Figure 18-1. Total Gastrectomy performed with Roux-en-Y Operation





A signet ring cell carcinoma of the stomach. Signet ring cells are seen in the lower half of the image. Gastric epithelium is seen in the upper half of the image. H&E stain.

Figure 18-2. Report on Endoscopy of Upper Digestive Tract

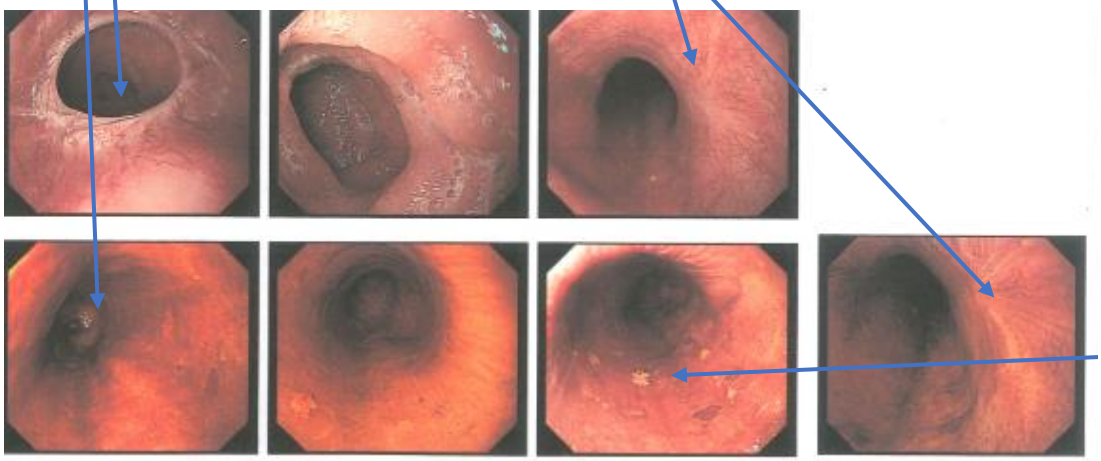
Findings of Endoscopy of upper digestive tract

Patient: H.S. Date of Examination 2017/02/22
Age 77 Sex: female Doctor in charge of examination Jun Aoki,M.D.

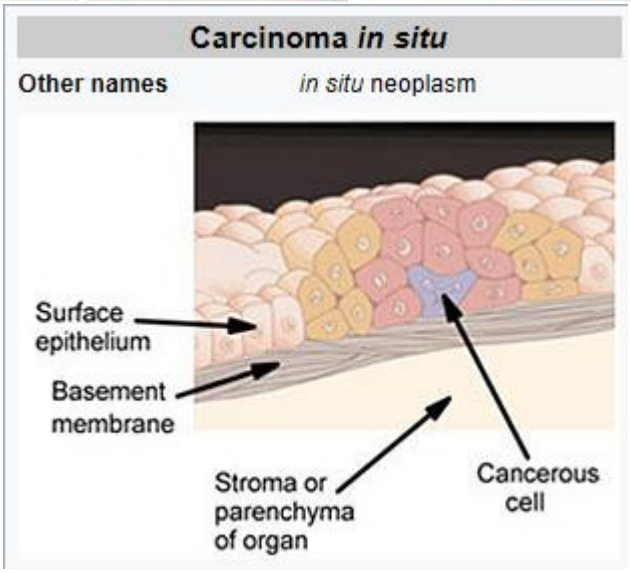
At an esophageal site some 21~23 cm from the patient's incisor teeth, a scar left by the 2007 esophageal endoscopic mucosal resection was present. At a separate site 25 cm from the teeth, a small area that could not be stained was detected.

A surgeon connected esophagus directly to jejunum seen below.

A scar left by the Esophageal Endoscopic Mucosal Resection



Small unstained area that has remained unchanged



CURRENT ILLNESS

In January 2006, the patient restarted skiing. In December 2008, she sustained a mild damage at her costal cartilage while she was doing gardening at home. On January 26, 2009, she drove to a skiing resort and began skiing even though she was still feeling pains at her chest. Shortly after she got down from a ski lift and began skiing, she lost her balance, swerving to the right and falling sideways. She could not stand up. She was taken by ambulance to the Towada City Hospital, where she was operated on two days later. She had sustained fractures of her left tibia and fibula, so the hospital's orthopedic surgeons inserted a cylindrically-shaped titanium alloy rod into the tibia shaft's medullary cavity. Nothing was done to fix the fractured fibula. She was told she has only to leave the fractured fibula to a natural bone remodeling mechanism. The orthopedic laisse-faire strategy worked for the fibula. On the outlook for the titanium rod, the doctors pledged that it would be later removed.

The patient remained hospitalized at the Towada City Hospital until the end of March 2009, when she was discharged. Then, she returned to her medical facility, where she has worked as an internal-medicine physicist.

Figure 19. Leaning Skiing from the instructor at Mt. Yakeyama near Towada caldera lake in January 2008

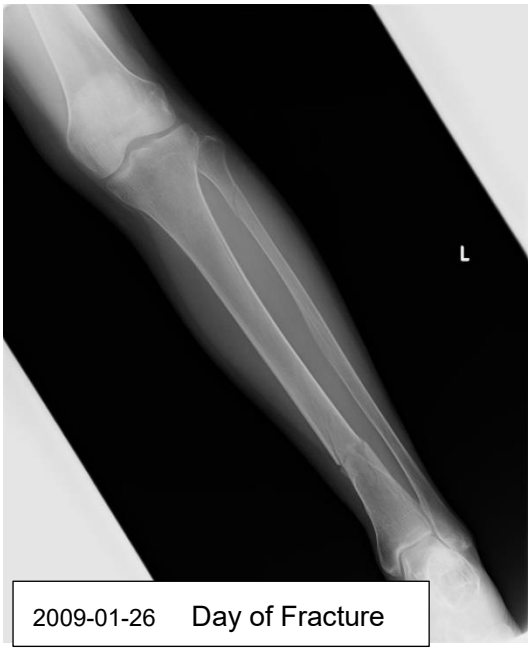
Sixteen months later, in May 2010, she visited the Hachinohe City Hospital to undergo a periodic checkup. Then she was told that doctors discussed the state of her tibia and decided against pulling up the titanium-alloy rod from her tibia shaft.

Even during the previous year's 2-month hospitalization, she had noticed that she had an osteoporosis when she was examining the X-ray photos of her own left lower limb, taken at the time of her tibia fracture. At time of the 2010 check, the degree of the severity of her osteoporosis grew so advanced that her doctors determined that her tibia would not be able to withstand shocks from a rod-removal operation.

She correctly concluded the doctors have remained recalcitrant to pull up the rod because they judged that the severity of her osteoporosis has progressed so greatly that her still-fragile tibia would not be able to support and prop up her entire bodyweight without the aid of the alloy rod. Then, she asked her surgical team's chief to start administering treatments to cure or soften her osteoporosis. (Figure 1) Since then, she has been receiving a range of anti-osteoporosis treatments, including the administration of the monoclonal antibody against RANKL. As of March, 2020, she is in good shape.

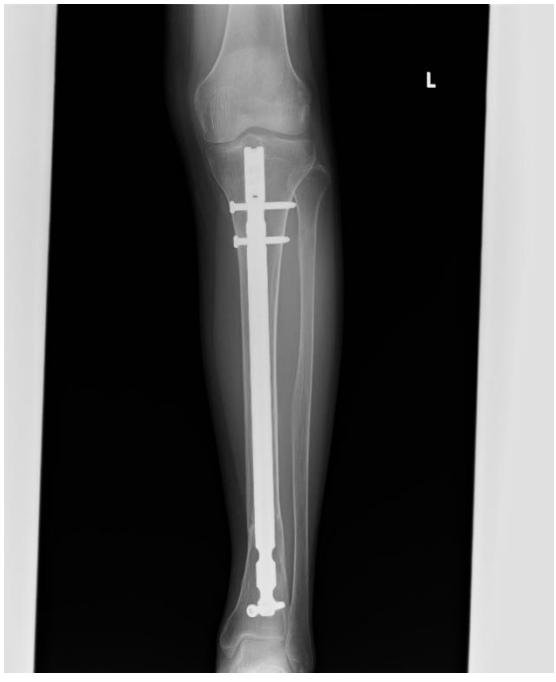
Figure 20. Now-bouncing Patient with her official car (black) and private car (scarlet) who was photographed in August 2019

Figure 21. Chronological Series of X-ray photos of left lower limb taken at Towada City Hospital and Keio University Hospital



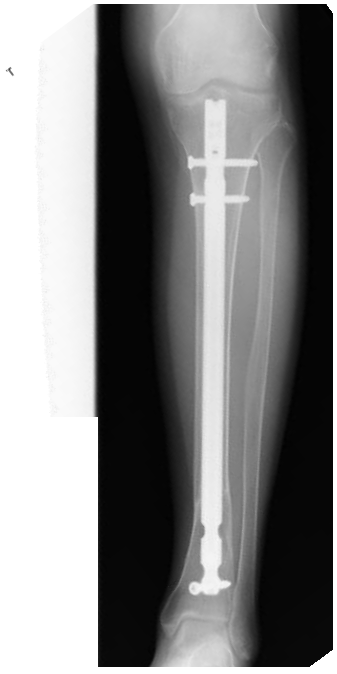
2009-01-26 Day of Fracture

2009-01-29 2nd day of operation



2009-06-10 Four and half months after fracture

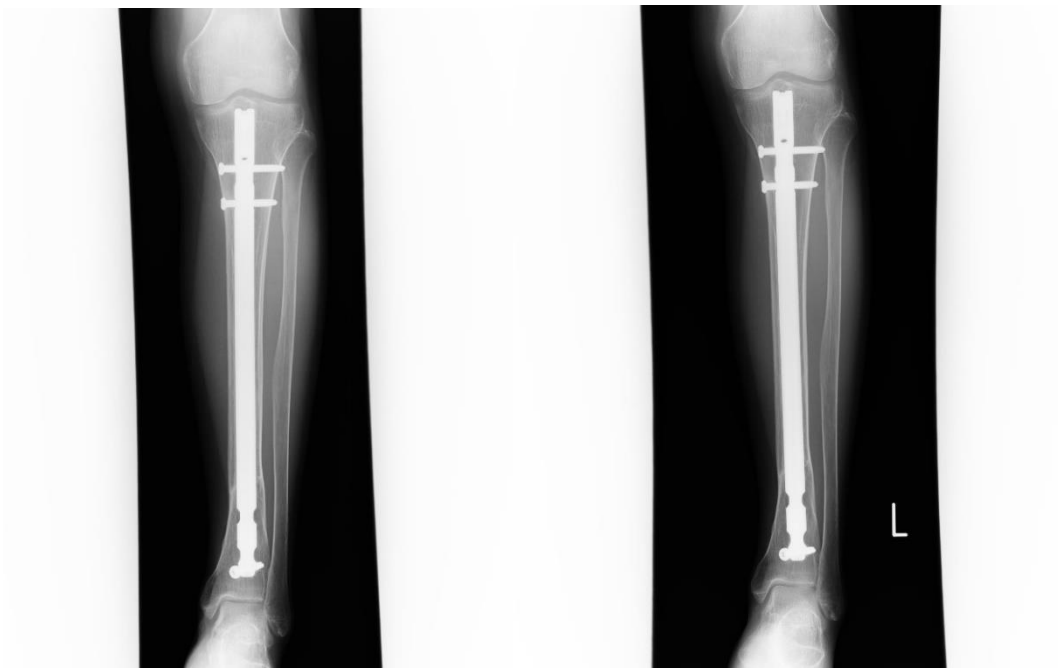
2010-03-15 1 Year and 1 month after fracture



2010-12-20 1 Year and 10 month after fracture

2010/5/21 Alphacalcidol

2010/7/30 Bisphosphonate

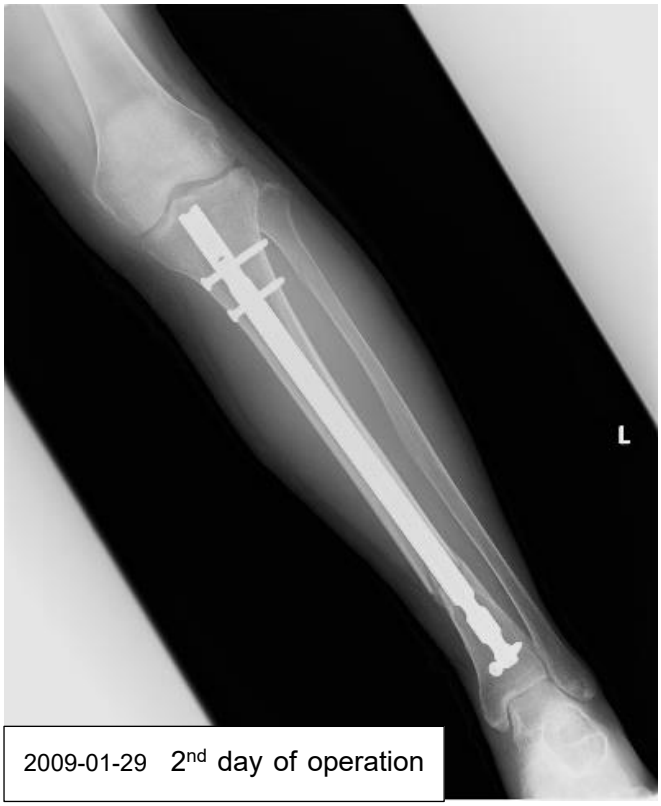


2011-07-04 Two years and five months after fracture

2012-07-02 Three years and five months after fracture

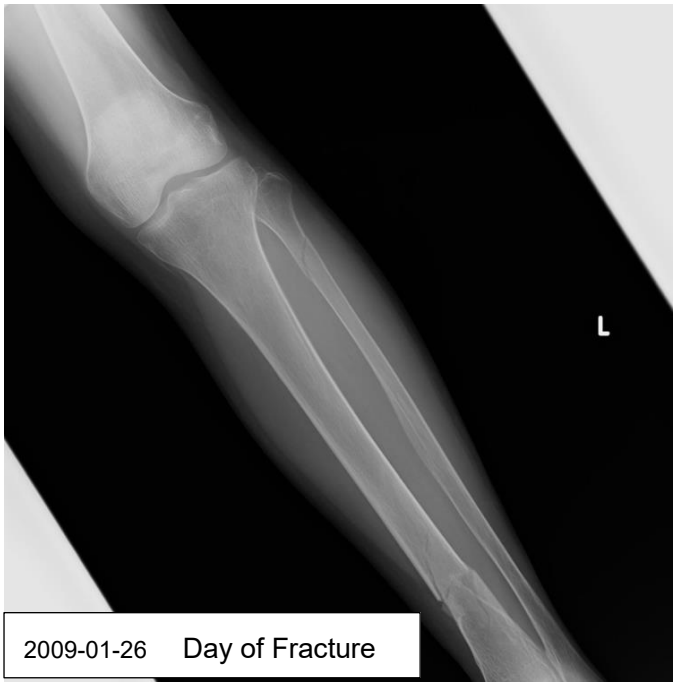
Alphacalcidol

Bisphosphonate

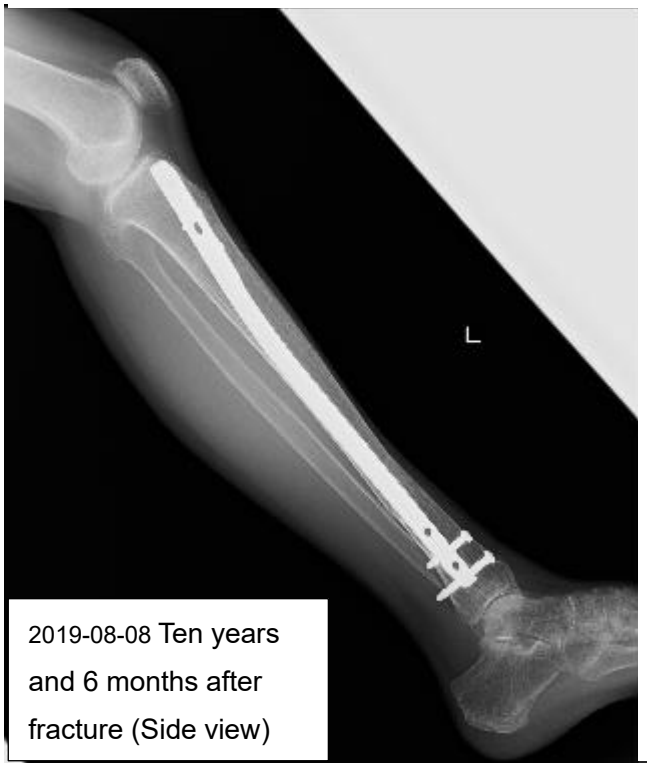


2009-01-29 2nd day of operation

2019-08-08 Ten years and 6 months after fracture (Front view)



2009-01-26 Day of Fracture



2019-08-08 Ten years and 6 months after fracture (Side view)

Ten years' treatment for osteoporosis

Figure 22. Report on Bone Mineral Density

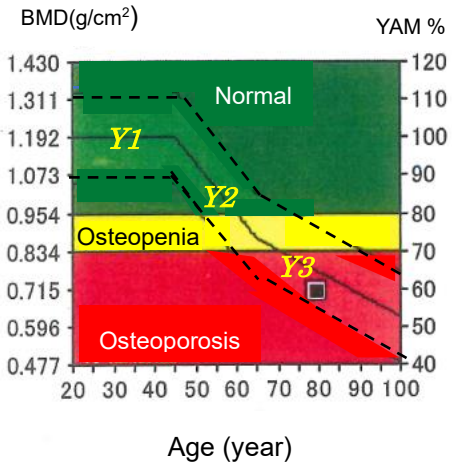
Name: H.S.

Birth Date: 1940/01/17 Height/Weight: 147.0 cm/ 38.1 Kg

Sex: Female Date of Examination: 2019/08/08

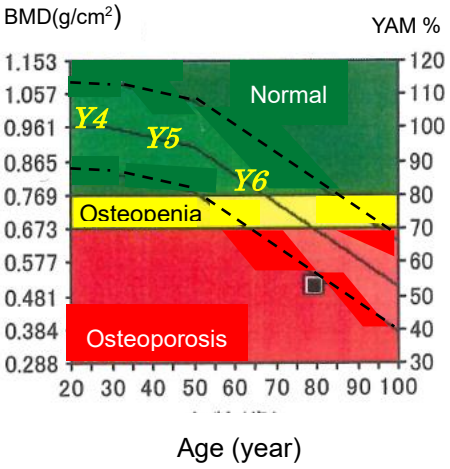
Examined by JSBMR's 2012 norms

Lumber Vertebrae Front View: L2-L4 (BMD)



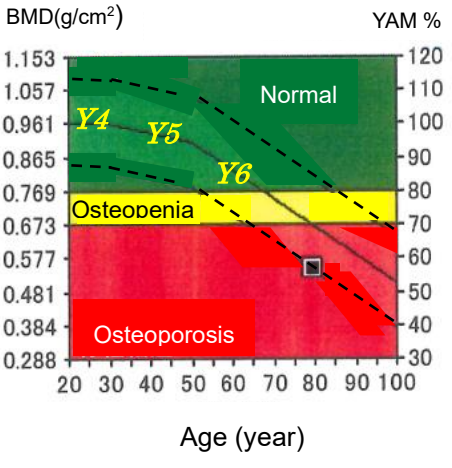
JSBMR's 2012 norms

Right Proximal Femur: Total (BMD)



JSBMR's 2012 norms

Left Proximal Femur: Total (BMD)



Natural Course of BMD readings Described in GE Catalogue describing Features of High Definition Multi-Slice Bone Densitometer Lunar iDXA

JSBMR2012

Femur: Neck (BMD)

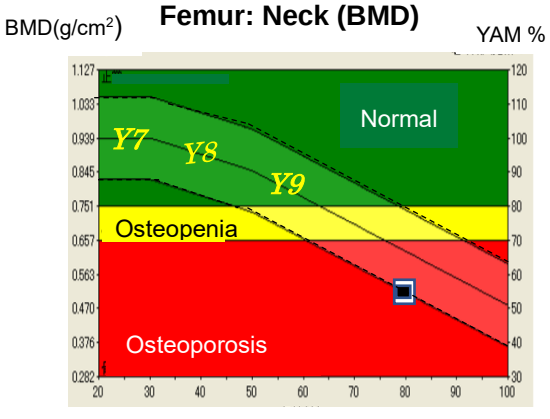


Table 8

Linear Equations based on JSBMR's 2012 Criteria

Lumber Vertebrae Front View L2-L4 (BMD): Age specific BMD -Linear Equations

Age (Year)	BMD (g/cm²)
20~40	Y1 =1.192
40~65	Y2 =1.192 -0.012 x (Patient's Age-40)
65~100	Y3 =0.894 - 0.0067 x (Patient's Age-65)

Right & Left Proximal Femur, Total (BMD) / Age specific BMD-Linear Equations

Age (Year)	BMD (g/cm²)
20~30	Y4 = 0.961
30~50	Y5 = 0.961 – 0.0036x (Patient's Age-30)
50~100	Y6 = 0.889 – 0.0077 x (Patient's Age-50)

Right & Left Femur, Neck (BMD) / Age specific BMD-Linear Equations

Age (Year)	BMD (g/cm²)
20~30	Y7 = 0.939
30~50	Y8 = 0.939 – 0.0047x (Patient's Age-30)
50~100	Y9 = 0.845 – 0.0075 x (Patient's Age-50)

Table 9

L2-L4: Young Adult (Female, Age Range: 20-44 old), BMD:YAM±1 SD 1.192 ±0.146 g/cm^2

Date	Patient Age (Year)	L2-L4	Patient/ YAM	**T score**: (Patient-YAM)/ 0.146	Age specific BMD (g/cm^2)	Age specific BMD Mean+ 1 SD	Age specific BMD Mean- 1 SD	Patient/ Age specific Mean	**Z score**: (Patient-Age specific Mean)/ 0.146
2012/11/2	72.7	0.526	44%	**-4.6**	0.841	0.987	0.695	63%	**-2.2**
2013/2/1	73.0	0.526	44%	**-4.6**	0.839	0.985	0.693	63%	**-2.1**
2013/6/28	73.4	0.563	47%	**-4.3**	0.837	0.983	0.691	67%	**-1.9**
2013/12/27	73.9	0.595	50%	**-4.1**	0.833	0.979	0.687	71%	**-1.6**
2015/1/16	74.9	0.581	49%	**-4.2**	0.827	0.973	0.681	70%	**-1.7**
2015/7/17	75.4	0.643	54%	**-3.8**	0.823	0.969	0.677	78%	**-1.2**
2017/1/13	76.9	0.672	56%	**-3.6**	0.813	0.959	0.667	83%	**-1.0**
2017/7/14	77.4	0.664	56%	**-3.6**	0.810	0.956	0.664	82%	**-1.0**
2018/1/12	77.9	0.677	57%	**-3.5**	0.807	0.953	0.661	84%	**-0.9**
2019/1/11	78.9	0.694	58%	**-3.4**	0.800	0.946	0.654	87%	**-0.7**
2019/8/8	79.5	0.706	59%	**-3.3**	0.796	0.942	0.650	89%	**-0.6**

Figure 23

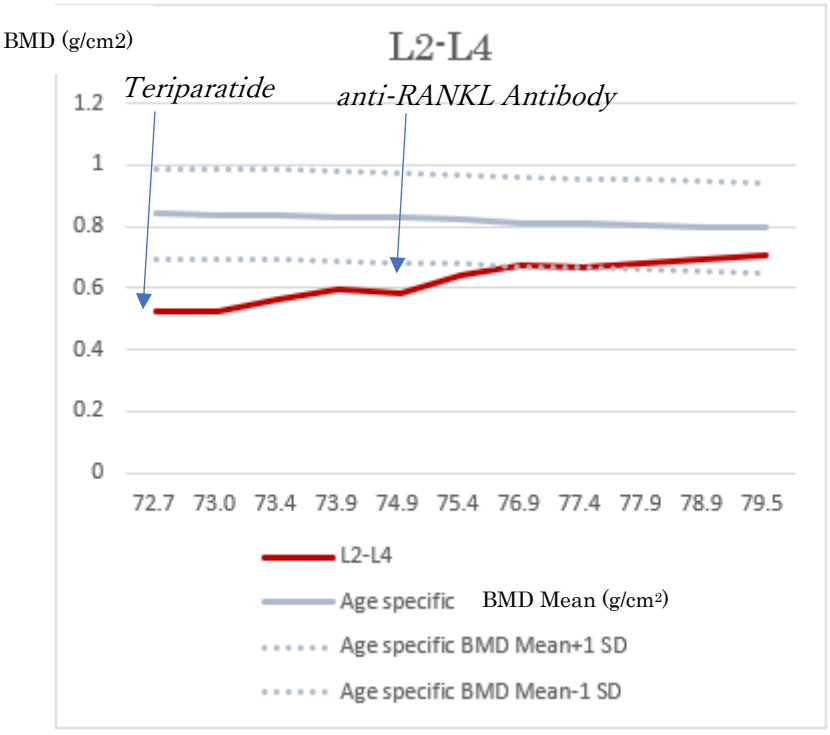


Table10

Right Femur Neck: Young Adult (Female, Age Range: 20-29 old), BMD: YAM±1 SD 0.939 ±0.114 g/cm^2

Date	Patient Age (Year)	Right Femur Neck	Patient/ YAM	**T score**: (Patient-YAM)/ 0.114	Age specific BMD (g/cm^2)	Age specific BMD Mean+ 1 SD	Age specific BMD Mean- 1 SD	Patient/ Age specific Mean	**Z score**: (Patient-Age specific Mean)/ 0.114
2012/11/2	72.7	0.462	49%	**-4.2**	0.675	0.789	0.561	68%	**-1.8**
2013/2/1	73.0	0.455	48%	**-4.2**	0.673	0.787	0.559	68%	**-1.9**
2013/6/28	73.4	0.467	50%	**-4.1**	0.670	0.784	0.556	70%	**-1.8**
2013/12/27	73.9	0.459	49%	**-4.2**	0.666	0.780	0.552	69%	**-1.8**
2015/1/16	74.9	0.469	50%	**-4.1**	0.658	0.772	0.544	71%	**-1.7**
2015/7/17	75.4	0.476	51%	**-4.1**	0.655	0.769	0.541	73%	**-1.6**
2017/1/13	76.9				0.643	0.757	0.529		
2017/7/14	77.4				0.640	0.754	0.526		
2018/1/12	77.9				0.636	0.750	0.522		
2019/1/11	78.9				0.628	0.742	0.514		
2019/8/8	79.5	0.507	54%	**-3.8**	0.624	0.738	0.510	81%	**-1.0**

Figure 24

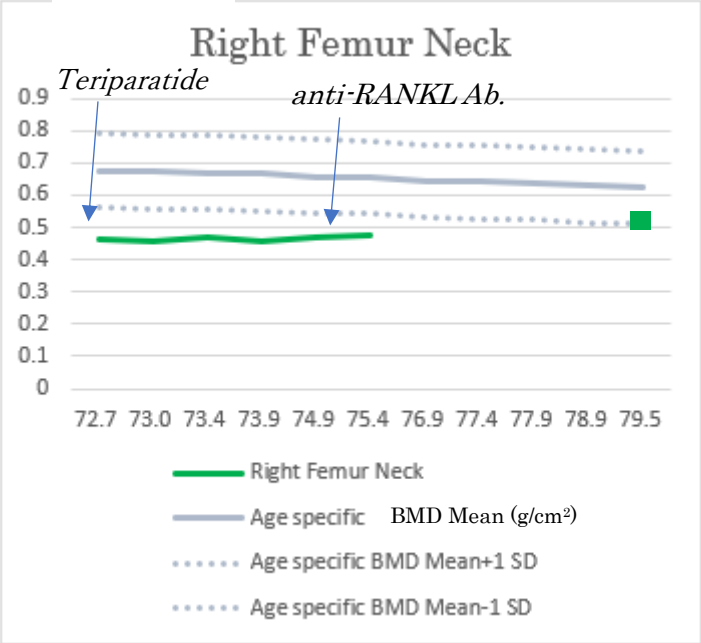


Table 11

Right Femur Proximal Total: Young Adult (Female, Age Range: 20-29 old), BMD: YAM±1 SD 0.961 ±0.130 g/cm^2

Date	Patient Age (Year)	Right Femur Proximal Total	Patient/ YAM	**T score**: (Patient-YAM)/ 0.130	Age specific BMD (g/cm^2)	Age specific BMD Mean+ 1 SD	Age specific BMD Mean- 1 SD	Patient/ Age specific Mean	**Z score**: (Patient-Age specific Mean)/ 0.130
2012/11/2	72.7				0.714	0.844	0.584		
2013/2/1	73.0				0.712	0.842	0.582		
2013/6/28	73.4				0.709	0.839	0.579		
2013/12/27	73.9				0.705	0.835	0.575		
2015/1/16	74.9				0.697	0.827	0.567		
2015/7/17	75.4				0.693	0.823	0.563		
2017/1/13	76.9	0.480	50%	**-3.7**	0.682	0.812	0.552	70%	**-1.6**
2017/7/14	77.4	0.492	51%	**-3.6**	0.678	0.808	0.548	73%	**-1.4**
2018/1/12	77.9	0.479	50%	**-3.7**	0.674	0.804	0.544	71%	**-1.5**
2019/1/11	78.9	0.506	53%	**-3.5**	0.666	0.796	0.536	76%	**-1.2**
2019/8/8	79.5	0.509	53%	**-3.5**	0.662	0.792	0.532	77%	**-1.2**

Figure 25

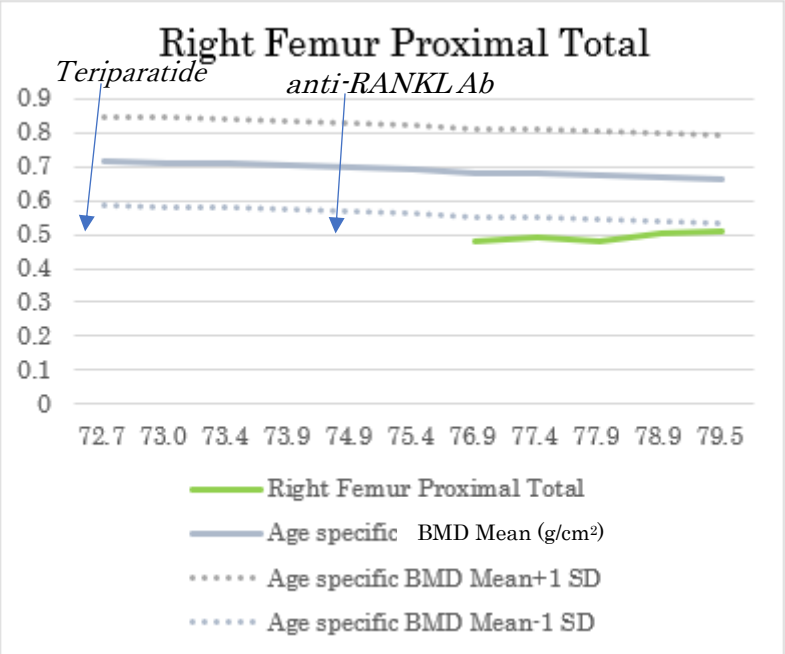


Table12

Left Femur Neck: Young Adult (Female, Age Range: 20-29 old, BMD: YAM±1 SD 0.939 ±0.114 g/cm^2

Date	Patient Age (Year)	Left Femur Neck	Patient/ YAM	**T score**: (Patient-YAM)/ 0.114	Age specific BMD (g/cm^2)	Age specific BMD Mean+ 1 SD	Age specific BMD Mean- 1 SD	Patient/ Age specific Mean	**Z score**: (Patient-Age specific Mean)/ 0.114
2012/11/2	72.7	0.422	45%	**-4.4**	0.675	0.789	0.561	63%	**-2.2**
2013/2/1	73.0	0.450	48%	**-4.2**	0.673	0.787	0.559	67%	**-2.0**
2013/6/28	73.4	0.449	48%	**-4.2**	0.670	0.784	0.556	67%	**-1.9**
2013/12/27	73.9	0.452	48%	**-4.2**	0.666	0.780	0.552	68%	**-1.9**
2015/1/16	74.9	0.453	48%	**-4.2**	0.658	0.772	0.544	69%	**-1.8**
2015/7/17	75.4	0.453	48%	**-4.2**	0.655	0.769	0.541	69%	**-1.8**
2017/1/13	76.9				0.643	0.757	0.529		
2017/7/14	77.4				0.640	0.754	0.526		
2018/1/12	77.9				0.636	0.750	0.522		
2019/1/11	78.9				0.628	0.742	0.514		
2019/8/8	79.5	0.506	54%	**-3.7**	0.624	0.738	0.510	81%	**-1.0**

Figure 26

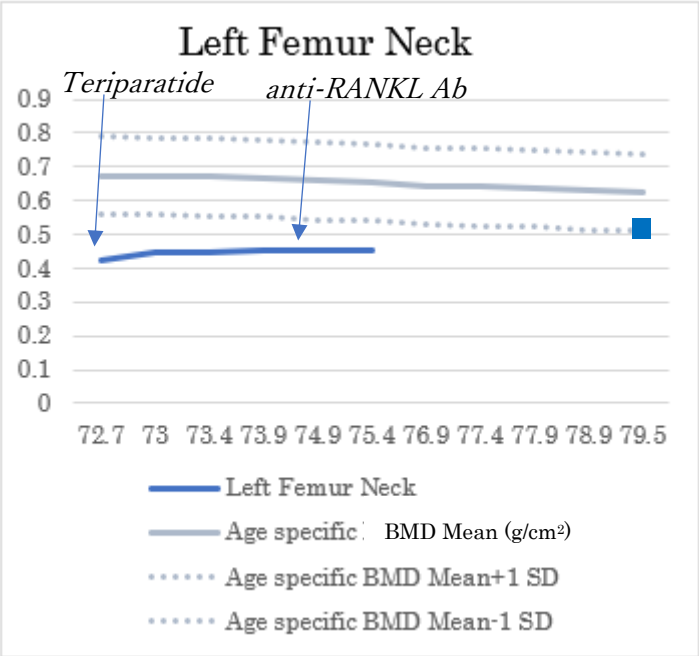


Table13

Left Femur Proximal Total: Young Adult (Female, Age Range: 20-29 old), BMD: YAM±1 SD 0.961 ±0.130 g/cm^2

Date	Patient Age (Year)	Left Femur Proximal Total	Patient/ YAM	**T score**: (Patient-YAM)/ 0.130	Age specific BMD (g/cm^2)	Age specific BMD Mean+ 1 SD	Age specific BMD Mean- 1 SD	Patient/ Age specific Mean	**Z score**: (Patient-Age specific Mean)/ 0.130
2012/11/2	72.7				0.714	0.844	0.584		
2013/2/1	73.0				0.712	0.842	0.582		
2013/6/28	73.4				0.709	0.839	0.579		
2013/12/27	73.9				0.705	0.835	0.575		
2015/1/16	74.9				0.697	0.827	0.567		
2015/7/17	75.4				0.693	0.823	0.563		
2017/1/13	76.9	0.495	52%	**-3.6**	0.682	0.812	0.552	73%	**-1.4**
2017/7/14	77.4	0.526	55%	**-3.3**	0.678	0.808	0.548	78%	**-1.2**
2018/1/12	77.9	0.522	54%	**-3.4**	0.674	0.804	0.544	77%	**-1.2**
2019/1/11	78.9	0.531	55%	**-3.3**	0.666	0.796	0.536	80%	**-1.0**
2019/8/8	79.5	0.545	57%	**-3.2**	0.662	0.792	0.532	82%	**-0.9**

Figure 27

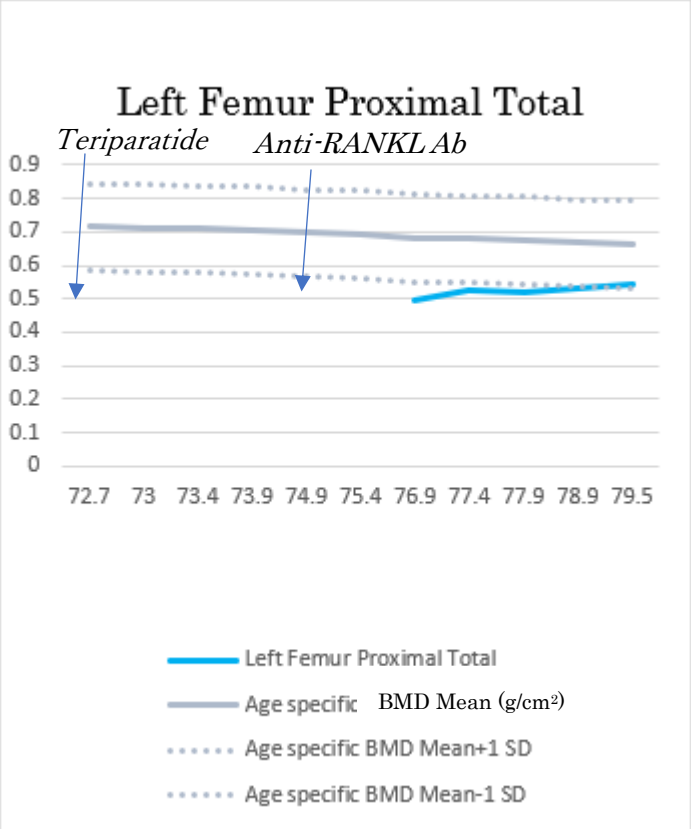
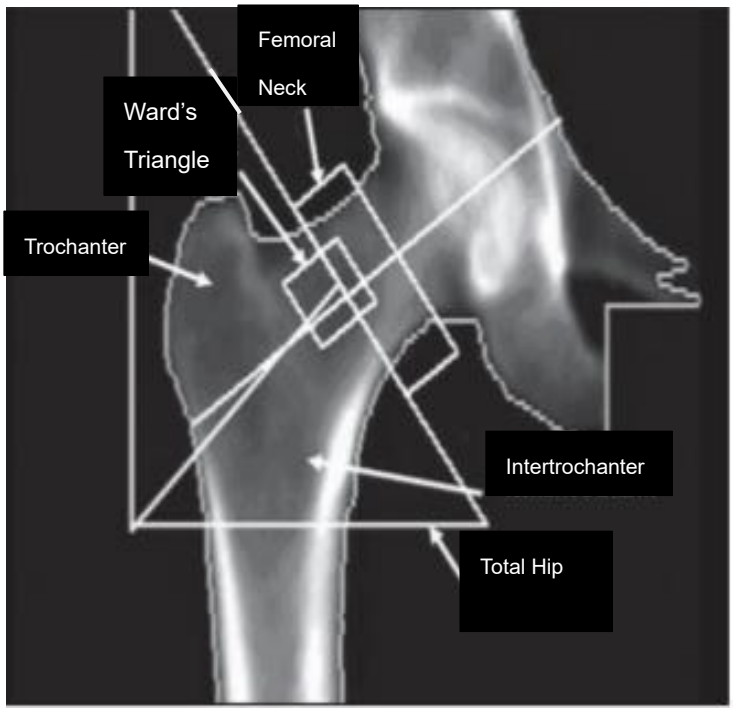


Figure 28

DEXA images of Right Proximal Femur



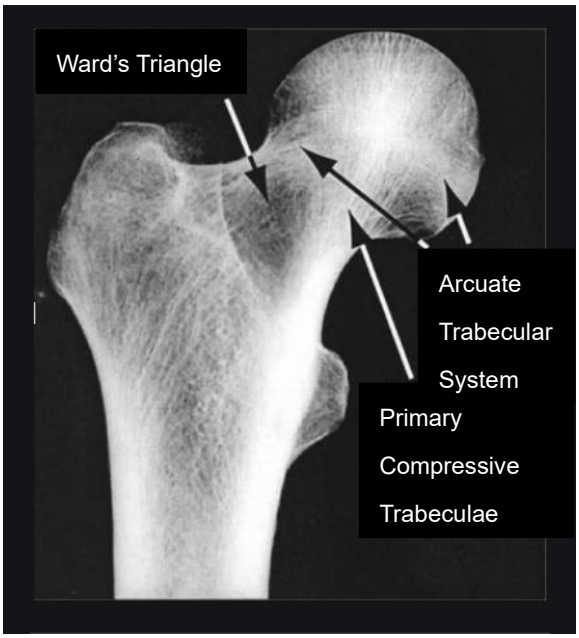


Table 14

BMD of Right Femur Neck, Ward's Triangle, Greater Trochanter, Femur Proximal Total

Date	Patient Age (Year)	Femur Neck	Ward's Triangle	Greater Trochanter	Femur Proximal Total
2015/7/17	75.4	0.476	0.299	0.374	0.488
2020/1/17	80.0	0.501	0.313	0.368	0.490
% increase		5%	5%	-2%	0%

Table 15

BMD of Left Femur Neck, Ward's Triangle, Greater Trochanter, Femur Proximal Total

Date	Patient Age (Year)	Femur Neck	Ward's Triangle	Greater Trochanter	Femur Proximal Total
2015/7/17	75.4	0.453	0.307	0.387	0.492
2020/1/17	80.0	0.493	0.345	0.399	0.517
% increase		9%	12%	3%	5%

Table 16

Serologic Measurement results of osteoporosis-associated substances via Laboratory Examinations (1)

Date (Age)	Ca (mg/dL)	In-organic Phos-phate (mg/dL)	Vitamin D (pg/mL)	Para-thormone Intact (pg/mL)	Estra-diol (pg/mL)	Oste-ocarcine (ng/mL)/ **Undercarboxylated osteocalcin(ng/mL)***	Total P1NP (μg/L)**	Bone Type Alkaline Phosphatase (U/L)	Tartrate-resistant Acid Phosphatase 5b***
2019/01/11 (78Y11M)	8.4	4.0	38.0 [Active Vit D [1A.25-(OH)2 Vit D]	143 (H)	<10	3.4(normal 8.3~32.7) / **0.66 (normal range 0~4.49)**	11.6	8.1 (normal range 12.1~42.7)	151 （normal range 120~420）
2019/08/08 (79Y6M)	9.0	3.4	71.0				20.6 (total PI)		

$1\ \mathrm{mg} = 1000\ \mu\mathrm{g}$

$1\ \mu\mathrm{g} = 1000\mathrm{ng}$

$1\mathrm{ng} = 1000\mathrm{pg}$

Notes:

*Undercarboxylated osteocalcin is a type of protein produced by osteoblasts into a bone matrix in cases where their host humans are undergoing a Vitamin-K deficiency, with greater amounts of resultant undercarboxylated osteocalcin released into their bloodstreams.

The levels of this substance in a bloodstream can be used as an indicator of levels of Vitamin-K.

**Procollagen type 1 N-terminal propeptide is a soluble precursor of type 1 collagen formed in the process of collagen synthesis. This precursor is found in great quantities in bone tissues. Measurement findings of this substance are used as an early detection marker of bone formation in helping doctors judge the

efficaciousness of the medicines they administered to cure patients' osteoporosis

***Tartrate-resistant Acid Phosphatase 5bis an enzyme that is expressed in high amounts by bone-resorbing osteoclast. Levels of this type of tartrate-resistant acid phosphatase which are released into a bloodstream alongside bone resorption-associated cleave products act as a marker of osteoclast number and bone resorption. The more actively bone is reabsorbed, the higher the quantity of TRACP-5b in a bloodstream. In humans, TRACP-5b derive only from osteoclasts, so this characteristic makes the enzyme's levels an excellent indicator. Measurement of TRACP-5b levels are useful in diagnosing degree of the severity of osteoporosis and judging the effectiveness of medicines to suppress osteoporosis. The enzyme is identified as a bone resorption level marker by the guidelines devised by the Japan Society of Osteoporosis concerning the appropriate use of bone remodeling markers.

Table 17

Serologic Measurement Results of Obesity-associated Substances via Laboratory Examinations (2)

Date (Age)	Total cholesterol (mg/dL)	Tri-glyceride (mg/dL)	HDL-Cholesterol (mg/dL)	LDL-Cholesterol (mg/dL)	TRACP-5b (mU/dL)
2019/01/11 (78Y11M)	177 (normal 135~240)	90 (normal 30~150)	63	94	
2019/08/08 (79Y6M)	179	76	71	96	250 (normal 120~420)

Osteoclast-specific Hypoxia-inducible Factor 1alpha　(HIF 1α) [7,8)]

Estrogen secreted by an ovary limits and restrains bone resorption activities by osteoclasts. In so doing, estrogen restrains and suppresses a protein inside osteoclasts called the Hypoxia-inducible Factor 1 alpha　(HIF 1α) as the factor plays a pivotal role in promoting bone resorption by osteoclasts.

But even under estrogen-deficient conditions at postmenopausal female mammals, a team of researchers from various universities including Keio University has found that bone resorption can be suppressed by administering an inhibitor against the factor, whose activity is accelerated in a hypoxic environment. The factor's activity is destabilized in the presence of oxygen.

The team first removed ovaries from model mice, making them unable to secret estrogen. This accelerated the activities of osteoclasts.

But when the researchers administered the　HIF 1α　inhibitor to those ovariectomized (Ovx) mice, the inhibitor blocked an osteoclast activation, restraining bone loss.

The team concluded that the Hypoxia-inducible Factor 1 alpha　(HIF 1α) represents a key therapeutic target in osteoporosis treatments and that the inhibitor is a promising anti-osteoporotic agent.

On Preparing the Animal Model of Young Adult Human Female

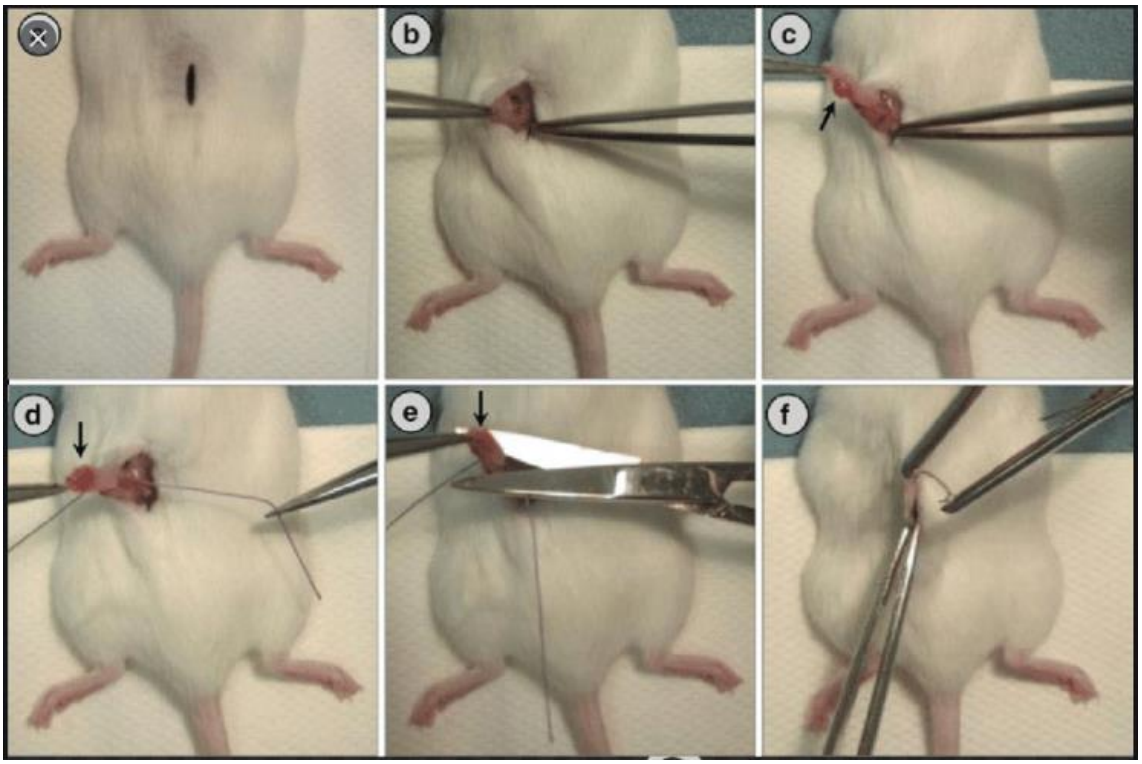
Estrogen secreted by young adult mice destabilizes the Hypoxia-inducible Factor 1 alpha　(HIF 1α).　The research team prepared young adult mice that cannot secret estrogen by a string of ovariectomies.

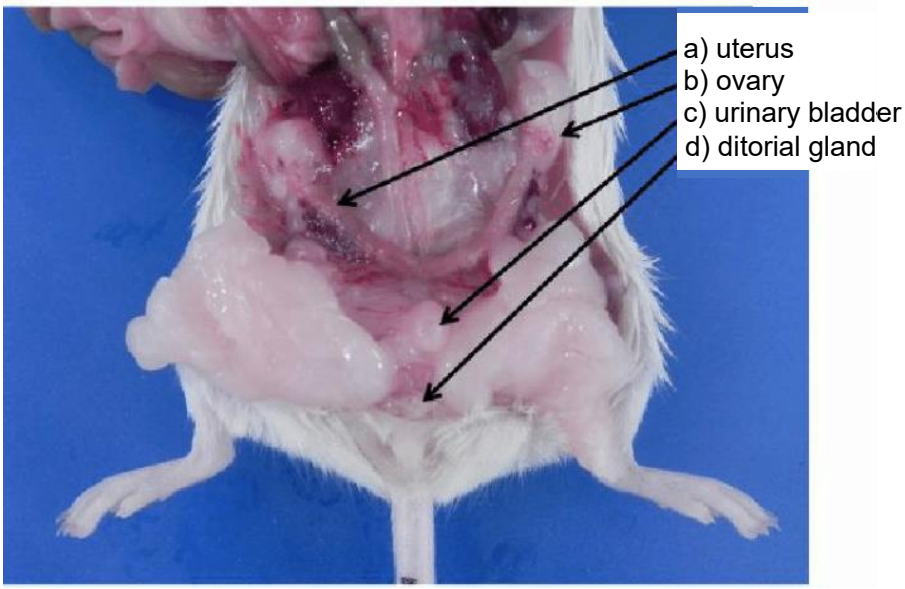
Although the young mice have been freed from the effects of estrogen, the inhibitor administered by the team still blocked the activity of osteoclasts and their bone resorption.

Figure 29. Animal Model that Can Substitute Postmenopausal Human Female as the Subject of an Experiment

Figure 30

***Surgical Removal of Ovaries from the Animal Model of Postmenopausal Human Females to force a stoppage to estrogen secretion by* such ovariectomized (Ovx) mice**





In ovariectomized (Ovx) mice, the research team confirmed that the secretion of estrogen was halted. Although the HIF 1α at those mice were freed from estrogen's suppressive effects, it was confirmed that bone resorbing by osteoclasts remained blockaded by the oral administration of t HIF 1α inhibitor.

Figure 31. Body Weight Change after Oviectomy

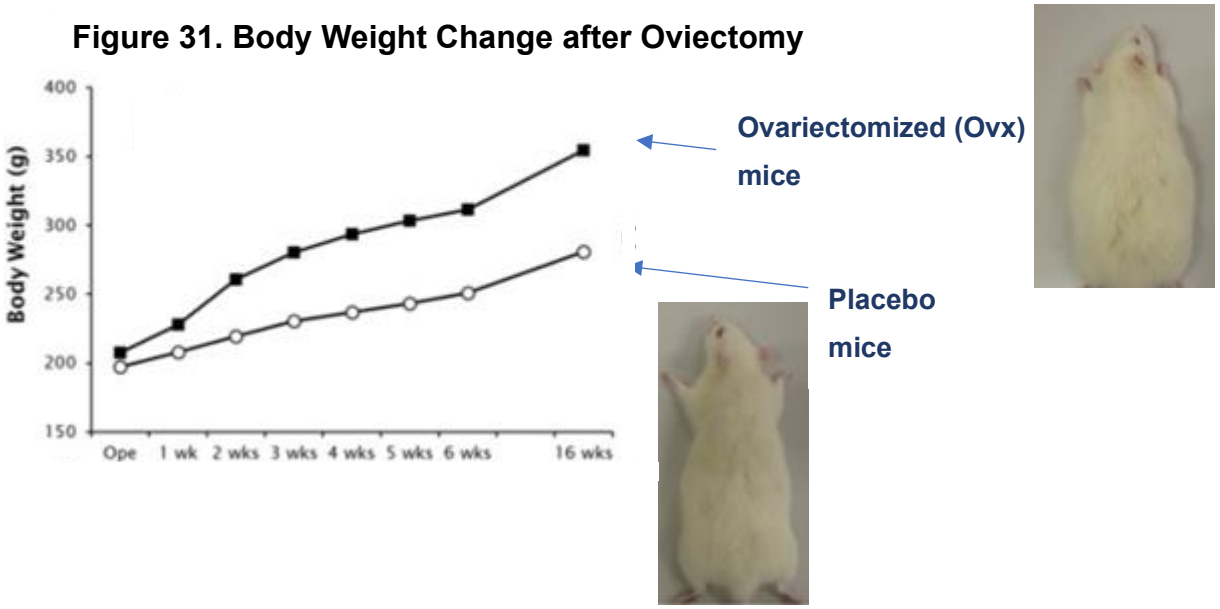


Figure 32. *Obesity observed with Postmenopausal Human Female*

Picture taken on November 3 1983
43 year old, Body weight 43 Kg

Picture taken on June 5 1997
57 year old, Body weight 52 Kg

DISCUSSION

Let us ponder this case from a genetical standpoint. Both her maternal grandmother as well as her mother suffered an advanced osteoporosis. On the other hand, this patient has blue sclera. The van der Hoeve syndrome is an autosomal dominant disease characterized by the triad; blue sclera, a tendency to sustain spontaneous fractures due to an osteogenesis imperfecta (a connective tissue disorder caused by genetic defect in the synthesis of type I collagen), and a conductive hearing loss stemming from a stapedial fixation.

Although this patient does not have a hearing loss, there springs up a question of whether she is suffering from an incomplete form of the van der Hoeve syndrome. On March 5, 2012, the patient signed an agreement with the director of Keio University Medical School to the effect that she would contribute to a study of gene analysis, organized by Dr. Takeshi Miyamoto. It remains to be seen whether this patient has any genetic tint to develop an osteoporosis or not.

A total gastrectomy is one of risk factors of bone fractures. Humans who underwent a total gastrectomy come to lack a gastric intrinsic factor, a small mucoprotein secreted by the parietal cells of the stomach's gastric glands. The gastric intrinsic factor is necessary to facilitate a human body's absorption of Vitamin B12 at the terminal part of an ileum.

Since Vitamin B12 is necessary to conduct a synthesis of red blood cells, the post-gastrectomy patients become prone to suffer an anemia. In addition, patients whose stomach were totally excised come to lack a capability to secrete gastric acid which is necessary to transform ion into easily absorbable form. Post-total gastrectomy patients, therefore, often suffer an ionic deficiency-associated anemia. In humans, the factor is encoded by the gastric intrinsic factor gene.

The patient, the object of this paper's analysis, is a medical doctor specializing in internal medicine especially in the pediatrics field, so she did not have adequate levels of knowledge about the mechanism of bone remodeling and about the possibility that certain anti-osteoporosis medicine may reduce,

offset or even eliminate the effects of other anti-osteoporosis medicines to some or serious degrees.

After she began receiving a range of treatments for her own osteoporosis, she visited those multiple hospitals mentioned in this paper in addition to a clinic run by her own son, also a physician (Internal Medicine) who has acted as the entire family's medical doctor for decades.

Looking back, we may have to conclude that she may have been somewhat careless in that she did not fully share, with the Keio University osteoporosis specialist, information on the medicines which was, or are being, prescribed by the non-Keio University Hospital doctors whom she saw or was seeing in parallel.

This means that she herself plunged her doctors into a situation where they did not know fully what medicines were, or are being, prescribed and administered to her, denying them access to information which could have let them discern the risk of such coadministration.

A key universal lesson from her and her doctors' mildly bitter experiences may be that any patient's behavioral principle – which posits that the greater the variety of excellent medicines that are being administered to a patient, the better health results may be attainable -- may backfire from time to time, especially in cases where the patient's ailments concern medical fields with which even professionals are not familiar, like cell-level players responsible for a bone remodeling mechanism.

But this does not diminish the importance of the fact that the anti-RANKL monoclonal antibody designed to suppress the activity of osteoclasts worked brilliantly in turning around the patient's BMD readings and that she has remained almost as bouncing as the 12-year-old girl when she sustained the first tibia fracture on the Mt. Akakura slope, as shown in Figures 17 and 20.

Dr. Takeshi Miyamoto, who had been working at Keio University Hospital, taking care of this patient at the hospital's outpatient department specializing in

osteoporosis and making the clever decision to administer the anti-RANKL monoclonal antibody, gave her the following insightful written comments.

"As for those events that took place in the course of your treatments, I have constantly followed a policy of discontinuing the administration of bisphosphonates whenever I treat my patients with teriparatides, be the brand of the teriparatide a Forteo or a Teribone. Although I should have checked if you may have been administered a bisphosphonate by some other doctors, I may have been led to drop my usual vigilance because I remember your having told me that you would like to let your internal medicine physician-son give you orally-administered types of prescription medicines. A coadministration of a teriparatide and a bisphosphonate is not practiced widely, because it is possible that a bone remodeling process accelerated by a teriparatide is restrained by a bisphosphonate. Let me give you this comment for the present."

In them, he also noted, "Besides this point, let me inform you that a coadministration of a teriparatide and an active Vitamin-D analogue is not practiced widely, again, be the brand of the teriparatide a Forteo or a Teribone. Attention has been called to a possible outbreak of negative effects emanating from such a coadministration, because such a mix could bolster a blood calcium concentration excessively."

"Again, it may be said that my vigilance against the possibility of such a coadministration being present may have been inadequate. This teriparatide-active Vitamin-D agent coadministration strategy can be appropriately followed only in cases where patients readily allowed a doctor to keep track of ups and downs in his or her blood calcium concentrations longitudinally," He said in the writing.

"On the other hand, a coadministration of a bisphosphonate and an active Vitamin-D agent and a coadministration of an anti-RANKL monoclonal antibody and an active Vitamin-D analogue are widely practiced," according to the writing.

Secondly, let us ponder the ultra-violet ray irradiation-treated titanium-alloy rod insertion operation at the Towada City Hospital. This patient did not experience any foreign body reaction, a metal allergy nor an infection after the

UV-irradiated titanium alloy rod was inserted into the medullary cavity of her tibia shaft in the 2009 operation.

Dr. Taito Itabashi, M.D., at the Towada City Hospital and his co-researchers have called attention to their findings concerning the key bactericidal and antimicrobial effects of titanium alloy implants which were treated with short-term, low-energy ultra-violet ray irradiation [5], with the publication of a paper entitled “Photo-functionalized Ti6Al4V Implants Enhance Early-phase Osseointegration.”[6]

Dr. Itabashi says that this technology helps reduce the incidence of bacterial infection that might be triggered by an UV irradiation-free titanium alloy implants that have been used to fix bone fractures.

Therefore, the truthfulness of this research team’s findings was corroborated by the lack of this patient’s foreign body response to his team’s UV-irradiated titanium alloy rod.

Meanwhile, a separate team of researchers headed by Dr. Miyamoto, now a Kumamoto University professor, has reported that an inhibitor to suppress osteoclast-specific Hypoxia-Inducible Factor 1 alpha （HIF 1α） is one of the most promising candidate drugs for a successful treatment and prevention of postmenopausal osteoporosis.[7,8]

Estrogen secreted by an ovary limits and restrains bone resorption activities by osteoclasts. In so doing, estrogen restrains and suppresses a protein inside osteoclasts which is called the Hypoxia-Inducible Factor 1 alpha （HIF 1α） because the factor plays a pivotal role in promoting bone resorption by osteoclasts.

But even under estrogen-deficient conditions at postmenopausal female mammals, the team has found that bone resorption can be suppressed by administering an inhibitor against the factor, whose activity is accelerated in a hypoxic environment. The factor’s activity is destabilized in the presence of oxygen.

In proving the inhibitor's efficaciousness against osteoporosis, the team first removed ovaries from model mice, making them incapable to secrete an estrogen.

The removal of the estrogen-emitting gland accelerated the activities of osteoclasts.

But when the researchers administered the HIF 1α inhibitor to these ovariectomized mice (Ovx), the inhibitor successfully blocked an osteoclast activation, thereby restraining bone loss.

After analyzing the experimental results, the research team concluded that the Hypoxia-Inducible Factor HIF 1 alpha (HIF 1α) is a key therapeutic target in osteoporosis treatments and that the inhibitor is a promising anti-osteoporotic agent.

CONCLUSION

Table 18. Positive Changes in BMD readings before and after the administration of Teriparatide and anti-RANKL Monoclonal antibody

	Start of Teriparatide	Start of Monoclonal Ab. Against RANKL	%Increase from Teriparatide start	Continuation of Monoclonal Ab. Against RANKL	%Increase from Teriparatide start
	Age 72.7 year	Age 74.9 year		Age 79.5 year	
Parts of the Body	(2012/11/2)	(2015/1/16)		(2019/8/8)	
Lumbar Vertebrae (L2-L4)	0.526 g/cm^2	0.581 g/cm^2	10%	0.706 g/cm^2	34%
Right Femur Neck	0.462 g/cm^2	0.469 g/cm^2	7%	0.507 g/cm^2	10%
Left Femur Neck	0.422 g/cm^2	0.453 g/cm^2	7%	0.506 g/cm^2	20%

Osteoporosis is a kind of emerging post-World War II diseases in Japan and in other developed countries with access to high levels of medical services. About seventy-five years have elapsed since Japan's unconditional surrender to the Allied Powers on August 15, 1945, when Japanese society was in for a string of baby booms and had only a small number of osteoporosis patients.

Now in Japan, one quarter of the nation's entire population are postmenopausal females. In other words, such postmenopausal females account for more than half of all Japanese females even if we statistically include female babies, toddlers and teenagers into such Japanese females. The more aged a postmenopausal female is, the more likely the degree of the severity of her osteoporosis has worsened.

Fractures are a very common complication of osteoporosis. Consequently, often-repeated fractures have left many aged females bedridden and have left them dependent on nursing care at home or at some nursing-care institutions for the elderly. In Japan, osteoporosis is one of the most important diseases that threaten to put heavy strains on both family budgets and the national treasury.

The only way to manage this situation and wage a preemptive attack on burgeoning "advanced osteoporosis" treatments-associated national fiscal constraints is to monitor the health conditions of postmenopausal females – for example, getting them to undergo a BMD checkup once they pass the threshold of the age 50 -- and perform an early medical intervention to treat aging or aged females before it is too late for the nation to counteract the potentially explosive problem with an eye to delaying a progression of their osteoporosis.

This paper reported a case who successfully delayed an osteoporotic progression and turned around sagging BDM readings on the strength of the mix of excellent medicines; a Teriparatide, Alphacalcidol/Eldecalcitol Vitamin D3 agents, a risedronate-category Bisphosphonate and, most importantly, the monoclonal antibody against RANKL.

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