Case Report

Efficaciousness of Postmenopausal Osteoporosis Treatment with the Mix of active Vitamin D3 agents, a Bisphosphonate (risedronate), a Teriparatide, and the Monoclonal Antibody against RANKL: A 10-year follow-up report on a female patient

Harumi Kuno-Sakai, MD, PhD¹⁾, Mutsuo Fukushima²⁾, Hiroyuki Sakai, MD, PhD³⁾, Takeshi Miyamoto, MD, PhD⁴⁾Taito Itabashi, MD, PhD⁵⁾, Hideto Sakai, MD, PhD⁶⁾

(Translation completed on March 3, 2020)

¹ Director, Geriatric Health Services Facility Towada run by Social Welfare Corporation Miyagikai in the SG Group

² Regular member of the Japanese Society of Clinical Virology. Journalist, former staff reporter at the World Services Section of Kyodo News' International Department

³ Director, Sakai Clinic, 9-34 Imaiminami-cho, Nakahara-ku, Kawasaki city, Kanagawa 211-0064 Japan

⁴ Formerly Associate Professor, Department of Orthopedics, Medical School Keio University, Professor, Department of Orthopedics, Kumamoto University Medical School, Honjyo 1-1-1 Chuo-ku, Kumamoto city, 860-0811 Japan

⁵ Associate Professor, Hirosaki University, Director Division of Orthopedics, Towada City Hospital, 14-8 West No.12 Towada city, Aomori Prefecture, 034-0093, Japan
 ⁶ Director, Geriatric Health Services Facility Shimoda run by Jinsenkai, a medical corporation run by the SG Group of nursing-care facilities for the elderly.

Corresponding author:

Harumi Kuno-Sakai, MD, Director, Geriatric Health Services Facility Towada, run by Miyagikai, a social welfare corporation of the SG Group of nursing-care facilities for the elderly, Towada City, Aomori 034-0107, former professor at Tokai University School of Medicine's Department of Public Health and Pediatrics, Isehara City, Kanagawa Prefecture, Japan. Former President of the Japanese Society of Clinical Virology Japan Tel: +81- 176-27-3131

e mail address:<u>clin.virol@nifty.com</u>

Key words: Osteoporosis, Teriparatide, Monoclonal Antibody against RANKL, Long-term follow-up of tibia fracture of a patient whose fractured tibia shaft was reinforced with a titanium alloy insertion.

ABSTRACT

Objective: An osteoporotic fracture is one of the most serious health problems among the Japanese elderly, especially for aged females. A large number of such females have come to sustain osteoporotic fractures at either a proximal femur, a proximal humerus, a distal radius, or/and lumbar vertebrae. Those osteoporotic fractures have left numerous elderly bedridden and susceptible to severe pains emanating from fractures at these sites.

Consequently, this widespread health woe has left numerous Japanese people with no alternative but to rely on nursing care during the entire rest of their lives. Oftentimes, those osteoporotic fractures act as a milestone which aged persons in Japan pass before undergoing a death. A steady and serious progression in the degree of the severity in osteoporosis have especially come to afflict numerous postmenopausal females.

However, it is crucial to note that a recently developed monoclonal antibody against the RANKL-- a type of ligand which, unless bound and neutralized by the recombinant antibody, would bind RANK (Receptor Activator of Nuclear Factor-kB) receptors expressed on the surface of osteoclasts like feelers put out by the osteoclasts -- has made it possible to halt bone resorption by osteoclasts, thereby stopping a progression in osteoporosis and even inducing bone mass mineral density (BMD) upsurges by suppressing osteoclasts' activity, although the antibody oftentimes make deep cuts in osteoblasts' bone-forming activity. (See Appendix to Figure 1on Page 14)

The purpose of this paper is to report a case who has been treated with a mix of this anti-RANKL monoclonal antibody and other leading-edge antiosteoporotic drugs to the point of undergoing upsurges in her BMD readings.

She has been treated for more than a decade, starting in May, 2010, fifteen months after she sustained fractures of her left tibia and fibula during a skiing accident at the age 69.

Patient and Method:The patient, herself a female physician (InternalMedicine) and author of numerous books on infectious diseases, was born on

January 17, 1940. On January 26, 2009, at the age of 69, she sustained fractures of her left leg's tibia and fibula at a holiday skiing accident, minutes after she began to descend down a slope on Mt. Yakeyama adjacent to a caldera lake in Aomori Prefecture in Japan's northeast.

She was taken by ambulance to the Towada City Hospital, where its team of orthopedic surgeons inserted a cylindrical-shaped titanium alloy rod into the medullary cavity of her tibia shaft to enable her fractured tibia to support her body weight again and let her restart walking.

Her condition has been followed up since the fateful January 26 of 2009, with an X-ray imaging apparatus at the Towada City Hospital, where she was operated on two days after the accident.

On top of this follow-up site near an Aomori medical facility where she practices internal medicine, the Keio University Hospital in Tokyo's Shinanomachi, to which she volunteered to go in search of an osteoporosis specialist in late 2012, has since kept track of the state of her osteoporosis by way of BMD measurements, starting on December 25, 2012.

The post-operative course of the female doctor, who was discharged from the Towada City Hospital in April, 2009, after undergoing a three-month rehabilitation training course, returned to her medical facility to assume her own duty as an internal medicine doctor again, was uneventful until May, 2010.

However, on March 15, 2010 -- one year and one months after the operation -- she was baffled at clear radiographical signs of the progression in the degree of the severity of her osteoporosis when she was examining the X-ray photographs of her own tibia and fibula in the aftermath of a periodical X-ray checkup at the Hachinohe City Hospital.

The X-ray images convinced her that she is in an urgent need to ask her doctors to administer therapeutic treatments for her osteoporosis because the X-ray images of the trabeculae (spongy bone) side of her tibia and fibula (the side closer to the medullary cavity) – when compared with those taken immediately after the 2009 fracture – were of a darker shade, giving her the

judgement that her lower limb-bones and other key bones have become even more porous due to a falling calcium density and the prospective judgment that she must not leave her osteoporosis to take its own course. (see Figure 21)

She went to the Hachinohe City Hospital to undergo a checkup because the chief of her orthopedic surgical team at Towada City Hospital had been reassigned to assume a duty at the Hachinohe hospital affiliated with Hirosaki University in the wake of the 2009 operation.

Doctors at this and other hospitals have not prescribed any estrogenic hormone to the patient.

At the time of the 2010 X-ray examination, the osteoporosis-saddled female doctor, the then 70, thought it might run counter to the nature's laws to get estrogenic hormones to be administered to her in view of the passage of more than a decade since her own menopause, although she was aware that a menopause-induced estrogenic deficiency is chiefly responsible for the breakout and progression of an osteoporosis at all postmenopausal women.

Against this background, she decided to get her doctors to administer whatever medicines are diagnosed as being necessary and useful to block a further progression in the degree of the severity of her osteoporosis and, if possible, to turn around a falling BMD, disregards of whether the necessary agents are administered orally or with injections.

Her positive attitude, or a sort of "whatever-medicines-necessary-to-stiflemy osteoporosis-should-be-administered" strategy, has ultimately produced brilliant fruits to the point of driving up her abysmal BMD readings at L2-L4 lumbar vertebrae from **-4.6 standards deviations** as of July 2, 2012, to **-3.3 standard deviations** in terms of the T-score system during the seven-year period from that summer day of 2012.

The positive turnaround stemmed from the fact that she luckily found, in late 2012, a Keio University osteoporosis authority, who made up his mind to administer the anti-RANKL antibody injections to the patient from early 2015 in the aftermath of his own 19-month efforts to treat her with a Teriparatide administration, whose results were not so excellent.

It is noteworthy that her "whatever-medicines-necessary-to-stifle-my osteoporosis-should-be-administered" strategy backfired to some extents during the initial 19 months of the same seven-year period, because an incompatible coadministration of the risedronate-category bisphosphonate and a teriparatide took place, with the sodium risedronate appearing to counteract the effects of the teriparatide.

Table 1 lists all types of medicines with which she has been treated over the past 10 years, while Figure 1 provides an overview of this patient's history of anti-osteoporotic treatments and medical agents that have been prescribed for her from May 21, 2010 until March 2020, when this dissertation was published.

Between May 2010 to July 2012, the patient was administered Alphacalcidol tablets, whose active principle is a vitamin D3 analogue that exhibits the biologic activity of calciferols. But the administration of this active vitamin D3 agent was discontinued in July 20, 2012, when Hachinohe City Hospital doctors began to administer the Eldecalcidol tablets, a different type of Vitamin D3 analogue.

Besides the Alphacalcidol, the doctors began to administer the risedronate to the patient on July 30, 2010. Inspired by her analysis based on years of observation of her own osteoporosis and a sort of professional instinct, the patient decided against letting the doctors administer the risedronate to her in November 2014 after taking it for as long as three years and four months.

By this time, the patient found the risedronate to be almost inefficacious for her case in arresting a further BMD fall or turning around sagging BMD readings.

On December 25, 2012, she visited the outpatient department of Tokyo's Keio University Hospital, the hospital affiliated with her alma mater Keio University's School of Medicine, explaining her physical conditions to the hospital's osteoporosis authority and asking for an effective treatment. It is this Keio University physician who prescribed the Teriparatide, a genetically recombinant 34-amino-acid parathormone whose N-terminal is identical to that of the parathormone secreted by a human's parathyroid.

Between December 25, 2012, and August 1, 2014, she administered subcutaneous injections of the Teriparatide to herself on a daily basis, in accordance with the Keio doctor's prescription, on top of orally taking the Hachinohe hospital-prescribed tablets of the Eldecalcidol and the risedronate tablets, which is known as the 4-Amino-1-Hydroxybutylidene 1,1-Bisphosphonate in medical circles.

Disheartened at the smaller-than-expected effectiveness of the Teriparatide, the Keio physician decided to inject her with the Denosumab monoclonal antibody against RANKL, periodically at an interval of once in all six months, starting on January 16, 2015, with an eye to suppressing osteoclast activities.

Since then, the patient began to produce a string of clear-cut upsurges in her BMD readings.

During the subsequent five years and two months, the patient was administered injections of the Denosumab antibody against RANKL for a combined 11 times. RANKL is the cytokine responsible for communication between osteoblasts, other marrow cells and osteoclasts, so inhibiting the RANKL helps prevent osteoclasts from being activated by the cytokine and thereby removing osseous tissue. The U.S. brand of the Denosumab antibody is the Prolia, whereas it was given the brand name of PRALIA by its licensed manufacturer Daiichi Sankyo Co. for sales in Japan.

The Keio University doctor later noticed that the effects of the teriparatide, which should usually induce architectural improvement in a skeletal structure at its recipients, appear to have been largely offset by his patient's continual oral intake of the risedronate, whose prescription remained an unknown to him until 2019.

It was only late in 2019 that the patient notified the Keio University physician of the history of the administration of the risedronate for the first time ever. Therefore, the coadministration of the risedronate and the Teriparatide from December 25, 2012 through August 1, 2014, was done without the knowledge of the Keio University physician.

Meanwhile, any ups and downs in the patient's BMD readings have been monitored serially by doctors who began to use a leading-edge multi-slice bone densitometer in November 2012 -- one month before the start of the teriparatide administration. Her multi-slice densitometer was the Lunar iDXA of a General Electric Co. subsidiary of the United States. (Figure 2) (Table 1)

Results: Table 4 and Table 5 provide summaries of BMD data measured between November 2, 2012, and August 8, 2019. The teriparatide was given during the initial 19-month period through August 1, 2014. Almost six months after the discontinuation of the teriparatide's administration, the Keio University doctor began to inject her with the anti-RANKL monoclonal antibody.

Figures 2 – 7 graphically represent changes in the patient's BMD readings with Tables 4 and Table 5 making evidence of BDM upsurges induced by the periodic injections of the anti-RANKL monoclonal antibody.

Clearly, the antibody against the RANK ligand put a strong brake on the bone-absorption and removal activities of osteoclasts, which were now stripped of access to the ligand which should have triggered their activities. The ligand, unless bound by the monoclonal antibody, would have bound the osteoclasts' RANK receptors, thereby activating osteoclasts.

But the ligand's binding with the receptors have been obstructed and impeded by the injected antibody which had preemptively bound and disabled the cytokine.

Table 4 shows that <u>the T-score reading of her L2-L4 lumbar vertebrae</u> was as low as **-4.6** at the age 72.7. The Keio University doctor began to administer the monoclonal antibody against RANKL only in January 16, 2015 -- more than five months after the discontinuation of the teriparatide's administration.

Table 4 also shows that her T-score reading at her L2-L4 lumbar vertebrae improved to **-3.3** at the age 79.5. This means that **a marked T-score improvement of 1.3 took place during the seven-year period, especially after** the start of the anti-RANKL antibody's injections.

T-score readings at her right and left femur necks were also as low as **-4.2** and **-4.4**, respectively, at the age 72.7, according to the same table. But it shows that her T-score readings at the femoral necks improved to **-3.8** and **-3.7**, respectively, at the age 79.5, witnessing improvements of 0.4 and 0.6, respectively. Femoral necks are susceptible to fractures at postmenopausal females who have shied away from getting the sites to be treated with appropriate medicines.

The patient's Z-score readings have been kept track of on top of these T-score readings. Table 5 shows that <u>the Z-score reading at the patient's L2-L4</u> <u>lumbar vertebrae</u> stood at **-2.2** at the age 72.7. A Z-score reading at the same site improved sharply to **-0.6** during the subsequent seven-year period at the age 79.5. The Denosumab administration was started in January 2015.

Z-score readings at the patient's right and left femur necks stood at **-1.8 and -2.2**, *respectively*, at the age 72.7. The patient's Z-score readings as of August 8, 2019 also improved to **-1.0** at both femoral sites at the age 79.5.

Conclusion: The treatment of the osteoporotic patient with the mix of the Eldecalcitol and the teriparatide during the seven-year period since August 2012, bolstered up by the monoclonal antibody against RANKL from January 2015, was efficacious in preventing a progression in the degree of the severity of osteoporosis.

The administration of the anti-RANKL monoclonal antibody proved especially effective in suppressing osteoclasts' activity and thereby driving up BMD readings.

We conclude that an early start of medical interventions designed to delay or suppress a natural progression of osteoporosis at postmenopausal human females with leading-edge drugs, especially with agents capable of suppressing osteoclasts' bone-absorption and removal activities, could slash the possibility that such females will sustain fractures of their lumbar vertebrae and/or femur necks.

Period (Menstruation)	The regular discharge of blood and mucosal tissue (known as					
	<i>menses</i>) from the inner lining of the uterus through a vagina.					
Menarche	The first menstrual cycle, or the first menstrual bleeding, in female					
	humans.					
Menopause	The time when there has been no menstrual period for 12					
	consecutive months due to an ovarian failure and when no other					
	biological or physiological cause can be identified.					
Osteoporosis	Osteoporosis literally means porous bone. It is a disease in which the					
	density and quality of bone are reduced. As bones become more					
	porous and fragile, the risk of a fracture increases greatly.					
Osteoporotic fractures	Osteoporotic fractures are a consequence of osteoporosis, a					
	condition in which bones become more fragile due to bone quality					
	deterioration or low bone mass. More fragile bones are at greater risk					
	of sustaining fractures. Typically, significant back pains along the					
	spine is experienced once a vertebral <i>fracture</i> occurs.					
Bone mineral density	Bone mineral density (BMD), a measure of bone density, mirrors the					
(BMD)	strength of bones as represented by calcium content. A BMD test					
	detects osteopenia (mild bone loss, usually without symptoms) and					
	osteoporosis (more severe bone loss, which may cause symptoms).					
Young Adult Mean	Young Adult Mean (YAM), a statistical value, is the mean bone mineral					
(YAM)	density at young adult Japanese females. YAM is the basic value used					
	to diagnose whether a patient should be classified as being in the					
	category of osteoporosis or that of osteopenia, or neither.					
	Under diagnostic criteria (issued in 2012), the lumbar vertebrae YAM					
	has been computed by using data collected from a cohort of Japanese					
	females between ages 20~44, while the proximal femur YAM has been					
	computed by using data of a cohort of Japanese females between ages					
	20~29. ²⁾					
Normal bone density	Normal bone density is signified by BMD readings within 1 standard					
	deviation (SD +1 or -1) from the mean for young adult females.					

Table 1. Technical terms with explanations

Low bone density	BMD readings of osteopenia-affected persons are between -1 and -2.5
(Osteopenia)	SD below the YAM (−1 to −2.5 SD).
	Comments: Postmenopausal women whose T-scores fell to less than
	-1.0 SD are defined as having low bone density. They are also at
	greater risk of developing osteoporosis. Although risk is lower than
	among females with osteoporosis, >50% of fractures among
	postmenopausal women, including hip fractures, occur in this
	osteopenia group.
DEXA (Dual-energy x-	DEXA is short for Dual-energy X-ray Absorptiometry. It is a technique
ray absorptiometry.	for scanning bone and measuring BMD. A DEXA scanner is a large
	machine that beams X-ray beams of two different energies. One beam
	carries higher energy, while the other bears lower energy. The quantity
	of x-rays that pass through a bone site is measured for each beam.
	Resultant energy readings vary depending on the thickness of a bone.
	By examining a difference in energy levels between the 2 beams that
	successfully passed through a bone site, the site's BMD can be
	measured. A DEXA scan is relatively easy to perform and the quantity
	of radiation to which an examinee is exposed can be limited.
T-score (DEXA score)	A T-score value is computed through a comparison of a patient's BMD
	with the YAM density at persons of the same sex. T-score of -2.5 or
	lower indicates that the examined has osteoporosis . The greater the
	absolute value of a negative number, the more severe the examinee's
	osteoporosis.
	patient's bone density – young adult mean
	Standard Deviation (SD)
	A T-score shows how much an examinee's bone density is higher or
	lower, when compared with the YAM density. T-score values of -1.0 or
	above mean that holders of the values carry a normal bone density.
	But a T-score value between -1.0 and -2.5 indicate that a bone
	density at such holders is low and that the examinee has osteopenia.
	(Figure 2, Left & Right half)

Z score (DEXA score)	Z-score values are computed through a comparison of a person's bone				
	density with the mean for persons of the same age. (Mean of age-				
	matched healthy humans)				
	Patient's bone density – Mean density of				
	same-age humans				
	Z-score = Standard Deviation (SD)				

Table 2. List of the medicines prescribed for the case reported in this article

Chemical name	Brand name	Comments
Alfacalcidol. 1- Hydroxycholecalciferol. 1alpha- Hydroxyvitamin D3.	Alpharol cap 1µg	This hepatically-metabolized medicine turns into activated vitamin D3 and promotes digestive tracts' absorption of calcium.
Eldecalcitol, Vitamin D3	Edirol cap 0.75µg	Launch date: April 8, 2011. Eldecalcitol hikes bone mineral density, strengthening bones and making osteoporosis-induced fractures less likely.
4-Amino-1-Hydroxybutylidene 1,1- Bisphosphonate	Benet (Sodium risedronate hydrate) 17.5mg	Bisphosphonates are used to both prevent and treat osteoporosis at postmenopausal women. It helps inhibit osteoclasts' activity, slowing bone density cutbacks and lowering the risk of spinal and hip fractures.
Teriparatide	Forteo for subcutaneous injection 600µg	Human parathormone's 34-amino-acid N-terminal (recombinant). A human- derived parathormone must be administered intermittently. By this manipulation, osteoblasts can be activated. This medicine is useful for osteoporosis treatment.
Monoclonal antibody against RANKL	Denosumab	Japan approved this drug's manufacturing and sales on March 25, 2013. PROLIA ® is a fully human-derived monoclonal

antibody that specifically inhibits RANKL*,
IA an essential mediator for bone resorption.
an It is given via a subcutaneous injection for
use once in every six months. Warnings:
Patients need to receive regular Prolia
injections on a life-long basis, since a
rebound or activation of osteoclasts
would occur if a six-month injection
interval were interrupted or discontinued.

Figure 1 (Left) This patient's Drug Prescription History from May 2010 to December 2019

		2010	2011	2012		2013	2014
		1 2 3 4	5 6 7 8 9 10 11 12 1 2 3 4	1 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7	8 9 10 11	1212345678	9 10 11 12 1 2 3 4 5 6 7 8 9
	Alphacalcidol		2010/5/10				
	Eldecalcidol						
	Bisphosphonate		2010/7/30				
	Teriparatide					2012/12/25	
	Monoclonal antibody against RANKL						
_			Towada City Hosp.			Keio Univ. Hosp	
	Hospital and Clinic		Hachinohe City Hosp.			Sakai Clinic	
			Sakai Clinic				

Appendix to Figure 1 (Teriparatide)



Effects of Parathormon (Parathyroid Hormone PTH) Treatment on bone microarchitecture. The photos show paired biopsy specimens from a 64-year-old woman before (A) and after (B) treatments with Teriparatide. From DW Dempster et al. J bone Miner Res 16:0846, 2001



Inhibitor

Bisphosphonate () prevents active bone resorption by osteoclasts

Figure 1 (Right) This patient's Drug Prescription History from May 2010 to December 2019



Appendix to Figure 1 (Monoclonal antibody against RANKL : Denosumab)



Figure 2 (Left half). T-score values' distribution (The shape of this distribution curb is the same as normal distribution curb's)



T score

Figure 2 (Right half). Graph represents changes in this case's T-score readings as Y-coordinates, with changes in the case's age expressed as X-coordinates



Table 3. T-scores, YAM bone densities at L2-L4, Right Femur Neck, Right Femur Proximal Total, Left Femur Neck, Left Femur Proximal Total, BMD figures corresponding to Standard Deviation (SD) for each site, Percentage figures against YAM densities which correspond to Each of the T-scores

		L2-L4	Right Femur Neck	Right Femur, Proximal Total	Left Femur Neck	Left Femur, Proximal Total
Sex, Age range		Female, 20-44 year	Female, 20-29 year	Female, 20-29 year	Female, 20-29 year	Female, 20-29 year
Mean , SD		1.192, 0.146	0.939, 0.114	0.961, 0.130	0.939, 0.114	0.961, 0.130
T score	% of YAM BMD	L2-L4 BMD	Right Femur Neck BMD	Right Femur, Proximal Total BMD	Left Femur Neck BMD	Left Femur, Proximal Total BMD
0	100%	1.192 g/cm ²	0.939 g/cm ²	0.961 g/cm^2	0.939 g/cm ²	0.961 g/cm^2
-1	80%	1.046 g/cm^2	0.825 g/cm^2	0.831 g/cm ²	0.825 g/cm^2	0.831 g/cm ²
-2	76%	0.900 g/cm^2	0.711 g/cm^2	0.701 g/cm^2	0.711 g/cm^2	0.701 g/cm^2
-3	63%	0.754 g/cm^2	0.597 g/cm^2	0.571 g/cm^2	0.597 g/cm^2	0.571 g/cm^2
-4	51%	0.608 g/cm^2	0.483 g/cm ²	0.441 g/cm^2	0.483 g/cm ²	0.441 g/cm^2
-5	39%	0.462 g/cm^2	0.369 g/cm^2	0.311 g/cm ²	0.369 g/cm^2	0.311 g/cm^2

Table 4. T-score Improvements after Teriparatide and Antibody Interventions: BMD Rises at L2-L4, R & L Femur Necks before and after the administration of Teriparatide (in 2012) and then of Anti-RANKL Monoclonal antibody (in 2019)

		Start of Teriparatide	Start of Monoclonal Ab. Against RANKL	Continuation of Monoclonal Ab. Against RANKL
		Age 72.7 year	Age 74.9 year	Age 79.5 year
Parts of the Body	Items	(2012/11/2)	(2015/1/16)	(2019/8/8)
	Patient Bone Mineral Density (BMD)	$0.526~\mathrm{g/cm}^2$	$0.581~\mathrm{g/cm}^2$	$0.706 \mathrm{~g/cm}^2$
I umbar Vertebres (I 2-I 4)	Young Adult (20-44) Mean	1.192	1.192	1.192
Lumbar vertebrae (L2 L4)	Standard Deviation	0.146	0.146	0.146
	T score	-4.6	-4.2	-3.3
	Patient Bone Mineral Density (BMD)	$0.462 \mathrm{~g/cm}^2$	0.469 g/cm^2	$0.507 \mathrm{~g/cm}^2$
Pight Fomus Neels	Young Adult (20-29) Mean	0.939	0.939	0.939
Right Femur Neck	Standard Deviation	0.114	0.114	0.114
	T score	-4.2	-4.1	-3.8
Left Femur Neck	Patient Bone Mineral Density (BMD)	$0.422~{ m g/cm}^2$	$0.453~{ m g/cm}^2$	$0.506 \mathrm{~g/cm}^2$
	Young Adult (20-29) Mean	0.939	0.939	0.939
	Standard Deviation	0.114	0.114	0.114
	T score	-4.4	-4.2	-3.7



Figure 3. (Right half) Changes in this case's Z-score values represented as Y-coordinates with the passage of time expressed as X-coordinates

Table 5. Changes in this case's Z-score values: BMD Values at L2-L4, FemurNecks before and after the start of the administrations of Teriparatide (in2012) and then of anti-RANKL monoclonal antibody (in 2015)

			Start of Monoclonal	Continuation of
			Ab. Against RANKL	Monoclonal Ab. Against RANKL
		Age 72.7 year	Age 74.9 year	Age 79.5 year
Parts of the Body	Items	(2012/11/2)	(2015/1/16)	(2019/8/8)
	Patient Bone Mineral Density (BMD)	$0.526 \mathrm{~g/cm}^2$	$0.581 \mathrm{~g/cm}^2$	0.706 g/cm^2
I umbar Vortobrac (I 2-I 4)	Age Specific Mean	$0.841~{ m g/cm}^2$	0.827g/cm ²	$0.796 \mathrm{g/cm}^2$
Lumbar vertebrae (L2 L4)	Standard Deviation	0.146	0.146	0.146
	Z score	-2.2	-1.7	-0.6
	Patient Bone Mineral Density (BMD)	0.462 g/cm^2	$0.469 \mathrm{~g/cm}^2$	$0.507 \mathrm{~g/cm}^2$
Right Formur Nook	Age Specific Mean	$0.675 \mathrm{~g/cm}^2$	0.658 g/cm^2	$0.624 \mathrm{~g/cm}^2$
Right Femur Neck	Standard Deviation	0.114	0.114	0.114
	Z score	-1.8	-1.7	-1.0
Left Femur Neck	Patient Bone Mineral Density (BMD)	$0.422~{ m g/cm}^2$	$0.453~{ m g/cm}^2$	$0.506 \mathrm{~g/cm}^2$
	Age Specific Mean	$0.675 \mathrm{~g/cm}^2$	0.658 g/cm^2	0.624 g/cm^2
	Standard Deviation	0.114	0.114	0.114
	Z score	-2.2	-1.8	-1.0

Figure 4. Females' Normal Age-specific BMD Value Distribution at L2-L4 and Improvements in this case's Z-score readings with the passage of time



-6.0

0.0

-4.0

0.0

1.0

.0

0.5

4.0

1.5

.0

6.0

2.0

19

Z score

g/cm²

2.5

Figure 5. Females' Normal Age-specific BMD Value Distribution at Right Femur Neck vs Improvements in this case's Z-score readings with the passage of time







Figure 6. Females' Normal Age-specific BMD Value Distribution at Left Femur Neck vs Improvements in this case's Z-score readings with the passage of time







INTRODUCTION

An osteoporosis-associated fractures is one of the most serious health problems among the elderly. A very large number of Japanese elderly have come to suffer osteoporosis-associated fractures of proximal femur and/or those of lumbar vertebrae. Even in 2007 alone, about 150,000 fractures at the femur neck/greater trochanter region have been reported in Japan.

Females tend to sustain osteoporosis-associated fractures far more frequently than males. Statistics show that the incidence of fractures increases gradually from the period when females are in their 40s, soaring once they enter their 70s. Fractures at a certain bone site tend to prove to be risk factors for fractures at other bone sites. Repeated fractures of different bones have left many elderly patients bedridden, causing them to suffer severe pains stemming especially from fractures of lumber vertebrae. Consequently, those people are left with no alternative but to rely on nursing care during the entire rest of their lives, either at their family households or nursing-care facilities run by various corporate care providers that receive fiscal subsidies under the governmentfunded nursing-care insurance program.

Osteoporosis

Osteoporosis is one of the most critical diseases for postmenopausal women. The present set of diagnostic criteria for primary osteoporosis is shown in the box below. (This set of diagnostic criteria was drawn up as a result of a revision in 2012 by a joint committee of academics from the Japan Osteoporosis Society and the Japan Society of Bone and Mineral Research (JSBMR). (The revised criteria are now known as the JSBMR 2012¹)

Diagnostic criteria of Primary Osteoporosis (JSBMR 2012)¹⁾

A person must be diagnosed as a primary-osteoporosis sufferer if the results of an assessment of their bones satisfy either one of the following two conditions and in cases where doctors neither recognize the presence of non-osteoporosis ailments that induce low bone mass nor recognize the presence of secondary osteoporosis.

I In cases where the person has a history of sustaining a bone fragilityassociated fracture, which is a fracture sustained as a result of being subjected to an external force such as a fall from a standing position.

1. The person has a history of sustaining a vertebral fracture, including asymptomatic fractures (It is key to note that two-thirds of vertebral fracture cases are asymptomatic and can only be diagnosed with an X-ray examination of vertebrae) or of sustaining a fracture of proximal femur.

2. The person has a history of sustaining fragility-associated fracture(s) at sites other than a vertebrae and proximal femur on top of having a bone mineral density of less than 80% of the mean density for young adults (YAM: Young Adult Mean, i.e., the mean for young healthy adults of the same sex and race).

II. In cases where the person does not have a history of sustaining a bone fragility-associated fracture.

The person provides a bone mineral density of 70% or less of YAM or the person's BMD was found to have fallen more than 2.5 standard deviations (SD) below the YAM. T-score values for this condition is referred to as -2.5 or less.

Classification of Bones

Human bones are classified into four categories as shown in Figure 8. Plane bones: Skull, Shoulder girdle, Irregular bones: vertebrae, Mandible Long bones: Femur (Lower extremity), Humerus (Upper extremity), etc. Short bones: Foot bones, Wrist bones



Classification of Ossification

Bones are formed through two osteogenic pathways: Intramembranous ossification and endochondral ossification.

1. Intramembranous Ossification (Development of Flat Bones of Skull, Mandible and Clavicle)

In intramembranous ossification cases, a group of mesenchymal cells within a highly vascularized area of the embryonic connective tissue proliferates and differentiates directly into osteoblast precursors before differentiating into osteoblasts. These cells synthesize and secrete osteoid which is calcified to become woven bone. Blood vessels incorporated between the woven bone trabeculae subsequently form a hematopoietic bone marrow.

Later, the woven bone is remodeled and is progressively replaced by mature lamellar bone. In the early stage of a human's fetal life, resorption and apposition begin to take place so that the cancellous bone (also called trabecular or spongy bone) occupies the center of the mass while a layer of cortical bone is formed on each side of the cancellous bone through a continuous addition of new sheets of bone by active osteoblasts. Osteoclasts resorb bone from the inner surface to maintain a balanced thickness and shape of the bone.

2. Endochondral ossification

In an endochondral ossification, epiphyseal cartilage is involved during the ossification process at which osseous tissue is formed by the replacement of calcified cartilage. The endochondral ossification is an essential process during the rudimentary formation of long bones, which is the growth of the length of long bones at the epiphyseal plate where osteoblasts form bone trabeculae on a framework of calcified cartilage.



in diameter.

Figure 8. Bone Growth

structures that are typically between 0.25 mm and 0.35 mm

Menopause

Figure 8 shows line and bar graphs of ages at which Japanese women remember their menses ceased permanently. ²⁾ This is the data taken from Japanese women of ages 35 ~59. (This means that they were born between April 1929 and March 1953). Although the graph representing the distribution of such menopause ages is not that of a typical normal distribution and has a tailing to the left, if we boldly supposed that this is roughly a graph of a normal distribution, it would be possible for us to calculate the mean menopausal age and a standard deviation (S.D) as shown in the figure.

Even if we assume that this pattern is not that of a normal distribution, we still can calculate percentiles in place of the mean and standard deviation numbers. To the right-hand side of the graphs, we showed the results of our calculations which determined that the mean menopausal age came to 49.47 year with the median coming to 50.54 (in terms of 50 percentile). Whichever supposition we may select, we could conclude that Japanese female's menopause occurs most frequently at around the age 50.

Estrogen is one of the hormones excreted from ovaries and a menopause occurs when ovary stops producing the estrogen.



Figure 9. Age of Menopause of Japanese Women by Memory (n=456)²⁾

In human females, their bone mass increases during their childhood and puberty, attaining its peak quantities when they reach around 30 years old. Then, their bone mass starts to decrease. Estrogen plays an important role in keeping a balance between formation and degradation of bone mass. In other words, the estrogen works to prevent calcium from eluding bones, maintaining certain levels of bone mineral density.

Right after the permanent cessation of the menses, estrogen levels drop abruptly. This triggers a speedy and never-ending loss of bone mass which is expressed as steady and sharp BMD decreases. Consequently, an incidence of osteoporosis zooms up. As human females age, they are exposed to higher risk of developing osteoporosis. (Figure 9)





Itsuo Yamamoto: Osteoporosis Japan 7(1): 10, 1999



Figure 11. Activities of Osteoblasts and Osteoclasts

or

Figure12. Analogy among ups and downs in human females' lifetime menstruation activity levels, estrogen secretion levels, bone mass fluctuation, and the sun's appearances as the earth rotates on its axis



30

Demographic basis of osteoporosis

Since an ovary's life span is a biological phenomenon that does not undergo ups and downs in a span of decades, the median age at which a menopause occurs has remained almost the same for decades, although the average duration of Japanese women's lifetimes has become much longer over the past several decades.

Figure 8 shows a breakdown of the Japanese people by age and sex as of 2019. In 2019, a cohort of postmenopausal females accounted for 25.3% of the entire Japanese population, while making up 51.5% of all Japanese females who in turn accounted for 49.1% of the entire Japanese population. A steady progression in the degree of the severity in osteoporosis is unfolding at all these females.

The mean life expectancy of Japanese females was below 50 years throughout the several decades that preceded the 1941 outbreak of bloody hostilities on the Pacific theater of the Second World War (which got under way with the Japanese Navy's attack on Pearl Harbor, Hawaii, on December 8, 1941, and ended with an radio broadcast August 15, 1945, of a SP recording of Emperor Hirohito's reading-out of an imperial rescript, with which he notified the nation and Japanese armed forces deployed in Japan and elsewhere of the cabinet's decision to accept the unconditional surrender terms demanded by the Allied Powers with the July 26 Potsdam Declaration issued in Potsdam, Germany).

Even the longest among such life expectancy means of Japanese females during these pre-World War II decades was 49.63 years recorded in the years 1936~1937 (Figure 7)

The mean age of their menopause at which Japanese human females' ovarian estrogen-secreting functions come to a halt has remained 50 even after the 1945 Japanese surrender to the Allied Powers.

The menopausal threshold age has remained immovable throughout the 20th century and the current initial phase of the 21st century. It is noteworthy to recall the fact that before the start of the World War II, the percentage of Japanese

females who were alive even after their menopauses was almost nil. Therefore, osteoporosis was not a serious health problem for Japanese society in the decades preceding the outbreak of the World War II.

But a turning point came. In 1947, just two years after the surrender, Japan carried out its first post-WWII national census, finding that the mean life expectancy of Japanese females has eclipsed the 50-year-old line by standing at 53.96.

Since then, the mean life expectancy of Japanese females has been ascending steadily, reaching as high as 87.32 years old as of 2018 against the backdrop of advances in scientific levels of medical services to which they have access, better nutritious intakes and some other factors.

This means that a very large number of postmenopausal females are alive in Japan at present.

These postmenopausal females are at extremely high risk of developing osteoporosis because estrogen (one of the hormones secreted by an ovary) plays a key role of enabling females to maintain normal BMD levels by placing the activity of osteoclasts under control.

Females who have lost ovarian functions have come to suffer a continual loss of bone mineral density throughout their skeletons.

Summing up, it is now highly likely that numerous Japanese females are developing, and will likely go on developing, an osteoporosis, now that their ovaries stopped carrying out their usual estrogen-secreting function. (Figures 13 and 14, Table 6)



Figure 13. Mean Japanese Life Expectancy (Red graph denotes females') Age (year)

http://www.ritsumei.ac.jp/~satokei/sociallaw/compulsoryretirement.html



Table	6. <i>I</i>	Appen	dix to	Figure 8
-------	-------------	-------	--------	----------

Cohort	Age	Population	Percentage
	(year)		of total
			population
Total of females		61,572,829	49.1%
Post-menopausal females	50~	31,726,936	25.3%
Female of reproductive ages	20~49	22,070,912	17.6%
Female from babyhood to	0~19	7,900,383	6.3%
puberty			

Mammals other than human beings walk on their four legs, although a few mammal species like kangaroos move on the basis of bipedal locomotion. Only humans walk erect on their legs on the basis of bipedalism. The back bone postures of non-human mammals are arraigned largely horizontally in relation to the ground. Three-dimensional morphologies of human beings' vertebral column, femurs and tibias are arraigned vertically in relation to the ground.

Hence in human beings, their back bone must endure the weight of a human's head, which accounts for some 10% of his whole body's weight. Let us take a look at an example. If a human female weighs 50 Kg, her head's weight comes to approximately 5 Kg. During a daytime when humans generally maintain an upright posture, his back bone (vertebral column) needs to endure the head-associated weight of 5 Kg (as a result of universal gravity) all the time. This 5 Kg weight stress is shared evenly by his two legs with each of his great trochanters enduring a 2.5 Kg weight. (See Figure 9)

On the other hand, a reaction force springs up against the gravitational pull, whose magnitude is equivalent to that of the gravitational pull. The sole difference between the two forces lies in the direction in which each of the forces is applied. Consequently, the reaction forces whose magnitude comes to 2.5 Kg, respectively, is transmitted via each of his femurs to his proximal epiphysis, or the top edge of femurs' trunks of femurs. Therefore, the necks of his two greater trochanters must bear these two forces which are applied in two opposite directions, with one force weighing down on the femoral necks from above via the vertebral column, while the other force being communicated upward via his femoral trunks.

When we ponder the medical significance of this reality, we can easily understand that fractures of vertebrae and the necks of greater trochanters are most often experienced by postmenopausal, osteoporotic females.

Figure 15. Vertebrae and Femoral Necks bear both gravitational pull and reaction force against it

Weight of Head (10% of Body Weight) (In cases where a person weighs 50 Kg, the weight of his head comes to 5Kg)



MEASUREMENT OF BONE MINERAL DENSITY

The patient's BMD has been measured with two models of the highdefinition multi-slice bone densitometer (Lunar iDXA and DPX) of General Electric Co. arms of the U.S. (Figure 10) The DEXA technology involves shooting two X-ray beams of different energies to targeted bone sites to estimate the size of the area where its tissue has been mineralized. Then, the mineral content is computed by dividing the site's weight by the size of such mineralized tissue area, with its calculation results corrected in view of a patient's body and his bone size. However, this correction cannot be described as being perfect since a DEXA is a two-dimensional scanning technique that makes it impossible to estimate a depth and post-anterior length of the targeted site accurately enough. To counteract this factor, DEXA scanners cleverly take into accounts the fact that small slim people tend to have lower-than-average BMDs, a feature that is taken into accounts in interpreting their BMD measurements.

Figure 16. Direct Digital & Multi-Slice Bone Densitometer (Lunar iDXA)



The patient has been visiting two different hospitals: Keio University Hospital and Towada City Hospital. Both hospitals have been measuring her BMD values with GE's DEXA scanners. However, they use different GE scanner models. Each model analyzes measured results with an automatic analytical software. The programs use different YAM values as basis for calculations. Table 5 explains this criteria difference situation in details. Since Towada City Hospital is using the most up-to-date YAM values (identical to the JSBMR's 2012 criteria) as its diagnostic criteria in evaluate patients' BMD readings and checking if their BMD values are in a normal range. All data in this report have been converted by the authors by adopting the YAM values used by Towada City Hospital's scanner as the sole calculation basis. Table 7. Comparison of the BMD Mean for Young Adult Females in terms of the unit (gram/cm²) used by Prodigy scanner at Towada City Hospital and the BDM YAM Mean used by the Lunar Prodigy scanner of GE Medical Systems, USA, at Keio University Hospital. Both GE scanners use Dual-Energy X-ray Absorptiometry. The difference is that Towada's criteria are consistent with JSBMR's 2012 norms, whereas Keio's are consistent with 2000 JSBMR norms.

Date of Patient's Visit to Out Patient Clinic	Hospital	System	Diagnostic criteria	Lumbar Vertebrae (Front) L2-L4	Proximal Femur (Total)	Femur Neck
2019/8/8	Towada City Hospital	Dual-energy X-ray absorptiometry (PRODIGY, GE Healthcare; Madison, Wisconsin, USA) Software version 13.15 compatible)	2012 Diagnostic criteria ¹⁾ (based on 1996 Guideline data ³⁾ (Capable of using Software Version 13.1)	YAM (young adult female age: 20~44 year) 1.192 g/cm²	YAM (young adult female age: 20~29 year) 0.961 g/cm²	YAM (young adult female age: 20~29 year) 0.939 g/cm²
2012/11/0 2~2019/1/ 11	Keio University Hospital	Another DEXA scanner: Lunar Prodigy; GE Medical Systems, Madison, Wisconsin, USA)	2000 Diagnosis criteria ⁴⁾ (based on 1996 Guideline ³⁾ Data)	YAM (young adult female age: 20~44 year) 1.12 g/cm ²	YAM (young adult female age: 20~44 year) 0.934 g/cm²	YAM (young adult female age: 20~44 year) 0.9 g/cm²