Osteoporosis and Sarcopenia 3 (2017) 174–184

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: http://www.elsevier.com/locate/afos

Original article

Understanding the factors associated with initiation and adherence of osteoporosis medication in Japan: An analysis of patient perceptions

Hajime Orimo [a], Masayo Sato [b, *], Shuichi Kimura [b], Keiko Wada [c], Xuelu Chen [c], Shigeto Yoshida [c], Bruce Crawford [c]

[a] Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan
[b] Eli Lilly Japan K.K., Kobe, Japan
[c] QuintilesIMS, Tokyo, Japan

ARTICLE INFO

Article history:
Received 28 August 2017
Received in revised form
19 September 2017
Accepted 19 October 2017
Available online 3 November 2017

Keywords:
Osteoporosis
Adherence
Japan
Patient-centered care

ABSTRACT

Objectives: This study aimed to identify factors associated with initiation and adherence of osteoporosis medication from a patient perspective.
Methods: A web-based survey was developed based on health behavior theories. Descriptive analyses were conducted for all survey items. Analyses in a structural equation modeling framework were conducted to identify factors associated with treatment initiation and adherence.
Results: Five hundred forty-five women completed the questionnaire. A majority were currently receiving medications for osteoporosis (n = 376, 69.0%) and 25.0% of these patients (n = 94) were considered adherent to their treatment. Knowledge was strongly associated with osteoporosis treatment initiation (standard error [SE], 0.58). Greater knowledge of disease was associated with increased likelihood of initiating medication. Medication complexity (SE, 0.49) and perceived susceptibility to fracture and loss of independence (SE, −0.37) were also associated with initiation. Perceived barriers (SE, −0.85) such as inconvenience, lack of efficacy and financial burden were observed to be the greatest obstacle to adherence. The greater the perceived barriers, the less likely patients were to adhere to medication. Patients' perception of self-efficacy (SE, 0.37) also affected adherence. The greater the patient perception of ability to independently manage their medication, the more likely they were to adhere to the medication.
Conclusions: Different factors were found to be associated with initiation and adherence of osteoporosis medication. Patient knowledge of their disease and the perception of barriers were found to be the most influential. Empowering patients with the knowledge to better understand their disease and decreasing the perception of barriers through education initiatives may be effective in improving patient outcomes.

1. Introduction

Osteoporosis is clinically characterized by an increased risk of fracture due to compromised bone strength and a reduction in bone mass [1,2]. In Japan, the prevalence of osteoporotic patients aged 40 or above was estimated to have reached 12.8 million in 2012, and 9.8 million among them were women [3]. The estimated annual incidence of osteoporosis in Japan was reported to be 0.6% in men and 2.3% in women, resulting in approximately 970,000 incident cases (160,000 men and 810,000 women) per year [3].

Osteoporosis leads to decreased quality of life (QoL) for patients, due to comorbidities, level of independence and morbidity, and complications [4,5]. QoL is significantly decreased when a patient experiences a fracture, and decreases in QoL following vertebral fractures, lumbar fractures, and hip fractures have been repeatedly documented in the literature [4]. While evidence from Japan has shown that approximately 148,100 individuals (31,300 men and 116,800 women) sustained proximal femoral fractures due to osteoporosis in 2007, recent estimates of the incidence of hip fractures in 2012 totaled 175,700 (37,600 men and 138,100 women), a 19% increase compared to 2007 [5]. In addition to reductions in QoL, osteoporosis is also associated with a substantial

* Corresponding author. Eli Lilly Japan K.K., Sannomiya Plaza Building, 7-1-5 Isogami-dori, Chuo-ku, Kobe, 651-0086, Japan.
E-mail address: sato_masayo@lilly.com (M. Sato).
Peer review under responsibility of The Korean Society of Osteoporosis.

https://doi.org/10.1016/j.afos.2017.10.002

economic burden. In the United States, the cost of osteoporosis-related fractures was estimated to be approximately US $17 billion in 2005 and was projected to grow by approximately 48%, incurring more than US $25.3 billion by 2025 [6]. In Europe, the economic burden of incident and prior fragility fractures was estimated to reach €37 billion [7]. Although osteoporosis-related economic data in Japan are scarce, recent estimates have reported that the per-patient burden of hip fracture was US $25,599 in treatment costs per fracture event and in excess of US $43,755 per year for nursing care [8]. A similar pattern of high cost has been reported in other countries in Asia [9,10].

The 2011 Japanese osteoporosis guidelines state that the goals of osteoporosis treatment are prevention of fracture and maintenance of good skeletal health [3]. A recent review of osteoporosis studies has consolidated evidence that drug therapy can reduce osteoporosis-related fracture risk in patients over 50 years of age [11]; however, medication effectiveness has been limited due to low treatment rate and poor medication adherence [11]. Evidence from multiple countries, together with evidence from Japan [12] has shown that poor adherence to osteoporosis medication is associated with a high risk of fracture, high medical costs and/or a high frequency of hospitalization [11]. In contrast, good adherence can help achieve better therapeutic benefit [13]. The association between fracture rate reduction and good adherence has been reported in numerous previous studies [11,14–16].

Real world adherence to osteoporosis therapy has been reported to be low both globally and in Japan [11,17]. The results of a recent review of osteoporosis studies reporting treatment persistence and adherence with bisphosphonates suggested that less than 50% of patients remained on therapy after 1 year [11]. The primary explanation for this poor treatment persistence and adherence was the presence of mild adverse effects, dosing frequency, and costs. In Japan, it has been estimated that only 20% of osteoporosis patients actively seek treatment [18]. Furthermore, osteoporosis treatment persistence and adherence have been reported to vary with approximately 28%–60% of patients discontinuing their daily medication after 1 year [16,19–21] and 39%–61% of patients considered to be adherent to their daily treatment at 1 year [16,19].

To understand why some patients do not initiate treatment and why some patients do not adhere to their prescribed medication, it is important to obtain insights on patients' perspectives, decision making processes, particularly in regard to the complexity of variables influencing treatment initiation and adherence outcomes. The past decade has seen a growth in the use of sophisticated analytical techniques such as structural equation modeling (SEM) to address these questions in the research of social and behavioral sciences. SEM techniques use a combination of statistical data and qualitative causal assumptions to test causal relations [22]. An increasing number of studies have utilized SEM in the medical sciences to learn about patient behaviors and decision making related to pharmacological and psychotherapeutic treatments in various therapeutic areas including oncology, infectious diseases, diabetes, cardiovascular diseases, and osteoporosis [23–25].

Medication initiation and adherence are complex, multifactorial and individual behaviors. Patient perception of medication effectiveness, safety, and necessity have been previously reported to be obstacles of medication adherence in osteoporosis [26]. In a study evaluating the influence of patient characteristics, perceptions, knowledge and beliefs about osteoporosis on the decision to initiate osteoporosis treatment, knowledge of osteoporosis and beliefs in the benefits of medications were reported to have a positive impact on medication initiation [27]. Patients who had started treatment were also more likely to believe in the effectiveness of osteoporosis medication and less likely to worry about side-effects of the medication [27]. Improved patient education, availability of better tolerated and less frequently-dosed medications, and increased health care provider-patient interaction could possibly improve patient adherence [26]. This narrative-based approach to facilitating treatment adherence focusing on the perspective of each individual patient can help to improve patient-centered treatment and management of osteoporosis. Such an approach would be helpful in supporting existing evidence-based medicine to reach its full potential.

The aim of this study was to identify the factors that are associated with treatment initiation and adherence of osteoporosis medication using a patient internet survey based on health behavior theories and analyses in a SEM framework.

2. Methods

2.1. Study participants

Study participants were recruited from a patient panel developed and managed by an internet-based research company. Eligible participants were female aged 50 years or older with a self-reported diagnosis of osteoporosis. At the screening phase of the online survey, participants were asked if they have been diagnosed with any of 16 chronic conditions presented, including osteoporosis. Only responders who reported osteoporosis were able to move forward to the full survey. Participants were excluded if they reported a diagnosis of cancer or human immunodeficiency virus due to a potentially high number of prescription drugs utilized by these patients. Participants were also excluded if they reported dementia, Alzheimer disease, or psychiatric disorders which were considered to potentially affect patients' perception and decision making processes.

2.2. Patient survey

The survey was developed specifically for this study, using a hypothesized conceptual framework based on behavioral psychology theories related to health behaviors, decision making processes, and perception of the illness and treatments [28–30]. The literature search was guided by using a combination of different keywords in PubMed or Google Scholar, including osteoporosis, health behavior model, social cognitive theory, self-regulation, and adherence. The instruments that measure these topics and have been validated in osteoporosis patients included the Osteoporosis Self-Efficacy Scale [31], the Osteoporosis Health Belief Scale [32], the Beliefs about Medicines Questionnaire, and the Osteoporosis-Specific Morisky Medication Adherence Scale 8-Item (MMAS-8) [33]. The authors believe it is important to use validated measures wherever possible, so the Osteoporosis-Specific MMAS-8 was selected to measure adherence in our study. As for other concepts, none of the instruments were validated in Japanese language or osteoporosis patients in Japan; therefore, the questions included in the original instruments were reviewed closely. The survey developed for this study contained a total of 31 questions for patients who are not currently treated with osteoporosis medications and 44 questions, including the 8 MMAS questions, for patients who are currently treated with osteoporosis medications (Supplementary Table 1).

2.3. Outcome definition and variables

There were 2 outcome measures for this study: whether patients ever initiated treatment for osteoporosis; and whether patients were adherent to osteoporosis medication. For initiation, patients who reported that they were currently or previously treated with osteoporosis medications were categorized as

'initiated' and patients who were never treated with osteoporosis medication were categorized as 'not initiated.' For adherence, the MMAS-8 was used for measuring level of adherence and was scored according to the developer's recommendations. Adherence to medication was defined based on a score of 8 on the MMAS-8, and nonadherence was defined as a score of less than 8 based on the recommendations from the developer of the MMAS-8 [34–37].

Demographics included age, geographical region, number of people in household, occupation, and education. Health and disease information included height, weight, height loss since 40 years old, fracture history, family history of fracture, experience with bone mineral density (BMD) test, comorbidities, smoking status, alcohol intake, current health, health change, age of diagnosis, severity of osteoporosis, treatment history, average daily back pain, and frequency of doctor's visit for osteoporosis.

Lastly, a number of constructs hypothesized to be related to medication initiation and adherence were examined based on the following theories. The Health Belief Model uses a socio-psychological, behavioral theory of decision-making to explain and predict health behaviors, suggesting that people's belief about the disease and belief about the benefits of the recommended health behavior influences the likelihood of them adopting this health behavior [29]. The Self Regulation Model, also known as the Common-Sense Model of Illness Representations, suggests that people develop a mental representation of their illness based on their personal experiences such as physical symptoms, emotions, cultural and social influences, and interactions with healthcare providers [30]. Our survey was developed based on these 2 theoretical models to explore, explain, and predict the relationships among theoretical concepts associated with patients' decision making regarding initiation and adherence of osteoporosis medication. Specifically, the survey included questions on knowledge of osteoporosis, perceived severity of the disease (patients' opinion of how serious a condition and its consequences are), perceived susceptibility (patients' opinion of chances of getting a condition and adverse outcomes), perceived side effects of medication, perceived benefits (patients' belief in the efficacy of the advised action to reduce risk or seriousness of impact), perceived barriers (patients' opinion of the tangible and psychological costs of taking medication), and patient self-efficacy (patients' confidence in their ability to take action).

2.4. Statistical analysis

Descriptive statistics were conducted for all survey items with proportions and mean ± standard deviation summarized as appropriate. Patient characteristics and survey item responses were also described for different patient groups: patients who were adherent and patients who were not; and patients who initiated treatment and patients who did not initiate.

Two SEMs, one for treatment initiation and another for adherence, were employed to test the paths for initiation and adherence and to identify variables associated with patients' behavioral decision making related to initiation and adherence [38]. Each SEM included 2 major components viewed as a combination of confirmatory factor analysis and multiple regression/path analysis: the measurement model and the structural model. The measurement model is used to define relationships between observed variables (i.e., survey question answers) and their underlying concepts. The structural model is used to define how the concepts and observed variables affect each other. Overall, the SEM is based on a range of multivariate methods at evaluating underlying relationships or structure and allows the evaluation of the relationships between the behavior of interest (initiation and adherence of osteoporosis treatment) and the variables included in the survey. Standardized parameter estimates for paths connecting constructs were calculated, and all paths regardless of standard errors (SEs) were kept in the models. In order to simplify the model presentation, only paths exceeding absolute SE of 0.2 or greater were shown in the model figures, indicating a 1 unit change in one construct would result in a 0.2 standard deviation change in the other construct.

In the evaluation of overall model fit, the chi-square value, comparative fit index (CFI), Tucker-Lewis Index (TLI), root mean square error of approximation (RMSEA) were calculated. Models with CFI and TLI above 0.95 were considered as good [39]. The RMSEA of 0.01, 0.05, and 0.08 indicated excellent, good and mediocre model fit, respectively [40]. For model building, fitting and evaluation, Lavaan, a program package for SEM for R language was used [41,42].

2.5. Ethical considerations

This study was approved by the Ethics Committee of the NPO Clinical Research Promotion Network Japan on July 23, 2015 (approved protocol number: 1015283).

3. Results

3.1. Overall patient characteristics

Patient selection process is shown in Fig. 1. A total of 36,532 women who are aged 50 years or older responded to the screening questions, and 1360 women reported to have a diagnosis of osteoporosis. Of those, a total of 545 women meeting the inclusion and exclusion criteria completed the online questionnaire in September 2015.

Patient characteristics for all patients (n = 545) are summarized in Table 1. The average age was 64.5 years old, ranging from 50 years old to 91 years old. More than half of the patients lived in the metropolitan region (74.1%) and were homemakers (54.7%). The most frequently reported comorbidities were hypertension (27.5%) and hyperlipidemia (22.6%). The average age of osteoporosis diagnosis was 60.3 years old. Majority of the patients perceived their osteoporotic condition only to be mild (72.8%). More than half of patients visited their doctors for osteoporosis either once a month (36.3%) or every 2 or 3 months (29.7%). While more than half of patients did not experience any back pain due to osteoporosis (59.6%), for those with pain (n = 220, 40.4%), the average pain score was low at 3.6, with pain score 0 indicating no pain and 10 indicating the worst pain imaginable. Most of the patients have been treated with prescribed medications for osteoporosis either currently (n = 376, 69.0%) or previously (n = 114, 20.9%), with 10.1% (n = 55) never initiated any medication for osteoporosis in the past. Of the patients currently on osteoporosis medication, 25.0% (n = 94) were evaluated to be adherent to their treatment, according to their response to the MMAS-8.

Further patient characteristics by osteoporosis medication initiation and adherence status are presented in Table 2. Overall, patients who have initiated osteoporosis medications were older, reported more height loss, visited their doctors frequently, and more likely to have severe osteoporosis, fracture history, and severe pain. Of those, patients who determined to be adherent to their osteoporosis medications reported height loss and severe pain less frequently than those determined to be not adherent to their osteoporosis medications.

Patients' responses to the questionnaire are detailed in Supplementary Table 1.

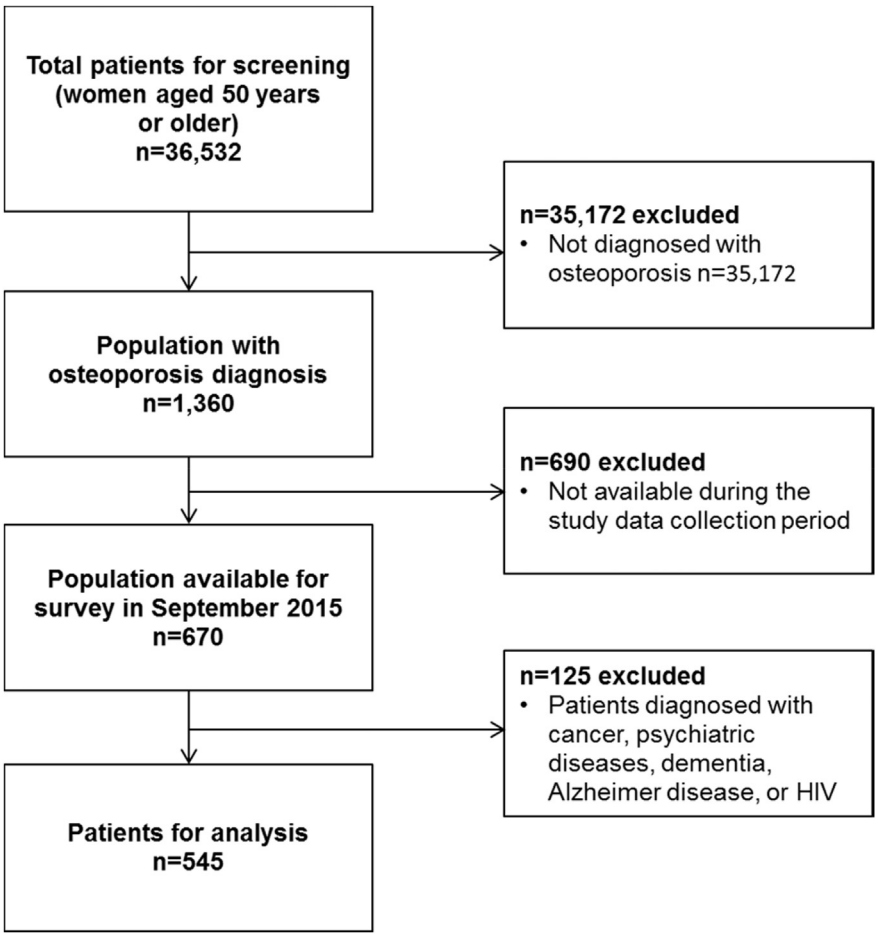

Fig. 1. Patient selection. HIV, human immunodeficiency virus.

3.2. Factors associated with osteoporosis medication initiation

Fig. 2 shows variables associated with osteoporosis treatment initiation whose SE is considered to be strong (absolute SE values $\geq$ 0.2). The initiation model was considered to have good model fit. Knowledge (SE, 0.58) was observed to be the strongest factor associated with initiation of osteoporosis treatment, indicating that the more knowledge patients had about their disease, the more likely they were to initiate treatment. Medication complexity for all current medications (including both osteoporosis and nonosteoporosis medications) (SE, 0.49) was also found to be strongly associated with treatment initiation. Perceived susceptibility to the disease's negative consequences such as vulnerability to fractures and loss of independence was also found to be associated with initiation (SE, −0.37). Patients who responded 'very true' or 'somewhat true' to the statement, 'I understand that once you have osteoporosis, bones are more susceptible to fractures' were more likely to have initiated treatment of osteoporosis. Perceived susceptibility was in turn associated strongly with knowledge (SE, 0.67) in that the more knowledge patients had about their disease, the more susceptible to fractures and loss of independence they perceived themselves to be. Frequency of hospital visit (SE, 0.25) was also found to be associated with treatment initiation in that the more frequently patients visited their doctor, the more likely they were to initiate treatment.

3.3. Factors associated with adherence for osteoporosis medication

Fig. 3 shows variables associated with treatment adherence whose SE is considered to be strong (absolute SE values $\geq$ 0.2). The adherence model was considered to have good model fit. Perceived barriers (SE, −0.85) was negatively associated with adherence, with the more barriers patients perceived, including inconvenience, lack of efficacy, and financial burden, the less likely patients were to adhere to their medication. Self-efficacy (SE, 0.37) was also strongly associated with adherence in that the more strongly patients felt that they were able to manage their medication on their own, the more likely they were to adhere to the medication. Perceived side-effects was directly related to both adherence (SE, 0.31) and perceived barriers (SE, 0.65). The more worried patients were about safety and side effects of their osteoporosis medication, the less likely they were to adhere to the medication. Due the strong negative path between perceived barriers and adherence as mentioned earlier (SE, −0.85), the effect of perceived side-effects on adherence cancelled out. This resulted in perceived side-effects having a negative impact through perceived barriers on adherence overall. Other variables were observed to impact adherence indirectly. As shown in Fig. 3, the more worried patients were about side-effects, the greater their perception of barriers was (SE, 0.65). The greater the severity of back pain patients that suffered, the more knowledge about the disease they tended to have (SE, 0.24). The more knowledge patients had of their disease, the greater their perception of the benefits of medication (SE, 0.74). The more susceptible patients perceived themselves to be (SE, 0.53), the more severe their perception of the disease (SE, 0.20). These constructs were linked to adherence through perceived benefits, but the links were not significant (nonsignificant path, shown in a dotted line in Fig. 3).

Table 1
Patient characteristics (n = 545).

Characteristic	Value
Age, yr	
Mean ± SD (range)	64.5 ± 8.0 (50–91)
Geographical area	
Metropolitan	404 (74.1)
Number of people in household including self	2.3 ± 1.06
Key comorbidities	
Hypertension	150 (27.5)
Hyperlipidemia	123 (22.6)
Gynecological disease	94 (17.3)
Arthritis	62 (11.4)
Respiratory disease	42 (7.7)
Age of diagnosis	60.3 ± 9.4
Severity of osteoporosis	
Mild	397 (72.8)
Moderate	115 (21.1)
Severe	33 (6.1)
Height loss since 40 years old	
No change	179 (32.8)
Reduction by 2 cm+	135 (24.8)
Back pain due to osteoporosis[a]	
No pain	325 (59.6)
Some pain	220 (40.4)
Mean pain score[b]	3.6
Severe pain (≥5)	81 (14.9)
Smoking status	
Current smoker	39 (7.2)
Alcohol intake	
Yes	51 (9.4)
Low BMD[c]	474 (87.0)
Fracture history[c]	49 (9.0)
Current health	
Excellent	4 (0.7)
Very good	48 (8.8)
Good	311 (57.1)
Not very good	142 (26.1)
Poor	40 (7.3)
Change in health status vs. 1 year ago	
Much better	4 (0.7)
Somewhat better	46 (8.4)
About the same	345 (63.3)
Not as good	124 (22.8)
Much worse	26 (4.8)
Frequency of doctor's visit	
Once a week or more	17 (3.1)
Once every 2–3 wk	23 (4.2)
Once a month	198 (36.3)
Once every 2–3 mo	162 (29.7)
Once every 4–5 mo	15 (2.8)
Once every 6 mo	19 (3.5)
Less than every 6 mo	111 (20.4)
Occupation	
Full time	55 (10.1)
Part time	83 (15.2)
Homemaker	298 (54.7)
Student	0 (0)
Retired/unemployed	84 (15.4)
Other	25 (4.6)
Education	
Graduate/postgraduate	11 (2.0)
University	201 (36.9)
High school	262 (48.1)
Secondary school	17 (3.1)
Other	54 (9.9)
Osteoporosis medication status	
Currently treated	376 (69.0)
Stopped	114 (20.9)
Never treated	55 (10.1)
Adherence to osteoporosis medication[d]	
Adherent	94/376 (25.0)
Not adherent	282/376 (75.0)

Values are presented as number (%) or mean ± standard deviation (SD) unless otherwise indicated.
BMD, bone mineral density.

[a] Back pain was measured by a scale of 0–10 where 0 indicates no pain and 10 indicates worst pain imaginable.
[b] For patients who reported pain.
[c] As told by their physician.
[d] Adherence was measured by the Morisky Medication Adherence Scale 8-Item (MMAS-8). Permission to use the MMAS-8 scale was granted to QuintilesIMS (formally IMS Japan K.K.) by Donald Morisky, the copyright holder of the scale and would require his permission for use outside of this survey.

3.4. Comparison in responses between 'initiated' and 'not initiated' patients

Overall, patients who initiated osteoporosis medication tended to have severe back pain, perceive the benefits of medication in preventing fractures, more likely to seek information from doctors or hospital brochures, and already taking medications for disease conditions other than osteoporosis. Conversely, patients who did not initiate osteoporosis medication tended not to see the need for the medication, were more likely to not be taking medications for other conditions, and were mostly uncertain about the benefits of medication in preventing fracture.

Specifically, there were several questions to which patients responded differently depending on their initiation status. A greater number of patients who initiated osteoporosis medication reported that they had severe back pain due to osteoporosis compared to those who had not received treatment (15.5% vs. 9.1%). More patients agreed with or were uncertain about the statement 'I do not need to take osteoporosis medication because I am taking Calcium' when they had never been treated with osteoporosis medication (27.3% strongly agreed or agreed; 50.9% uncertain) compared to those who had received treatment (9.4% strongly agreed or agreed; 29.4% uncertain). Fewer patients agreed with the statement 'Osteoporosis medication works to help prevent fractures' when they were never treated with osteoporosis medication (41.8% strongly agreed or agreed) compared to when treated with medication (61.2% strongly agreed or agreed). Treatment-experienced patients (either currently or previously) were more likely to have received information about osteoporosis from their doctor and/or brochures at hospitals/clinics (70.6% from doctors, 57.5% from brochures) compared to those not on treatment (28.1% from doctors, 31.5% from brochures). Patients who had not initiated treatment were more likely to be uncertain about the need for osteoporosis medication (52.7%, 61.8%, and 47.3% were uncertain about the statements 'There is no need for me to take medication for osteoporosis', 'I do not need osteoporosis medications when my osteoporosis back or lower back pain is improved', and 'I do not need osteoporosis medications if my diagnostic results such as BMD improved', respectively, compared to 24.5%, 28.6%, and 39.0%, respectively, for those who had initiated treatment).

3.5. Comparison in responses between 'adherent' and 'not adherent' patients

Overall, patients who were adherent tended to have less back pain, were able to take medications on their own, were less worried about drug effectiveness and financial aspects, saw the need to take medications, but found it more bothersome to be persistent with treatment.

Specifically, there were several questions that patients responded differently depending on their adherence level. The number of patients with back pain was observed to be lower when patients were adherent, compared to not adherent (30.9% vs. 39.0%). Fewer patients had severe back pain when adherent, compared to not adherent (6.4% vs. 18.4%). Patients who were adherent to their osteoporosis treatment rated their ability to manage medications higher, with 100% of them answering 'very true' or 'somewhat true'

Table 2
Selected patient characteristics by initiation and adherence status.

Characteristic	Osteoporosis medication initiation status		Adherence level	
	Initiated (n = 490)	Not initiated (n = 55)	Adherent (n = 94)	Not adherent (n = 282)
Age, yr	64.9 ± 8.1	60.8 ± 6.5	65.5 ± 7.7	65.1 ± 8.2
Number of people in household	2.3 ± 1.1	2.7 ± 1.0	2.2 ± 1.0	2.3 ± 1.1
Height loss since 40 yr				
No change	157 (32.0)	22 (40.0)	33 (35.1)	85 (30.1)
Reduction by 2 cm+	129 (26.3)	6 (10.9)	17 (18.0)	83 (29.4)
Current health				
Excellent	4 (0.8)	0 (0.0)	0 (0.0)	2 (0.7)
Very good	45 (9.2)	3 (5.5)	8 (8.5)	19 (6.7)
Good	278 (56.7)	33 (60.0)	58 (61.7)	152 (53.9)
Not very good	125 (25.5)	17 (30.9)	21 (22.3)	81 (28.7)
Poor	38 (7.8)	2 (3.6)	7 (7.4)	28 (9.9)
Age of diagnosis	60.6 ± 9.5	57.6 ± 8.5	61.5 ± 9.1	61.3 ± 9.5
Severity of osteoporosis				
Mild	352 (71.8)	45 (81.8)	71 (75.5)	184 (65.2)
Moderate	107 (21.8)	8 (14.5)	16 (17.0)	77 (27.3)
Severe	31 (6.3)	2 (3.6)	7 (7.4)	21 (7.4)
Fracture history	47 (9.6)	2 (3.6)	11 (11.7)	27 (9.6)
Low BMD informed by doctor	430 (87.8)	44 (80.0)	81 (86.2)	252 (89.4)
Back pain due to osteoporosis				
No pain	300 (61.2)	25 (45.5)	65 (69.1)	172 (61.0)
Some pain	190 (38.8)	30 (54.5)	29 (30.9)	110 (39.0)
Mean pain score[a] for patients with pain	3.8	2.7	3.0	4.0
Severe pain (≥5)	76 (15.5)	5 (9.1)	6 (6.4)	52 (18.4)
Frequency of doctor's visit for osteoporosis				
Once a week or more	16 (3.3)	1 (1.8)	2 (2.1)	11 (3.9)
Once every 2–3 wk	22 (4.5)	1 (1.8)	5 (5.3)	15 (5.3)
Once 1 mo	193 (39.4)	5 (9.1)	45 (47.9)	129 (45.7)
Once every 2–3 mo	159 (32.4)	3 (5.5)	37 (39.4)	108 (38.3)
Once every 4–5 mo	14 (2.9)	1 (1.8)	2 (2.1)	6 (2.1)
Once every 6 mo	14 (2.9)	5 (9.1)	2 (2.1)	4 (1.4)
Once every 6 mo or less	72 (14.7)	39 (70.9)	1 (1.1)	9 (3.2)

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
[a] Back pain was measured by a scale of 0–10 where 0 indications no pain and 10 indicates worst pain imaginable.

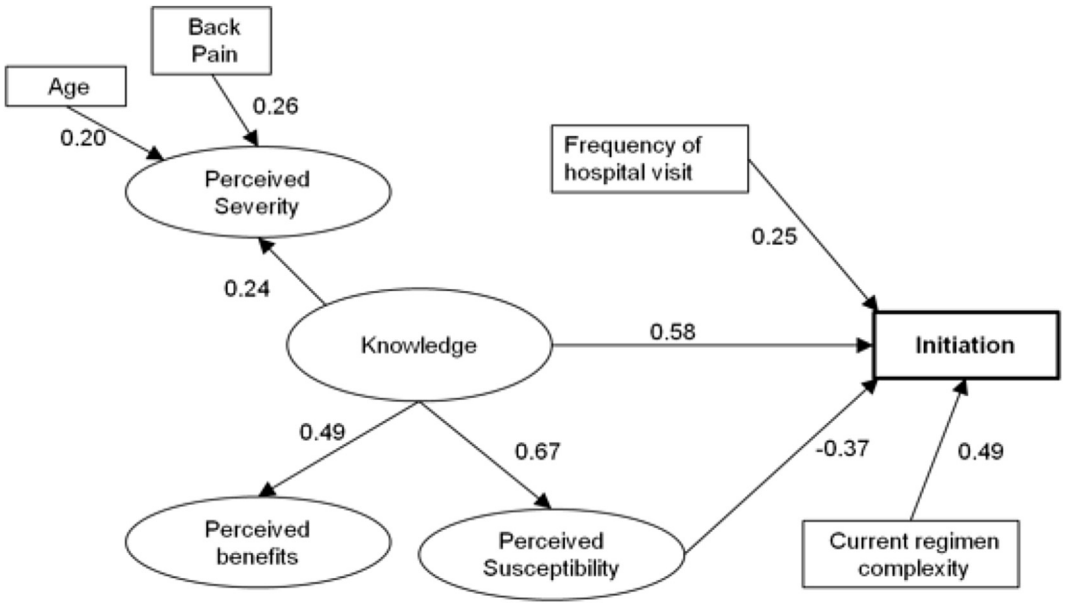

Fig. 2. Initiation structural equation modeling. Paths with standardized parameter estimates (absolute standard error) of 0.2 or higher shown in the figure. Solid lines indicate significance. Observed (measured) variables are represented by a rectangle or square box, and latent (or unmeasured) variables by a circle or ellipse.

to the statement 'I am able to self-manage my osteoporosis medications' compared to 89.7% of those who were not adherent. Patients who were adherent perceived greater benefits and fewer barriers to treatment, with 10.6%, 22.3%, 25.5%, and 29.8% of them responding 'very true' or 'somewhat true' to the statements, 'I feel hassled about sticking to my osteoporosis medication', 'I do not feel that my osteoporosis drug is effective', 'The amount of money I have to pay each month for osteoporosis medications is a significant

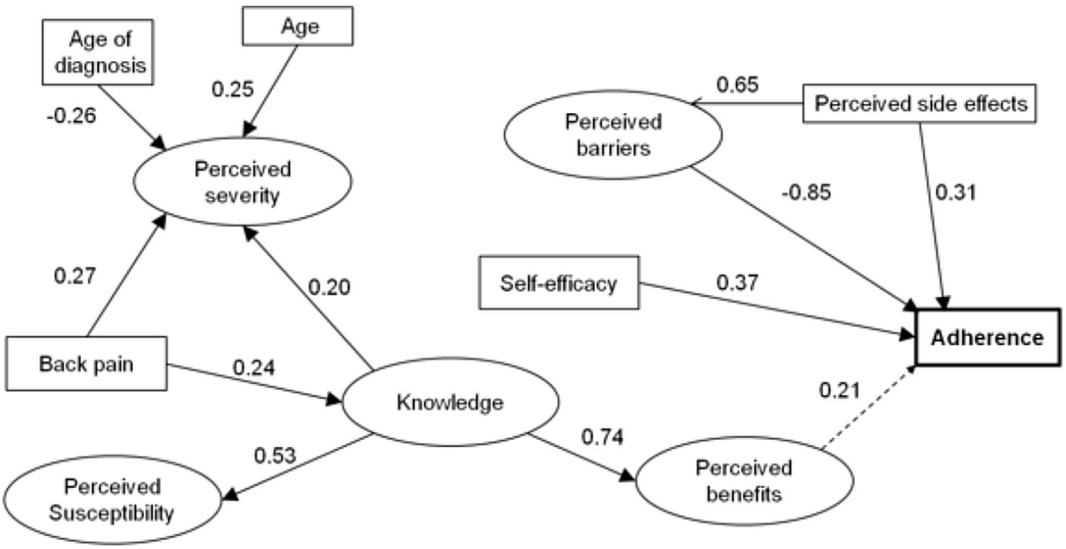

Fig. 3. Adherence structural equation modeling. Paths with standardized parameter estimates (absolute standard error) of 0.2 or higher shown in the figure. Solid lines indicate significance, and a dotted line indicates nonsignificance. Observed (measured) variables are represented by a rectangle or square box, and latent (or unmeasured) variables by a circle or ellipse.

financial burden to me', and 'I am worried about the safety and side-effects of my osteoporosis drug', respectively, compared to 39.4%, 37.6%, 44.7%, and 45.0% of those who are not adherent.

4. Discussion

The aim of this study was to identify the factors associated with initiation and adherence of osteoporosis medication among female Japanese osteoporosis patients, using a novel methodology. While some patients admitted that they sometimes forget to take their osteoporosis medications, nearly half of the patients were able to stay adherent to their treatment and did not feel that their treatments were burdensome. Patients' understanding of their disease and the impact of medications varied according to whether or not they had initiated treatment for osteoporosis, but some patients answered that they believed osteoporosis is a part of natural aging and that there is nothing they can do about it. Most patients participating in this internet survey were found to have initiated pharmacological treatment for osteoporosis at least once in the past, but more than a quarter of these initiated patients subsequently stopped their medications and were currently not treated. The treatment initiation rate in this survey was consistent with a recent study based on a national health survey which reported that approximately 1 out of 3 women with osteoporosis remain untreated [43]. The low adherence rate observed in the present study supports the low adherence rates of osteoporosis treatment reported in other studies in the literature [16,19].

This study provided real-world evidence on factors associated with treatment initiation and patient adherence behaviors based on the patient perceptions from the survey. Different sets of variables were found to be associated with treatment initiation and adherence, as seen in how different the 2 models are structured. The initiation of osteoporosis medication was most strongly associated with knowledge of their disease, whereas adherence to medication was strongly associated with perceived barriers, which in turn were at least partially a function of perceived side-effects. The finding from our study using SEMs that knowledge of disease is associated with initiation is consistent with a recently conducted review of osteoporosis studies in which concerns about medication side-effects was reported as one of the barriers to adherence across multiple studies [11]. Patients who obtained information from their physicians or healthcare institutions in the present study were also found to be more likely to initiate treatment, a finding that is consistent with recent evidence that higher education and the quality of the patient-provider relationship may influence patient prescription-filling behavior [11,44].

There are several limitations in this study. First, the results of this study are based on an online patient survey, and all disease and clinical characteristics, including a diagnosis of osteoporosis, were self-reported. We were not able to assure osteoporosis diagnosis with any clinical assessments such as X-ray and dual-energy X-ray absorptiometry; however, 87% reported being told they had low BMD by their physician indicating there was likely a low rate of misclassification bias if any. Most patients reported relatively mild osteoporosis, and the observed rate of fracture was lower than recently estimated hip fracture rates from across Japan [5]. We were not able to confirm an underlying cause of reported back pain or differentiate whether pain was due to osteoporosis and/or chronic lower back pain. A careful interpretation of the results is therefore recommended when generalizing these findings to those patients who have more severe osteoporosis, have more severe back pain, or have experienced a disease-related fracture. Second, the non-adherence rate was found to be higher than the rates reported in previous studies. This may be due to the relatively strict definition of adherence used in this study, as other studies have tended to employ different definitions such as the medication possession ratio. Using a less strict definition of adherence, the present study found that half of the patients were adherent (data not shown), which is consistent with previous data reported in the literature [16]. Third, while the results of this study suggest that patients who were already taking medications for medical conditions other than osteoporosis were more likely to initiate osteoporosis treatment, the questions posed in the survey did not differentiate between current medication regimens that were related to osteoporosis and those that were not. Finally, the knowledge construct measured in our survey included both knowledge itself (e.g., I think osteoporosis is a severe disease) and health information seeking behaviors (e.g., I actively seek out information about osteoporosis). In order to account for these different components, an exploratory analysis separating these 2 different types of knowledge was conducted, but

the decision was made to keep them together in the primary analysis as separating them greatly reduced the model fit (data not shown).

The results of the present study imply a number of ways in which treatment rate and adherence might be improved among Japanese osteoporosis patients, in particular, implementing an osteoporosis-specific patient care model involving healthcare professionals, patients, and caregivers to proactively and systematically identify and facilitate effective osteoporosis treatment for high-risk patients. In general, it is important to note that different factors were associated with patients who have initiated treatment and patients who were adherent to their treatment. Since knowledge was found to have the strongest factor, educational activities aimed at increasing patient knowledge about their disease may help improving initiation and adherence rates. Given that patients who initiated treatment tended to gather information about osteoporosis from their physicians or hospital brochures, the dissemination of information about osteoporosis and available treatments for patients at and through healthcare institutions is encouraged.

The current survey also revealed that some patients misunderstood osteoporosis as a consequence of natural aging and may have underestimated the importance of continuous medication treatment regardless of symptoms. As patients who initiated treatment also visited physician's office more frequently, effective physician-patient interaction at higher frequencies can allow patients to have greater exposure to information about their condition and treatment. Activities ensuring physicians to communicate critical information at treatment initiation may avoid potential misunderstanding about the disease and medication necessity and thus may lead to appropriate use of medication and adherence. Moreover, patients who initiated treatment also tended to recognize the risk of fractures and the benefits of preventing fractures through taking osteoporosis medication. Specifically, physician interaction and hospital brochures providing information regarding patient susceptibility to osteoporosis, the presentation of osteoporosis as a disease rather than a natural consequence of aging, and explanations of how osteoporosis medications can help prevent fractures may be helpful. Therefore, a patient-centered, coordinator-based osteoporosis-specific care system that provides systematic assessment of fracture patients, similar to the Fracture Liaison Services established across the United Kingdom may be helpful in ensuring that osteoporosis patients receive appropriate assessment, education, and treatment in Japan [45].

To improve adherence, further understanding of patients' concern or past experiences with medication side-effects is suggested for future studies. Measurements of treatment effectiveness, such as bone markers and BMD indicators, and indicators of back pain or QoL improvement can also be used in patient interactions as educational tools. Similarly, transparent, proactive communication from clinicians to patients about potential side effects may help patients feel less worried about their medications, and this in turn may be one of the ways to improve adherence among patients on osteoporosis medications.

5. Conclusions

Patient knowledge of their disease and the perception of barriers were found to be the most influential to treatment initiation and adherence respectively among Japanese osteoporosis patients. Empowering patients with the knowledge to better understand their disease and decrease the perception of barriers through healthcare education initiatives may be an effective way to improve patient outcomes.

Conflicts of interest

Doctors Sato and Kimura are employees of Eli Lilly Japan K.K. Mr. Crawford, Dr. Yoshida, Ms. Wada and Ms. Chen are employees of QuintilesIMS Japan K.K., a healthcare consulting firm contracted by Eli Lilly Japan K.K. for this research.

Acknowledgments

This study was funded by Eli Lilly Japan K.K.

Supplementary Table 1

Survey response (44 items)

1. At what age were you diagnosed with osteoporosis?

Age of diagnosis (yr)	No. (%)
<20	3 (0.6)
20–29	1 (0.2)
30–39	4 (0.7)
40–49	35 (6.4)
50–59	200 (36.7)
60–69	211 (38.7)
70–79	84 (15.4)
≥80	7 (1.3)
Total	545 (100)

2. Currently, in order to treat osteoporosis, are you using or taking any prescribed medication prescribed by healthcare institutions?

Treatment history	No. (%)
Currently using or taking prescribed medication	376 (69.0)
Used or took prescribed medication in the past, but stopped	114 (20.9)
Have not used or taken prescribed medication at all	55 (10.1)
Total	545 (100)

3. Do you currently have persistent pain in back which you think may be because of osteoporosis? Please rate your average daily pain in the figure below. If you have no back pain currently, please choose '0, no pain at all'.

Average daily pain	No. (%)
0 no pain	325 (59.6)
1	54 (9.9)
2	41 (7.5)
3	24 (4.4)
4	20 (3.7)
5	28 (5.1)
6	21 (3.9)
7	19 (3.5)
8	9 (1.7)
9	1 (0.2)
10 worst pain imaginable	3 (0.6)
Total	545 (100)

(Only treated patients) We understand that sometimes people

forget to take their medicines. Thinking about the past 6 months, please choose the option that best describes how you take your osteoporosis medication(s)?

4. MMAS item 1.
5. MMAS item 2.
6. MMAS item 3.
7. MMAS item 4.
8. MMAS item 5.
9. MMAS item 6.
10. MMAS item 7.
11. MMAS item 8.

Note: Morisky Medication Adherence Scale (MMAS) questions cannot be shared in a publication; however, they are available upon request to the developer.

MMAS Item 1–7	Patients currently on medication, n (%)		
	Total	Yes	No
1	376 (100)	119 (31.6)	257 (68.4)
2	376 (100)	69 (18.4)	307 (81.6)
3	376 (100)	18 (4.8)	358 (95.2)
4	376 (100)	40 (10.6)	336 (89.4)
5	376 (100)	268 (71.3)	108 (28.7)
6	376 (100)	15 (4.0)	361 (96.0)
7	376 (100)	128 (34.0)	248 (66.0)

MMAS Item 8	Patients currently on medication, n (%)
Response 1	191 (50.8)
Response 2	140 (37.2)
Response 3	38 (10.1)
Response 4	1 (0.3)
Response 5	6 (1.6)
Total	376 (100)

12. How serious do you perceive your osteoporosis to be?

Perceived severity: osteoporosis	No. (%)
Mild	397 (72.8)
Moderate	115 (21.1)
Severe	33 (6.1)
Total	545 (100)

13. How do you expect your osteoporosis to be in the future?

Perceived severity: osteoporosis in the future	No. (%)
Better	149 (27.3)
Worse	125 (22.9)
Stay the same	271 (49.7)
Total	545 (100)

Please choose the option that best describes your opinion.

14. I think osteoporosis is a severe disease
15. If I take calcium with food and supplements, I don't need to take osteoporosis medication.

Knowledge	Total	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
14	545 (100)	163 (29.9)	281 (51.6)	71 (13.0)	27 (5.0)	3 (0.6)
15	545 (100)	6 (1.1)	55 (10.1)	172 (31.6)	212 (38.9)	100 (18.3)

Values are presented as number (%).

16. I seek out information about osteoporosis.
17. My doctor gives me enough information about osteoporosis.
18. I obtain knowledge on osteoporosis from brochures provided by hospitals.
19. I understand that once I have osteoporosis, bones are more susceptible to fractures.

Knowledge	Total	Very true	Somewhat true	Slightly true	Not true at all
16	545 (100)	42 (7.7)	176 (32.3)	222 (40.7)	105 (19.3)
17	545 (100)	97 (17.8)	267 (49.0)	129 (23.7)	52 (9.5)
18	545 (100)	76 (13.9)	225 (41.3)	162 (29.7)	82 (15.0)
19	545 (100)	298 (54.7)	201 (36.9)	40 (7.3)	6 (1.1)

Values are presented as number (%).

Please choose the option that best describes your opinion.

20. I have a fear of having a fracture.
21. I am worried that lower back would get curved or my posture would get worse.
22. I am concerned that I may lose my independence and require family or caregiver support if my osteoporosis worsens.
23. Anybody could develop osteoporosis.
24. Osteoporosis is a natural and inevitable part of aging.

Perceived susceptibility	Total	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
20	545 (100)	160 (29.4)	247 (45.3)	55 (10.1)	70 (12.8)	13 (2.4)
21	545 (100)	153 (28.1)	265 (48.6)	63 (11.6)	51 (9.4)	13 (2.4)
22	545 (100)	146 (26.8)	221 (40.6)	104 (19.1)	52 (9.5)	22 (4.0)
23	545 (100)	79 (14.5)	253 (46.4)	131 (24.0)	73 (13.4)	9 (1.7)
24	545 (100)	16 (2.9)	178 (32.7)	162 (29.7)	159 (29.2)	30 (5.5)

Values are presented as number (%).

(Only treated patients) Please choose the option that best describes your opinion.

25. 1) I am able to self manage my osteoporosis medications.

Self-efficacy	Patients currently on medication, n (%)				
	Total	Very true	Somewhat true	Slightly true	Not true at all
25	376 (100)	205 (54.5)	142 (37.8)	25 (6.6)	4 (1.1)

Please choose the option that best describes your opinion.

26. Osteoporosis medication works to help prevent fractures.
27. I don't think I need to take osteoporosis medication.
28. I do not need to take osteoporosis medications when my osteoporosis-induced back or lower back pain is improved.

29. I think I don't need to take osteoporosis medications in case of my osteoporosis is shown to be improved based on test results such as bone mineral density (BMD).

Perceived benefits	Total	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
26	545 (100)	53 (9.7)	270 (49.5)	162 (29.7)	54 (9.9)	6 (1.1)
27	545 (100)	10 (1.8)	35 (6.4)	149 (27.3)	224 (41.1)	127 (23.3)
28	545 (100)	4 (0.7)	27 (5.0)	174 (31.9)	233 (42.8)	107 (19.6)
29	545 (100)	19 (3.5)	119 (21.8)	217 (39.8)	139 (25.5)	51 (9.4)

Values are presented as number (%).

(Only treated patients) Please choose the option that best describes your opinion about osteoporosis medication.

30. I feel hassled about sticking to my osteoporosis medication.
31. I do not feel my medication is working for treating my osteoporosis
32. My osteoporosis medication costs too much
33. I am worried about the safety and side-effects of my osteoporosis drug.

Perceived barriers	Patients currently or previously on medication, n (%)				
	Total	Very true	Somewhat true	Slightly true	Not true at all
30	490 (100)	59 (12.0)	125 (25.5)	169 (34.5)	137 (28.0)
31	490 (100)	57 (11.6)	126 (25.7)	225 (45.9)	82 (16.7)
32	490 (100)	84 (17.1)	129 (26.3)	172 (35.1)	105 (21.4)
33	490 (100)	90 (18.4)	139 (28.4)	183 (37.3)	78 (15.9)

34. Have any of your family members or relatives (such as your parents, grandparents, sisters/brothers and aunts/uncles) had hip fractures such as femoral neck fractures?

Family history	No. (%)
Yes	115 (21.1)
No	430 (78.9)
Total	545 (100)

35. Have you ever taken a BMD test?

BMD test	No. (%)
Yes	528 (96.9)
No	17 (3.1)
Total	545 (100)

Have you ever been told the following upon being diagnosed with osteoporosis? Please select several options that applies to you

36. BMD level is low.
37. You had a fracture.

Low BMD and fracture history	No. (%)
BMD level is low	474 (87)
You have a fracture	49 (9)
Neither one of the above	59 (10.8)
Total	545 (100)

38. How often do you visit the clinic/hospital for your osteoporosis?

Hospital visit	No. (%)
Once a week or more	17 (3.1)
Once every 2–3 weeks	23 (4.2)
Once a month	198 (36.3)
Once every 2–3 months	162 (29.7)
Once every 4–5 months	15 (2.8)
Once every 6 months	19 (3.5)
Less than once every 6 months	11 (20.4)
Total	545 (100)

39. Do you think your height has changed compared to when you were in your 40s?

Height loss	No. (%)
No	179 (32.8)
Yes; <2 cm shorter	200 (36.7)
Yes; >2 cm shorter	135 (24.8)
Yes; taller	6 (1.1)
Not sure	25 (4.6)
Total	545 (100)

40. Please indicate the number of all medications you are currently taking (osteoporosis + other medications). Please also indicate the frequency at which you take those medications on a daily basis.

Medication information	Total	0 type	1 type	2 types	3 types	>4 types
Once a day	545 (100)	216 (39.6)	176 (32.3)	90 (16.5)	31 (5.7)	32 (5.9)
2-3 times a day	545 (100)	431 (79.1)	41 (7.5)	36 (6.6)	16 (2.9)	21 (3.9)
>4 times a day	545 (100)	533 (97.8)	7 (1.3)	1 (0.2)	0 (0)	4 (0.7)
Once a week	545 (100)	433 (79.4)	103 (18.9)	5 (0.9)	4 (0.7)	0 (0)
Other (e.g., once biweekly, once monthly, once every half year etc.)	545 (100)	432 (79.3)	104 (19.1)	5 (0.9)	1 (0.2)	3 (0.6)

Values are presented as number (%).

41. Please indicate your smoking history.

Smoking	No. (%)
Nonsmoker	402 (73.8)
Current smoker	39 (7.2)
Ex-smoker	104 (19.1)
Total	545 (100)

42. Do you drink 3 or more units of alcohol a day? (a standard glass of beer [250 mL], 0.5 (gou) Nihonshu [80 mL], slightly less than one glass of wine [100 mL]).

Alcohol	No. (%)
Yes	51 (9.4)
No	494 (90.6)
Total	545 (100)

43. In general, how would you rate your current health?

Current health	No. (%)
Excellent	4 (0.7)
Very good	48 (8.8)
Good	311 (57.1)
Fair	142 (26.1)
Poor	40 (7.3)
Total	545 (100)

44. Compared to one year ago, how would you rate your health in general now?

Health change	No. (%)
Much better now than one year ago	4 (0.7)
Somewhat better now than one year ago	46 (8.4)
About the same	345 (63.3)
Not as good as on year ago	124 (22.8)
Much worse than one year ago	26 (4.8)
Total	545 (100)

References

[1] Zhou H, Mori S, Ishizaki T, Takahashi A, Matsuda K, Koretsune Y, et al. Genetic risk score based on the prevalence of vertebral fracture in Japanese women with osteoporosis. Bone Rep 2016;5:168–72.
[2] Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000;17:1–45.
[3] Orimo H, Nakamura T, Hosoi T, Iki M, Uenishi K, Endo N, et al. Japanese 2011 guidelines for prevention and treatment of osteoporosis: executive summary. Arch Osteoporos 2012;7:3–20.
[4] Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int 2005;16:447–55.
[5] Orimo H, Yaegashi Y, Hosoi T, Fukushima Y, Onoda T, Hashimoto T, et al. Hip fracture incidence in Japan: estimates of new patients in 2012 and 25-year trends. Osteoporos Int 2016;27:1777–84.
[6] Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Min Res 2007;22:465–75.
[7] Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.
[8] Ohta H, Mouri M, Kuroda T, Nakamura T, Shiraki M, Orimo H. Decreased rate of hip fracture and consequent reduction in estimated medical costs in Japan. J Bone Min Metab 2017;35:351–3.
[9] Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010-2050. Osteoporos Int 2015;26:1929–37.
[10] Yoshimura N, Kinoshita H, Oka H, Muraki S, Mabuchi A, Kawaguchi H, et al. Cumulative incidence and changes in the prevalence of vertebral fractures in a rural Japanese community: a 10-year follow-up of the Miyama cohort. Arch Osteoporos 2006;1:43–9.
[11] Chodick G, Moser SS, Goldshtein I. Non-adherence with bisphosphonates among patients with osteoporosis: impact on fracture risk and healthcare cost. Expert Rev Pharmacoecon Outcomes Res 2016;16:359–70.
[12] Burge R, Sato M, Sugihara T. Real-world clinical and economic outcomes for daily teriparatide patients in Japan. J Bone Min Metab 2016;34:692–702.
[13] Siris ES, Selby PL, Saag KG, Borgström F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med 2009;122(2 Suppl):S3–13.
[14] Yu S, Burge RT, Foster SA, Gelwicks S, Meadows ES. The impact of teriparatide adherence and persistence on fracture outcomes. Osteoporos Int 2012;23:1103–13.
[15] Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. Expert Rev Pharmacoecon Outcomes Res 2012;12:159–66.
[16] Tanaka I, Sato M, Sugihara T, Faries DE, Nojiri S, Graham-Clarke P, et al. Adherence and persistence with once-daily teriparatide in Japan: a retrospective, prescription database, cohort study. J Osteoporos 2013;2013.654218.
[17] Siris ES, Fan CS, Yang X, Sajjan S, Sen SS, Modi A. Association between gastrointestinal events and compliance with osteoporosis therapy. Bone Rep 2015;4:5–10.
[18] Iki M. Epidemiology of osteoporosis in Japan. Clin Calcium 2012;22:797–803.
[19] Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. Arch Osteoporos 2015;10:231.
[20] Yamamoto T, Taketsuna M, Guo X, Sato M, Sowa H. The safety and effectiveness profile of daily teriparatide in a prospective observational study in Japanese patients with osteoporosis at high risk for fracture: interim report. J Bone Min Metab 2014;32:699–708.
[21] Gorai I, Tanaka Y, Hattori S, Iwaoki Y. Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/or alfacalcidol in postmenopausal Japanese women. J Bone Min Metab 2010;28:176–84.
[22] Karimi L, Meyer D. Structural equation modeling in psychology: the history, development and current challenges. Int J Psychol Stud 2014;6:123–33.
[23] Hirai K, Arai H, Tokoro A, Naka N. Self-efficacy, psychological adjustment and decisional-balance regarding decision making for outpatient chemotherapy in Japanese advanced lung cancer. Psychol Health 2009;24:149–60.
[24] McHorney CA, Zhang NJ, Stump T, Zhao X. Structural equation modeling of the proximal-distal continuum of adherence drivers. Patient Prefer Adherence 2012;6:789–804.
[25] Södergård B, Höfer S, Halvarsson M, Sönnerborg A, Tully MP, Lindblad AK. A structural equation modeling approach to the concepts of adherence and readiness in antiretroviral treatment. Patient Educ Couns 2007;67:108–16.
[26] Warriner AH, Curtis JR. Adherence to osteoporosis treatments: room for improvement. Curr Opin Rheumatol 2009;21:356–62.
[27] Yood RA, Mazor KM, Andrade SE, Emani S, Chan W, Kahler KH. Patient decision to initiate therapy for osteoporosis: the influence of knowledge and beliefs. J Gen Intern Med 2008;23:1815–21.
[28] Hochbaum GM. Public participation in medical screening programs: a socio-psychological study. Washington, DC: Public Health Service publication; 1958.
[29] Janz NK, Becker MH. The health belief model: a decade later. Health Educ Q 1984;11:1–47.
[30] Leventhal H, Nerenz D, Steele D. Llness representations and coping with health threats. In: Baum A, Taylor SE, Singer JE, editors. Handbook of psychology and health. Hillsdale (NJ): Lawrence Erlbaum; 1984. p. 219–52.
[31] Horan ML, Kim KK, Gendler P, Froman RD, Patel MD. Development and evaluation of the osteoporosis self-efficacy scale. Res Nurs Health 1998;21:395–403.
[32] Kim KK, Horan ML, Gendler P, Patel MK. Development and evaluation of the osteoporosis health belief scale. Res Nurs Health 1991;14:155–63.
[33] Reynolds K, Viswanathan HN, O'Malley CD, Muntner P, Harrison TN, Cheetham TC, et al. Psychometric properties of the Osteoporosis-specific Morisky Medication Adherence Scale in postmenopausal women with osteoporosis newly treated with bisphosphonates. Ann Pharmacother 2012;46:659–70.
[34] Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008;10:348–54.
[35] Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. J Clin Epidemiol 2011;64:255–7.
[36] Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15:59–66.
[37] Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67–74.
[38] Kline RB. Principles and practice of structural equation modeling. third ed. New York: The Guilford Press; 2010.
[39] Toyoda H. Structural equation modeling in R. Tokyo: Tokyo-Tosho; 2014.
[40] Lt Hu, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equa Model Multidiscip J 1999;6:1–55.
[41] Rosseel Y. lavaan: an R package for structural equation modeling. J Stat Softw 2012;48:1–36.
[42] R Development Core Team. R: a language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2015.
[43] Sato M, Vietri J, Flynn JA, Fujiwara S. Treatment for osteoporosis among women in Japan: associations with patient characteristics and patient-reported outcomes in the 2008-2011 Japan National Health and Wellness Surveys. J Osteoporos 2014;2014:909153.
[44] Mathes T, Jaschinski T, Pieper D. Adherence influencing factors: a systematic review of systematic reviews. Arch Public Health 2014;72:37.
[45] Mitchell PJ. Fracture liaison services: the UK experience. Osteoporos Int 2011;22(Suppl 3):487–94.