VF did [21]. Furthermore, it was observed that no prior VF females with height loss or kyphosis suffered significantly more severe physical disorder than women with a history of prior VF but no postural manifestations such as height loss and/or kyphosis, making it more difficult for the former group to adapt to daily life [22]. Another report concluded that height loss and VF affected QOL in the elderly, both significantly from a statistical perspective and independently from each other [23]. It has been believed thus far that the phenomenon of height loss is mainly one outcome of VF development and that clinical significance thereof is not much more than as an indicator of osteoporosis. In these years, however, the phenomenon of height loss has also started to be considered a factor that affects HRQOL independently from VF.

Recently, increased incidence of bone-mass-independent fracture is also reported. For example, a one-year follow-up study targeting about 150,000 Caucasian females aged 50-104 years in the U.S. [24] reported that the group measuring below the osteoporosis diagnostic standards Young Adult Mean (YAM) advocated by WHO with -2.5SD (standard deviation) and developing fracture accounted for only 6.4% of all subjects; the other fracture cases were observed among high-BMD subjects, indicating involvement in fracture development of non-BMD factors causing bone fragility. In consideration of increased incidence of bone fracture despite the presence of effective preventive measures [25,26], the definition of osteoporosis has changed from "the diagnosis of osteoporosis was defined by BMD T score being lower than 2.5SD of young adult mean (WHO, 1994)" [27] to "disease prone to bone fracture, accompanied by disorder of bone strength evaluated with bone mass and bone quality (NIH Consensus Development Panel on Osteoporosis, 2001)" [28]. That is, it cannot be said that risk for VF, which occurs most frequently among the aged, has been fully elucidated, leading to a situation in which we await further review of factors surrounding VF. Furthermore, assessment of bone quality as a bone fracture risk factor, in addition to BMD, is carefully being monitored [25,26].

In consideration of the background mentioned above, it is likely necessary to discuss anew the association between HRQOL and such predictors as VF and height loss. As a first step, this paper attempts to summarize previous osteoporosis studies using HRQOL as an endpoint and thereby review the current situation surrounding HRQOL predictors. Only when effects of compression fracture, including effects on HRQOL, are elucidated will it become possible to determine the value of evidence regarding bone fracture prevention and to develop appropriate therapeutic measures. It is anticipated that data collected on the basis of HRQOL questionnaires will certainly provide valuable findings regarding how to improve QOL in osteoporosis patients and how to effectively distribute medical costs.

Conducting a search with PubMed using as key words "HRQOL" and "osteoporosis" resulted in detection of papers. From among them, only those specifically addressing VF among bone fragility fracture were used as references herein. We reviewed the papers, including those mentioned in the referenced papers that were thought to have relevance.

This paper will start by summarizing assessment methods of QOL in cases of osteoporosis and study designs adopted in those reviewed papers and then will report on the results of this review.

1. QOL Assessment in Osteoporosis

HRQOL is used to assess QOL in disease. HRQOL is generally classified into two categories: generic non-disease specific health-status instruments and disease-specific instruments. The scope of application of such generic health-status instruments is not limited to patients with specific disease and can include so-called "healthy" people who are disease-free [29]. The instruments can evaluate a wide range of people on a continuum, from patients with disease to healthy individuals. Such generic health-status instruments consist of general questions relating to health status, can be applied to various diseases, and can be used to compare different diseases. Since the instruments do not specify disease or age group, however, they may include unnecessary questions. Meanwhile, disease-specific instruments consist of disease-specific questions and thereby lessen the burden on patients, because of their existing awareness of their own heath problems. Inconveniently, however, it is impossible to compare different diseases with this method. Consequently, a majority of researchers recommend using a combination of this generic health-status model and the disease-specific instruments.

1. Generic Health-Status Instruments

Among these generic heath status instruments are Medical Outcome 36-Items Short Form (SF-36), EuroQOL (EQ-5D), and Nottingham Health Profile (NHP). EQ-5D is used mainly as a measurement instrument for functional values.

a. **SF-36** is used most frequently in the international community and is considered a standard measure that is already validated for the following reasons: it is applicable to both healthy people and patients with disease, it is a convenient tool because anyone can easily understand and quickly answer its questions, and the content to be measured is limited to basic heath-related factors [30]. It comprises 36 items, and offers two to six response options according to an ordinal scale, assessing eight health concepts or domains: physical functioning, role-physical (role limitations due to physical health problems), bodily pain, general health, vitality, social function, role-emotional (role limitations due to emotional problems), and mental health. From these eight domains, two summary scores were calculated: physical and mental component summary indexes [31].

b. **SF-12** was prepared by extracting 12 of the SF-36 items, is widely used, and is appropriate for multi-purpose measurement of health status.

c. **EQ-5D** is a questionnaire aimed at understanding of multiple aspects of HRQOL in patients. One feature characterizing the method is that it can be used to eventually calculate a single summary score [32].

d. **HUI** (the health utilities index)

The instrument focuses on the physical and emotional dimensions of health status and is based on concepts of functional capacity rather than performance [33]. Health states on HUI are measured using several 'attributes' (domains) of health.

2. Disease-Specific Instruments

The disease-specific instruments were prepared by taking into account symptoms specific to a given disease. They are more clinically sensitive and may be more responsive to detecting change [34].

The following six questionnaires were initially developed as osteoporosis-specific instruments: OQLQ (Osteoporosis Quality of Life Questionnaire), OFDQ (Osteoporosis Functional Disability Questionnaire), OPTQOL (Osteoporosis-Targeted Quality-of-Life Questionnaire), OPAQ (Osteoporosis Assessment Questionnaire), Qualeffo-41 (Questionnaire for Quality of Life by European Foundation for Osteoporosis), and QUALIOST (Quality-of-Life Questionnaire in Osteoporosis). Another questionnaire ECOS-16 (Assessment of health related quality of life in osteoporosis), JOQOL (the Japanese Osteoporosis Quality of Life Questionnaire) were derived from these six questionnaires. The individual questionnaires were prepared via different pathways and consequently have different features:

a. **OQLQ:** The development process of this instrument was the following: general inquiry items were first selected and then reviewed by patients, nurses, specialists, physiologists, and rheumatologists; from among those items, 168 were chosen and consolidated into 30 [35,36]. Its target population is women with osteoporosis and painful vertebral compression fracture, and it includes the domains of physical function, activity of daily living (hereinafter referred to as "ADL"), and emotional function.
b. **mini-OQLQ**: On the basis of the 30-item OQLQ, two questions were selected in each of five domains (symptoms, physical functioning, ADL, emotional functioning, and leisure activities) to prepare the 10-item mini-OQLQ. The mini-OQLQ is a reliable and valid test for osteoporotic women with back pain caused by VF [37]. The mini-OQLQ is self-administered, easy to fill out, and considerably effective for clinical settings.
c. **OPTQoL:** This questionnaire was developed for the purpose of determining effects of osteoporosis in the general population [38]. The final version consists of 26 scored items across three domains and six non-scored items regarding change and diagnosis of osteoporosis. The first domain consists of physical activity, adaptations, fears, change of osteoporosis, and questions about health status and demographic statistical questions. This questionnaire is said to be suitable specifically when testing aimed at QOL assessment in osteoporosis is performed for the general population, including patients with other disease. A higher score indicates a higher level of HRQOL.
d. **OPAQ**: This questionnaire was prepared based on the Arthritis Impact Measurement Scales Health Status Questionnaire 2, with the aim of self-assessment of HRQOL for all osteoporosis patients [39,40]. Its target population is postmenopausal women with

osteoporosis. The OPAQ initially prepared was composed of 79 questions, which were classified into 18 different health scales. The first domain (physical function) includes mobility, walking, forward bending, flexibility, self-management, jobs around the house, changing of location, and occupation; the second domain (psychological status) includes fear of falling, tension level, mood, body image, and independence; the third domain (symptoms) includes osteoporosis-related back pain and back discomfort, comfort during sleeping, and feeling of fatigue; and the fourth domain (social interaction) includes social function participation and support from family members and friends.

e. **QUALEFFO**: This questionnaire was initially composed of 48 questions and six visual analog scales. Its seven domains are pain, physical function, jobs around the house, mobility, leisure and social function, general health perception, and mental function [41,42]. The Quality of Life Questionnaire of the International Osteoporosis Foundation established a working party composed of physicians and QOL experts from eight European countries for the benefit of VF patients. The working party revised "Qualeffo" on December 10, 1997, by reducing the number of questions to 41 and putting into use **"Qualeffo-41"** [43]. This version's target population is European patients with osteoporosis and vertebral fracture, and the questionnaire is considered suitable for mail surveys. In QUALEFFO, questions concerning back pain focus on present/recent pain, and hence it is likely difficult to understand the status of development of back pain in the past [44].

f. **QUALIOST**: This questionnaire was developed as a module to supplement the generic instrument SF-36, with a special focus on effects from VF on QOL [45]. QUALIOST has the advantage of supplementing SF-36 with a descriptive strategy. As one advantage of SF-36, osteoporotic scores can be calculated. Furthermore, QUALIOST can be used to compare those with osteoporosis and healthy people; and it can also effectively adjust age effects among an elderly, osteoporosis patient population. Its domains are physical function and emotional status, and its target population is postmenopausal women with osteoporosis.

g. **ECOS-16:** This questionnaire was developed with the aim of measuring HRQOL in postmenopausal women with osteoporosis [45]. It is based on the combination of two disease-specific HRQOL questionnaires for women with osteoporosis, OQLQ and QUALEFFO.

h. **JOQOL** (QOL Evaluation Committee, Japanese Society for Bone and Mineral Research, 2000 Edition): This questionnaire was developed on the basis of OPAQ and the Qualeffo-41 by taking into account Japanese lifestyle and was revised in 2000 [46]. The JOQOL2000 consists of 39 question items. Calculation is performed for each of the first 38 scored items, excluding the 39th item, which is not subject to scoring, on a scale of 1-4, leading to a potential maximum score of 152 points. A higher score indicates a higher level of QOL. The 38 items are classified into six domains: pain (five items, 20 points), ADL (sixteen items, 64 points), recreation and social activity (five items, 20 points), general health (three items, 12 points), posture and figure (four items, 16 points), and falls and psychological factors (five items, 20 points). In principle, patients fill out the questionnaire by themselves.

This is the end of the summary of HRQOL assessment scales. Since many osteoporosis studies target elderly females, a scale that is written in as simple a style as possible and asks a limited number of questions is recommended.

2. Study Design

1. Cohort Study

Cohort studies comprise a research methodology in which two patient sub-groups, one exposed to a given item under study and a non-exposed sub-group, are identified and followed up until the cohort indicates outcomes of interest. Cohort studies are usually used to perform prospective analysis from the present to the future, but occasionally use past records. This is said to be the best methodology for studying diseases that develop among those exposed to a given risk factor, compared with a non-exposed group, appearance of any relevant clinical condition, and specifically the relevant rate of risk [47].

Among the advantages of cohort studies are: (a) follow-up observation allows understanding of the course of events; (b) measurement bias for predictors is limited; (c) there is no survivor bias; (d) it is possible to simultaneously study multiple outcome variables; (e) the number of occurrences of outcome variables increase with time; and (f) it is possible to obtain data about incidence, risk ratio, and excess risk. Furthermore, in the case of prospective cohort studies, (a) it is possible to control the selection of subjects before embarking on a study, and (b) it is also possible to control measurement items and methods before embarking on a study. Meanwhile, in the case of retrospective cohort studies, (a) low cost and (b) a relatively short study period can be referred to as advantages. In short, compared with case-control studies, cohort studies are harder to perform because they require: (a) a significant amount of time; (b) a significant amount of cost: (c) the need of a substantial number of cases and follow up without missing cases. However, this methodology also can come closer to approaching the truth.

2. Case-Control Study

Case-control studies start with identification of a case group for a certain disease, establishment of another group matched with the case group for exposure conditions under study, including sex, age, and social background, comparison of the two groups, and then performance of the analysis. Consequently, the analysis is oriented backward, to the past, or retrospectively. Events to be analyzed are all happenings that occurred in the past. Odds ratio, or ratio of exposure rate for the disease group to that for the control group, is considered similar to exposure risk. Since it is not easy in reality to set up an ideal control group, however, this methodology is said to be inferior to cohort studies in accuracy.

In terms of accuracy, a key problem is bias. For example, sampling bias is defined as bias occurring in the course of selection of the case and control groups. Survivor bias belongs to

this category. Survivor bias occurs because people who already died due to a disease of interest are not included in the scope of the contemporary study subjects. There is another problem: patients who do not visit a medical institution, patients who visit a different medical institution, patients who have yet to be diagnosed or who are misdiagnosed, and patients who die prior to diagnosis or whose disease becomes less severe cannot be included in the subject population. Since this methodology examines past events, measurement bias – sensitivity of predictor measurements to uncertainty – is a concern. It is extremely difficult to adjust effects of various confounders, with the constant possibility of unknown confounders, and hence case-control studies are thought to have limitations.

3. Randomized Controlled Trial (Hereinafter Referred to as "RCT")

In randomized controlled trials, with the aim of minimizing bias in data in clinical trials, clinical tests and others, subjects are randomly allocated to a treated group (experimental drug group) and a control group (therapeutic drug group, placebo group, etc.) and examined for evaluation purposes. RCT randomly assign subjects to multiple groups, perform experimental intervention on one group and administer a placebo (or existing treatment) on the other groups, follow up such groups for a certain period, and observe efficacy of treatment under study and presence and/or absence of harmful effects. The "double-blind" method is employed for stricter observation. From among healthcare providers, trial participants, observers, and statisticians, at least two parties are blinded regarding the issue of "to which group individual participants belong," mainly for the purpose of eliminating bias due to assumptions (placebo effects), such as the physician's assumption that, since a control drug was administered to the subject, his/her symptom should not be improved, and the patient's assumption that, since the drug received must be genuine, his/her symptoms must be improved. However, the use by the clinical testing of this double-blind method does not guarantee overall excellence of the study; it simply indicates that anti-bias measures have been adopted as one feature of the study.

4. Evidence Levels

The following represents a ranking of evidence levels: 1a. meta-analysis in RCTs; 1b. at least one RCT; 2a. concurrent cohort studies without random allocation of participants (prospective study, concurrent cohort study, etc.); 2b. cohort study without random allocation of participants but accompanied by retrospective controls (historical cohort study, retrospective cohort study, etc.); 3. case-control study (retrospective study); 4. study unaccompanied by before/after trials (e.g. pre-/post-treatment comparison) or control group; 5. case reports and case series; and 6. independent expert opinions (including expert panel reports). Other factors such as sample size and number of events are thought likely to affect the accuracy of the studies.

In consideration of HRQOL assessment methods, study design, and characteristics of the subject population, HRQOL predictors in patients with osteoporosis were reviewed as shown below.

3. HRQOL Predictors in Patients with Osteoporosis

1. Prevalent Vertebral Fracture

a. Presence of VF

Most studies reported that the HRQOL level decreased in VF cases, except for a study [66] in which identification of a history of VF was unclear and Study [74] in which study there were only eight of the prevalent VF (Table 1 [18, 22, 23, 33, 35, 37, 38, 43, 48—75]). The studies [53] and [18] observed a drop in HRQOL level in all domains except for mental function. Physical restrictions due to osteoporosis lower physical function, and subsequently inhibit social function, decrease autonomy, cause long-term changes to physical image, and lead to deterioration of general health, all of which it is believed are not caused by mental deterioration [18]. Study [55] reported on a decrease in HRQOL levels in all domains except social interaction.

Brenneman et al. released results of HRQOL assessment based on SF-12 in the large-scale cohort study [70] that HRQOL level declined the most in the VF cases, followed by the proximal femoral fracture cases. In the 50-64 age group, the level dropped significantly among VF cases, compared with proximal femoral fracture, forearm fracture, and rib fracture.

b. Severity

Severity of VF is defined by radiographic score through semiquantitative analysis. Some studies [76,77] observed HRQOL decline only among severe VF cases. Fechtenbaum et al. in study [67] also observed severity/HRQOL association. On the other hand, study [55] denied that there was a significant association between HRQOL and VF severity, but indicated an association between HRQOL and location of VF.

c. Number of vertebral fracture

Multiple prevalent VFs indicate a lower level of QOL. One study [53] observed a progressive decrease in HRQOL level with an increasing number of prevalent VFs in all domains except mental function. Another study [55] observed such a decrease in all domains excluding social interaction. A study [67] by Fechtenbaum et al. indicated that QUALEFFO scores increased with an increase in number and severity of VF; that is, HRQOL level declined. The study by Ettinger et al. [78] reported that increase in number of severe VF led to increase in pain and disability.

In contrast, the study [54] in 2001 by Adachi et al. reported that multiple VFs had no additive negative effects on HRQOL using SF-36. In the said study, however, the subjects with VFs did not have main osteoporotic fracture, had radiographic VFs only. Although we did not know the detail such as the number of radiographic VFs, the extent of VFs might be too modest.

It is acknowledged that both Qualeffo-41 and OPAQ show a considerable decrease in HRQOL level with an increase in number of VF [15].

d. Location of fracture

A large number of recent studies have placed emphasis on the impact of location of VF on HRQOL level. In this regard, there are reports stating that location of VF had a far larger impact on HRQOL than number of VF, and severity of spinal deformity [53,55]. According to study [53], scores in the pain, physical function, and general health domains, and total score were significantly higher in lumbar VF than in thoracic VF in QUALEFFO. A prospective study [59] in 2003 by Fink et al. reported that clinical lumbar VF was associated with post-fracture disability as severe as that from hip fracture, and that the disability level was more severe than the level from clinical thoracic VF. Study [55] in 2001 by Silverman observed a significant difference in physical function between lumbar VF and thoracic VF. Study [74] in 2008 by Hagino et al. described that there was a significant difference between patients with thoracic and lumbar fractures at 6 months after the fracture with a significant difference (Table 2).

Those location-specific differences could be attributable to a higher level of stiffness of thoracic vertebrae relative to that of lumbar vertebrae in that mobility is more severely restricted in lumbar VF than in thoracic VF [79]. The fact that the rib cage immobilizes the thoracic vertebrae, and thus lumbar VF presents clinical symptoms at a higher frequency than thoracic VF, provides further supporting evidence [74].

The study [67] in 2005 by Fechtenbaum et al. reported that QOL level declined considerably among patients with both thoracic and lumbar VF, but that such findings were attributable to number of prevalent VF, and that no difference was observed between patients with thoracic VF only and those with lumbar VF only. It also reported that HRQOL level declined by number and severity of VF. That study selected its subject population on the basis of clinically evident, fracture-related symptoms and compared it to a group without back pain, indicating that no significant disparity was observed in presence/absence, number, and severity of VF.

e. Time since last fracture

The study [52] in 1999 by Begerow et al. reported that HRQOL level in patients surveyed 0-24 months after VF diagnosis was lower than in those surveyed after 24 months or more. They also suggested that, in consideration of post-VF QOL and feelings of well being, time since last fracture likely serves as a far more important predictor of QOL than height loss and number of VF. Passage of time is one of the factors that should be taken into account when patient perception and approach to patient dealings change with time. Taking into account that pain abates in two-four years on average after fracture occurrence, Begerow et al. performed a controlled study between a group with time since last fracture of less than two years and another group with time since last fracture of two years or more.

A study [63] in 2004 by Hallberg et al. states that values in role-physical and social function domains had recovered two years after fracture but that the all-domain value was still

significantly lower than a standard level. Be reminded, however, that relevant VF information was self-reported and was not confirmed by vertebral X-ray. Another report stated that the score in the pain domain among patients with VF dropped to a stable level about three years after fracture [80], and yet another study reported that back pain was associated with VF that developed up to four years previous [48]. In reality, however, decline in function due to clinical VF may persist even after pain levels decrease.

VF cases shortly after diagnosis represent a larger decline in QOL level than that for VF involving the passage of a significant amount of time since diagnosis, at least for the short term (Table 3). Furthermore, a longer time since onset of VF brings about greater improvement in QOL, but restoring QOL to the original level is impossible [15,70,74]. In the case of clinical bone fragility fracture, hip fracture and VF greatly affect the HRQOL level in patients, which does not recover to pre-fracture level even one year after fracture. Hagino et al. described in study [74] that the mean value of EQ-5D utility for patients with VFs at 2 weeks, 3 months, 6 months, and 1 year after the fracture were 0.531, 0.758, 0.746, and 0.838 respectively. The value before VF was 0.882. The EQ-5D utility at 2 weeks after VF was remarkably decreased, slowly recovering over many months, but the utility did not reach the level of that before the VF. That is the reason why prevention of VF is considered to be of ultimate importance in maintenance of HRQOL [15].

In the population-based study, Papaioannou et at. [33] tracked incident fracture over 5 years and compared how the time after clinical VF impacted on HUI scores at year 5. In women, in most cases, it was the recent clinical VFs that exerted the greatest negative influence on HUI scores. However even after 5 years since clinical VFs, negative impacts were still observed.

The study [69] in 2006 by Papaioannou et al. and study [54] in 2001 by Adachi et al. reported that there were not an association between HRQOL and the time after VFs. In study [54], the average number of years (±standard deviation) since the last fractures was 8.0±7.2 and 6.9±6.0 for women and men respectively. In study [69], that was 4.3±9.0. In this study, not all VFs were confirmed by X-ray. The mean times since the last VF were over 4 years in both studies. It was too late. Their information about VFs was obtained through self-report from cross-sectional study.

2. Incident Vertebral Fracture

The Study [55] in 2001 by Silverman et al. reports that, from among 1395 patients, incident VF occurred in 157 individuals, diminishing HRQOL level in the domains of physical function, emotional status, and social interaction (Table 4).

The 2005 European-version MORE Study [65] by Oleksik et al. followed up a group of females with prevalent VF at baseline for three years and observed effects of incident VF. From among 357 subjects, incident VF developed in 67 people. Compared with the non-incident VF group, total score and the physical function domain score of Qualleffo-41 were significantly higher in the incident VF group. The 67 incident VF cases consisted of 20 clinical VF and 47 radiographic VF. In the clinical VF cases, a significant decrease in HRQOL level

was observed in all domains except for mental function; and in the radiographic VF cases, HRQOL level was significantly decreased in total score and in the physical function domain.

The study [57] in 2002 by Adachi et al., which employed mini-OQLO, reported that incident VF among females diminished scores of physical function, emotional function, ADL, and leisure. The study [58] in 2003 by Oglesby et al., which used VF as an endpoint, found significant decrease in physical function, emotional function, and symptoms. The EPOS Study [62] in 2004 by Cockerill et al. found significant difference between the subjects with both incident and pre-existing VFs and control group in total score of Qualeffo-41 as well as SF-12 and EQ-5D. However, the said difference was not observed between the incident VF group without pre-existing VF and the control group. The results suggested it was really the second VF that results in a marked reduction in HRQOL. This issue may be attributable only to the number of VF. That is, multiple VFs would likely exacerbate deterioration in HRQOL level [65]. The study [65] in 2005 by Oleksik et al. reported decreased HRQOL due to incident VF. The HRQOL level declined considerably in clinical VF cases, while the level of decrease was low in VF cases without clinical symptoms. However, such disparity may be attributed to severity of fracture. It is thought that the incident VF largely reduces HRQOL level specifically in the physical function domain, transforming itself into chronic pain with time. Hagino et al. reported in study [74], there were significant sequential changes in EQ-5D through the observational period among patients with VFs. They also showed a statistical difference in HRQOL between patients with thoracic and lumbar fractures. In study [33] in 2008 by Papaioannou et al., VFs in women exerted a negative influence on HRQOL, particularly on pain attributes. Self-care, mobility and ambulation were also negatively impacted.

3. Bone Mass

A large number of studies failed to find association between bone mass and HRQOL. However, the possibility exists that studies targeting osteoporosis patients, defined and based only on BMD, do not observe a general decrease in HRQOL level.

The study [43] in 2004 by Romagnoli et al. targeting relatively healthy screening subjects reviewed relevant associations in the general and mental domains. However, the said study applied QUALEFFO to healthy people, and the authors themselves acknowledged the inadequacy of such an application (Table 5). Furthermore, the study [63] in 2004 by Hallberg et al. found that patients with osteopenia or osteoporosis diagnosed only on BMD had lower HRQOL, meanwhile patients with normal BMD did not differ from normal in any SF-36 domain at 2-year follow-up. In this case, other cofounders, such as VFs, were not adjusted. The study [66] in 2005 by Dhillon et al. observed an association between HRQOL and BMD, but failed to prove that prevalent VF is a significant predictor. With regard to the said study, there was a problem with the reliability of prevalent VF data. The study [18] in 2005 by Bianchi et al. reported an association between Qualeffo-41 and lumbar spine BMD and femur BMD in all domains except pain and mental function. Adjustment factors were education, marriage, living alone or not, smoking, drinking, and presence of fracture. The study targeted 100 subjects, 38 of whom had clinical FV. That study made adjustments for clinical VF relative to 62 possible radiographic VF cases, and differs from other studies that failed to

detect such association, in that those studies made assessment by defining the combination of clinical VF and radiographic VF as prevalent VF.

The study [68] in 2006 by Dennison et al. demonstrated that among men, low total femoral BMD was associated with poor physical function, social function, and general health perception. They said that the poorer QOL found in osteoporotic patients was an indicator of comorbidity, which in turn contributed to low bone mass. Also, they reported that it was difficult to be certain whether poor physical function measured by the SF-36 questionnaire was the cause or an effect consequent upon low BMD. Regarding gender dimorphism, with poorer general health perception represented in male osteoporotics, one possible explanation would be the high frequency of secondary causes of osteoporosis among men. Furthermore, they had insufficient information concerning radiographic VF.

4. Education Level and Family History

The study [64] in 2004 by Badia et al. reported that educational history or the educational level of the patient were most significantly affect HRQOL. To the contrary, study [18] in 2005 by Bianch et al. denied any definitive significant association thereof. Furthermore, the study [64] reports on an association with comorbidity. The study [22] in 2002 by Martin et al. denied any decisive significant association with family history. The study [69] by Papaioannou et al. founds a strong positive association between HRQOL and post-secondary education (college or university), a family history of osteoporosis. They described that becoming more empowered and knowledgeable about the implications of managing the disease might be important.

Due to a large number of HRQOL predictor candidates in osteoporosis, as indicated above, many studies have failed to make sufficient adjustments among such factors, and it can be said that many obstacles remain for obtaining a consistent, standardized view.

5. Kyphosis and Height Loss

Among findings other than those mentioned above are: a decrease in HRQOL was observed even among osteoporosis patients without prevalent VF [18]; individuals with the most severe cases of kyphosis did not incur VF [19,20]; those with kyphosis but without spinal deformity suffered physical and emotional disorders of a similar level as those with kyphosis and its underlying condition spinal deformity [21]; females without prevalent VF, but with height loss and kyphosis, suffered significantly more severe physical disability than females with VF unaccompanied by such change of appearance as height loss and kyphosis, thereby facing more difficulties in adaptation than the latter group [22]; and low-BMD fracture accounts for only a small portion of all fracture, a majority of which developed in higher-BMD people [24]. Such findings suggested possible involvement of factors causing bone fragility other than BMD, in the onset of fractures that largely affect HRQOL, and efforts to elucidate such factors have commenced.

In this regard, it is reported that vitamin D deficiency diminished physical function of patients, thereby leading to decline in social function, psychological function and QOL [81].

Furthermore, even though sample size was small, Miyakoshi et al. conducted the study [72] with a focus on location of fracture in order to evaluate effects of multiple influencing factors on HRQOL in osteoporosis, and thereby analyzed associations between HRQOL and latent factors relating to the body of vertebrae. Correlations between JOQOL score, BMD of the lumbar spine/proximal femur/whole body, kyphosis angle and mobility of the thoracic and lumbar spine, number of VF, grip strengths of dominant and non-dominant hands, and isometric back extensor strength (hereinafter referred to as "BES") were analyzed. Finally, mobility of the lumbar spine and BES were screened as significant predictors. The said study has placed a special emphasis on possible spinal factors. As a result, back muscular strength is now receiving attention. Hongo et al. described that low-intensity back-strengthening exercise was effective in improving the QOL and BES in patients with osteoporosis [71].

Martin et al. [22] and Masunari et al. [23] reported that height loss affected HRQOL, independently of VF (Table 6). Masunari et al. defined height loss as the figure resulting from a calculation made by subtracting the measurement of height taken at a point in time during the survey from the tallest height of each subject based on 50-year follow-up survey records. Miyakoshi et al. demonstrated that lumbar kyphosis, which is a cause for height loss, also affected JOQOL independently of VF [61]. Meanwhile, Yoshimura et al. [73] did not observe an association between height loss and HRQOL. In that latter study, height loss was defined as height difference observed in each decade during the period from the subjects' 40s to their 70s. With regard to height loss, disparity was observed between those in each of these different age groups [23]. In assessments by Yoshimura et al., sufficient consideration may not have been paid to such age group-specific disparities in height loss. Furthermore, Yoshimura et al. did not make adjustments for VF. It is believed that a portion of height loss is attributable to VF, and hence it is crucial to make VF-based adjustments.

For the purpose of discussing causes of height loss, it is necessary to review the level of post-VF height loss. It is also assumed that associations between height loss and back muscular strength will receive growing attention.

Conclusion

Previous studies have shown that VF negatively affects physical function and emotional status, and strengthens back pain, thereby decreasing HRQOL. Furthermore, studies using disease-specific instruments report that the level of decrease of HRQOL varies significantly by number and location of VF.

HRQOL has a multi-dimensional structure that includes degree of satisfaction in four (physical, economic, social and psychological) dimensions. Moreover, HRQOL is time-dependent and is affected by a wide range of factors, from external effects to psychological effects. Therefore, one instrument can only provide a snapshot of HRQOL, and hence longitudinal data is indispensable for grasping the larger picture of HRQOL [82].

A majority of studies have reported that both prevalent VF and incident VF bring about physical outcomes. Now that similar effects of number, location, and severity of VF were

observed in both prevalent VF and incident VF, and that a causal relationship between prevalent VF and outcomes can be affirmed.

It is likely possible to understand effects of VF on HRQOL with greater accuracy, by performing research after determining severity, number, and location of VF, as well as time since onset of VF—for example, determining distinction between thoracic VF and lumbar VF, distinction between VF with time since fracture of up to two years and VF with time since fracture exceeding two years, number and severity of prevalent VF, and so on. Only after such effects are elucidated will it become possible to explore HRQOL predictors in osteoporosis patients other than VF. Elucidation of any association between height loss, back muscular strength and effects of vitamin D level on the living body, and clarification of HRQOL predictors in osteoporosis other than VF are expected to bring about improvement of HRQOL in osteoporosis patients.

It is still unknown to what extent HRQOL level deteriorates among VF patients and whether VF itself, disease complications, or other factors cause such deterioration. Several reports in recent years have suggested that VF and related conditions also may affect QOL [83].

Furthermore, which of the HRQOL instruments is appropriate for given situations in a clinical setting has not yet been fully clarified. When using generic health-status instruments, we must be careful to check for a concomitant illness that would substantially influence the patient's QOL (such as chronic pulmonary disease, asthma, angina, chronic congestive heart failure, stroke, blindness). Because HRQOL is a broad concept, many factors are part of it and it may be too strict to adjust for these factors. HRQOL predictors have not yet been completely identified because of a large number of predictor candidates. Consequently, on the basis of reports of future studies to be conducted with use of a combination of generic health-status instruments and disease-specific instruments, it will become possible to conduct other studies that allow the choosing of an HRQOL instrument appropriate to any given situation and the closing in on a true assessment of HRQOL, thereby leading to determination of actual HRQOL predictors in osteoporosis, enhancement of disease prevention, and improvement of prognosis for patients.

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PERSPECTIVE

Validation of the Japanese Osteoporosis Quality of Life Questionnaire

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Abstract The Japanese Society for Bone and Mineral Research developed the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) to evaluate the disease-specific Health-Related QOL, which is specific for osteoporosis of Japanese patients. JOQOL was revised in 2000; it consisted of 38 items with the scale graded from 0 to 4 and a total full score of 152. To elucidate the reliability and validity of the revised JOQOL, we enrolled 193 postmenopausal women as subjects and diagnosed them as having osteoporosis or osteopenia. The mean age of the subjects was 68.2 ± 8 years; 58 subjects (30.1%) had at least one vertebral fracture. Among them, 83 patients were retested for reliability. The mean lapse from the time of test to that of retest was 23.7(±9.5) days. The subjects were questioned using the JOQOL, Medical Outcomes Study Short Form 36 (SF-36), along with questions on subjects' characteristics and their ADL. The JOQOL scores at the test and the retest were significantly correlated ($r = 0.973$) without significant difference between their mean scores. All the JOQOL items showed significant correlations at the test and the retest (Kendall's $\tau = 0.599$–0.947). Cronbach's alpha coefficient of JOQOL was 0.918. These results proved the high reliability of JOQOL. The JOQOL

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