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Improvement in health status and quality of life in patients with osteoporosis treated with denosumab: results at a mean follow-up of six years

M. MERCURIO[1], F. FAMILIARI[1], R. DE FILIPPIS[2], C. VARANO[3], F. NAPOLEONE[1], O. GALASSO[2], G. GASPARINI[2]

[1]Department of Orthopedic and Trauma Surgery, "Magna Graecia" University, "Mater Domini" University Hospital, Catanzaro, Italy
[2]Department of Health Sciences, Psychiatry Unit, "Magna Graecia" University, Catanzaro, Italy
[3]Fisiocenter, Cariati, Cosenza, Italy

Abstract. – OBJECTIVE: The clinical efficacy and tolerability of denosumab in severe osteoporosis are well-known. However, the evaluation on general health and quality of life over time and compared to population norms is still lacking. We aimed at evaluating denosumab effectiveness in a real-world clinical sample with a 6-years average follow-up.

PATIENTS AND METHODS: In this retrospective-matched study with prospective data collection, a total of 101 patients affected by severe osteoporosis and treated with denosumab between 2014 and 2020 were evaluated. All patients completed the self-perceived quality of life (36-Item Short Form - SF-36) survey and visual analogue scale (VAS) before and after treatment.

RESULTS: Overall, 13 patients died of causes unrelated to the procedure, 12 stopped therapy with denosumab, and 30 did not participate in the follow-up; thus, 46 patients completed the study. There were 44 (95.7%) women and 93.4% of patients reported history of osteoporotic fractures. The mean follow-up was 59±17.8 months and the mean age at follow-up was 73.9±10.6 years. We found a significant improvement in bodily pain (baseline 53.8±33.4, follow-up 62.7±26.6; *p*=0.002) and in general health (baseline 35±25.4, follow-up 41.7±24.2; *p*=0.002) over time. The bodily pain score at follow-up was similar to the mean of the age-matched healthy population (62.7±26.6 *vs*. 67.6±26, *p*=0.374). The MCS-36 scores were higher than the normative values before treatment and at follow-up (51.6±9.8 *vs*. 45.8±9, *p*=0.004 and 50.6±11.7 *vs*. 45.8±9, *p*=0.030, respectively). The PCS-36 score at follow-up was comparable to the normative values (39.4±10.4 *vs*. 42.7±9, *p*=0.107).

CONCLUSIONS: Denosumab is effective to improve bone health and global mental and physical wellbeing, and quality of life over time.

Key Words:
Chronic disease, Denosumab, Mental health, Osteoporosis, Quality of life.

Introduction

Quality of life (QoL) is defined as a complete state of both mental and physical health, with adequate social and personal functioning, good perception of own health, high life satisfaction, and general well-being[1]. Several factors can contribute to reduce global health status and QoL, including, but not limiting to, childhood adversities[2], neighborhood environment[3], work situation[4], severe psychiatric conditions[5], treatment management[6], and chronic psychical disease[7].

On this regard, osteoporosis is one of the main chronic and disabling diseases affecting elderly people all over the world, with the highest incidence among female, especially in Europe, USA and Japan[1,8]. Osteoporosis is a skeletal disease leading to a weakness condition with reduced bone strength and mineral density, thus increasing the risk for fragility fractures, pain and physical impairment[8-10], whose progression can also be facilitated by severe mental and physical diseases and prolonged antidepressant prescription[11,12]. Therefore, a strong relationship exists between bone health, general health status and QoL, considering that people living with osteoporosis present an impaired global functioning, particularly relating to the physical, psychological and social aspects, with highest risk of obesity, sedentary lifestyle and loss of work[13].

Corresponding Author: Olimpio Galasso, MD; e-mail: galasso@unicz.it

Denosumab is a fully human IgG2 monoclonal antibody that neutralizes the receptor activator of nuclear factor kappa-B ligand (RANKL), blocking the interaction between the cytokine and its receptor (RANK), with a consequent inhibition of osteoclast-mediated bone resorption[14]. Petranova et al[15] found that denosumab treatment could improve bone microarchitecture and reduce pain in women with osteoporosis, improving general clinical outcome. Hence, denosumab represents a valid therapeutic option for osteoporosis[16], with direct positive consequences on physical status and indirect enhancements on global health status and patients' personal functioning[17].

Although the existing large body of literature on the negative role of chronic and debilitating diseases, such as osteoporosis on general health and global functioning, and although the clinical improvement induced by pharmacological therapy is evident, to the best of our knowledge there are no studies evaluating the definite improvement on health status of patients after treatment with denosumab compared to their own previous functioning and to the referring population in the medium-long term.

Therefore, the aim of this research was to evaluate the clinical improvement of general health status measured by the self-perceived QoL (36-Item Short Form Survey - SF-36) in a sample of patients suffering from osteoporosis and treated with denosumab.

Patients and Methods

A retrospective matched study with prospective data collection was performed on 101 patients treated with denosumab for severe osteoporosis that referred to our institution between December 2014 and December 2020. The study protocol was approved by the local ethics committee, and the research was conducted in compliance with the Declaration of Helsinki[18]. Informed consent was obtained from all individual participants included in the study before collecting any data. The inclusion criteria were: (1) patients treated with denosumab according to the Italian national health system reimbursement criteria for anti-osteoporotic pharmacological treatment, (2) a T-score of -2.5 standard deviations (SD) or less at the femoral neck, lumbar spine or both, verified by Dual X-ray Absorptiometry (DXA) scan, and (3) a minimum 1-year follow-up. The exclusion criteria were: (1) severe cognitive impairment (Mini-Mental State Examination score < 24), (2) high-impact fractures, (3) contraindications to the use of denosumab, and (4) failure to understand or complete the questionnaires.

Data gathered included the age of the patient, body mass index (BMI), the presence of rheumatoid arthritis, diabetes mellitus, chronic obstructive pulmonary disease, inflammatory bowel disease, acquired immunodeficiency syndrome, Parkinson's disease, multiple sclerosis, breast and prostate cancer, history of treatment with prednisone, and history, number, and type of fractures.

The lumbar spine and femoral neck BMD were assessed by the DXA exam at the baseline. Osteoporotic vertebral fractures were detected by lateral vertebral assessment from T4 to L4, using the Genant visual semi-quantitative method[19], as recommended by the International Society for Clinical Densitometry – ISCD[20], or by lateral thoracolumbar spine X-ray examination[21].

All the patients were treated with 60 mg denosumab which was administered subcutaneously every 6 months and a supplementation with cholecalciferol (800 IU daily) plus a supplementation with calcium carbonate (1,000 mg daily) in case of an inadequate nutritional calcium intake.

Health-Related Quality of Life and Pain Assessment

Before treatment and at follow-up, the Italian version of the SF-36 questionnaire[22] was administered to all patients. The SF-36 is a generic measure of health status that contains 36 questions measuring the physical, social, and mental components of respondents. This questionnaire yields eight domains of scores (i.e., physical functioning, PF; role physical, RP; bodily pain, BP; general health, GH; vitality, VT; social functioning, SF; role emotional, RE; and mental health, MH), as well as physical component summary (PCS) and mental component summary (MCS) measures. Each domain is scored on a standardized scale with values ranging from 0 to 100. Higher scores indicate better health-related QoL[23,24]. The SF-36 results were compared to normative data[22,25].

The visual analogue scale (VAS)[26] on a 0-10 scale was used as a subjective measure of low back pain perception. Patients' assessments were performed by two trained physicians who were not involved in the primary care of the patient.

Statistical Analysis

The mean, standard deviation, and range were noted for the continuous variables, and counts

were noted for the categorical variables. All data were collected, measured, and reported with one decimal accuracy. The distribution of the numeric samples was assessed with the Kolmogorov-Smirnov normality test. Based on this preliminary analysis, parametric tests were adopted. To evaluate the significance of differences between pretreatment and at follow-up values, a two-tailed paired sample Student's *t*-test was performed; a 2x2 contingency table was used to compare categorical variables. Post-hoc power was calculated by considering the sample size, the observed effect size, and an α-value of 0.05; a post-hoc power greater than 80% was considered appropriate. IBM SPSS Statistics software (version 26, IBM Corp., Armonk, NY, USA) and G*Power (version 3.1.9.2, Institut für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany) were used for database construction and statistical analysis. A *p*-value lower than 0.05 was considered significant.

Results

The demographics and clinical characteristics of the study population are summarized in Table I. From the original sample, 13 patients died of causes unrelated to the procedure, 12 discontinued denosumab during the follow-up period (8 patients reported difficulties in renewing the denosumab prescription due to logistical problems while for another 4 patients it was necessary to suspend treatment because they had to undergo major dental procedures), and 30 refused to participate in the follow-up; therefore, the final sample consisted of 46 patients, who were enrolled and fully evaluated.

There were 44 (95.7%) women. The mean follow-up was 59 ± 17.8 months (range 17-94) and the mean age at follow-up was 73.9 ± 10.6 years (range 46-90 years). History of osteoporotic fractures was reported in 93.4% of cases. Among the criteria for prescribing denosumab complications or intolerance to bisphosphonates treatment (n=33; 71.7%), contraindications to bisphosphonates (n=3; 6.5%), previous teriparatide treatment for 2 years (n=3; 6.5%), and new osteoporotic fracture that occurred during previous treatment with other antiresorptive drugs (n=3; 6.5%) have been reported. Four patients (8.7%) were naïve to anti-osteoporotic treatment.

Clinical Outcomes

Pre-treatment and at follow-up SF-36 scores are shown in Table II. The GH domain score significantly improved from 35 ± 25.4 to 41.7 ± 24.2 (p = 0.002). The BP domain score significantly improved from 53.8 ± 33.4 to 62.7 ± 26.6 (p = 0.002); the BP score at follow up was similar to the mean of the age-matched healthy population (62.7 ± 26.6 *vs.* 67.6 ± 26, p = 0.374).

Table I. Baseline characteristics of included patients.

Patients (n = 46)	Mean ± SD (range) or n (%)
Gender	
Male	2 (4.3 %)
Female	44 (95.7 %)
Age at follow-up (years)	73.9 ± 10.6 (46-90)
BMI (kg/m^2)	25 ± 4.1 (16.6-35.6)
Post-menopausal women	40 (90.9 %)
Breast cancer	11 (25 %)
Adjuvant treatment	9 (81.8 %)
History of osteoporotic hip and vertebral fractures	33 (71.7 %)
n of osteoporotic fractures per patient	1.4 ± 1.1 (0-3)
History of other osteoporotic fractures	10 (21.7 %)
Family history of hip or vertebral fractures	18 (39.1 %)
Rheumatoid arthritis	5 (10.9 %)
Diabetes mellitus	3 (6.5 %)
Chronic obstructive pulmonary disease	2 (4.3 %)
Parkinson's disease	1 (2.2 %)
> 12 months treatment with prednisone (> 5 mg daily)	3 (6.5 %)
Pre-treatment lumbar spine bone mineral density T-score	-3.2 ± 0.7 (0-4)
Pre-treatment hip bone mineral density T-score	-3.1 ± 0.2 (3-4)
Follow-up (months)	59 ± 17.8 (17-94)

BMI means body mass index; SD, Standard Deviation; n, Number of cases.

Table II. Differences in SF-36 scores over time and in comparison with the normative data.

SF-36 scale	Cases (n= 46) mean ± SD	Population norms* mean ± SD	*p*-value
Baseline PF	57.7 ± 34.8	71.7 ± 24	**0.027**
PF at follow-up	59 ± 29.5		**0.026**
p-value	0.847		
Baseline RP	51.1 ± 44.7	65.9 ± 38	0.091
RP at follow-up	51.6 ± 43.6		0.097
p-value	0.935		
Baseline BP	53.8 ± 33.4	67.6 ± 26	**0.030**
BP at follow-up	62.7 ± 26.6		0.374
p-value	0.002		
Baseline GH	35 ± 25.4	55.4 ± 19	< **0.001**
GH at follow-up	41.7 ± 24.2		**0.003**
p-value	0.002		
Baseline VT	62.7 ± 26.5	59.3 ± 19	0.481
VT at follow-up	60.5 ± 26.4		0.803
p-value	0.374		
Baseline SF	80.7 ± 27.2	75.8 ± 23	0.353
SF at follow-up	84.6 ± 23.1		0.070
p-value	0.736		
Baseline RE	76.2 ± 43.1	73.5 ± 34	0.740
RE at follow-up	70 ± 46.4		0.681
p-value	0.384		
Baseline MH	76.2 ± 23.1	64.7 ± 19	**0.011**
MH at follow-up	74.6 ± 25.6		**0.038**
p-value	0.296		
Baseline PCS-36	36.7 ± 11.1	42.7 ± 9	**0.006**
PCS-36 at follow-up	39.4 ± 10.4		0.107
p-value	0.339		
Baseline MCS-36	51.6 ± 9.8	45.8 ± 9	**0.004**
MCS-36 at follow-up	50.6 ± 11.7		**0.030**
p-value	0.131		

BP, bodily pain; GH, general health; MCS-36, Mental Component Summary; MH, mental health; PCS-36, Physical Component Summary; PF, physical functioning; RE, role emotional; RP, role physical; SD, standard deviation; SF-36, Short Form-36 Health Survey; SF, social functioning; VT, vitality. *65-74 years old individuals.

PF and GH scores were lower than the normative values (57.7 ± 34.8 *vs.* 71.7 ± 24, $p = 0.027$ and 59.9 ± 29.5 *vs.* 71.7 ± 24, $p = 0.026$ for the PF domain and 35 ± 25.4 *vs.* 55.4 ± 19, $p < 0.001$ and 41.7 ± 24.2 *vs.* 55.4 ± 19, $p = 0.003$ for the GH domain, respectively) both before treatment and at follow-up. MH scores were higher than the normative values (76.2 ± 23.1 *vs.* 64.7 ± 19, $p = 0.011$ and 74.6 ± 25.6 *vs.* 64.7 ± 19, $p = 0.038$) before treatment and at follow-up.

No differences were found for the MCS-36 and PCS-36 summary scores before treatment and at follow-up. The MCS-36 scores were higher than the normative values before treatment and at follow-up (51.6 ± 9.8 *vs.* 45.8 ± 9, $p = 0.004$ and 50.6 ± 11.7 *vs.* 45.8 ± 9, $p = 0.030$, respectively). The PCS-36 score at follow-up was comparable to the normative values (39.4 ± 10.4 *vs.* 42.7 ± 9, $p = 0.107$).

No difference was found between VAS scores before treatment and at follow-up (6.9 ± 2.6 *vs.* 6.5 ± 2.3, $p = 0.345$). No local or systemic adverse events, including new hip and vertebral osteoporotic fractures, and osteonecrosis of the jaw, were reported.

Discussion

In this study, we aimed at evaluating the efficacy of denosumab to improve general health and QoL in a real-world clinical sample of patients suffering from osteoporosis during a mean follow-up of 6 years. We used the SF-36 tool to assess several self-report generic clinical outcomes comparing the results both longitudinally and compared to the population norms, in order to obtain a relative and absolute measure of outcome

with respect to the changes achieved by patients. Bodily pain and general health status both significantly improved when compared to the baseline condition and to the populations norms values, thus suggesting positive and effective role for denosumab in improving bone health and global mental and physical wellbeing, and quality of life over time.

In our sample, 13 (12.9%) patients died of causes unrelated to the procedure, 12 patients (11.9%) discontinued denosumab during the follow-up period, while 30 (29.7%) refused to participate in the follow-up. These findings stand in line with similar prospective clinical studies[27-29], where even the main reasons for dropping out were similar, including treatment noncompliance, adverse events, consent withdrawn, subject request, disease progression, lost to follow-up, or death. Moreover, also demographics features we found in individuals included in the study were almost completely overlapping to literature data, considering the highest female sex prevalence[30], post-menopausal women rate[31], elderly age[32] and BMI average[33].

Overall, we found a global improvement in almost all the investigated categories, except for VT, RE and MH. In details, our results particularly highlighted a statistically significant improvement in BP reported by participants (baseline 53.8± 33.4, follow-up 62.7 ± 26.6; p= 0.002) along the follow-up observation and during the treatment course with denosumab. This data are even more sound when compared to the population norm; the significant improvement in BP scores over time that we found allowed us to reach a mean BP score similar to that of the referring population (baseline p=0.030; follow-up p=0.374).

These findings confirm what is already known about denosumab prescription approved indications, namely, to prevent and reduce bone pain in several conditions such as multiple myeloma or bone metastases from solid tumors, and osteoporosis in postmenopausal women as well as men with osteoporosis at high risk of fracture[34-36]. We also identified a clear and important improvement of general health condition reported by patients during the observation time (baseline 35 ± 25.4, follow-up 41.7 ± 24.2; p=0.002). In this case too, the results progress made it possible to bring the values of the reference population even closer, despite the fact that the improvement was not such as to allow for a significant overlap (baseline p=<0.001; follow-up p=0.003), thus confirming the persistence of an absolute difference in terms of general health compared to the healthy population. However, it is not surprising if considering the role that several chronic physical diseases play in the overall QoL, physical activity and personal functioning of individuals[37,38], which therefore may in some way limit the positive therapeutic effect of denosumab[39,40].

It is interesting to notice as well that we found an average higher level of MH scores if compared to the normative values (76.2 ± 23.1 *vs*. 64.7 ± 19, p = 0.011 and 74.6 ± 25.6 *vs*. 64.7 ± 19, p = 0.038) both before treatment and at follow-up. On the other hand, also MCS-36 and PCS-36 summary scores were higher than the normative values before treatment and at follow-up (51.6 ± 9.8 *vs*. 45.8 ± 9, p = 0.004 and 50.6 ± 11.7 *vs*. 45.8 ± 9, p = 0.030, respectively). Considering that these results have been recorded even before the pharmacological intervention itself, it does not seem to be related to the treatment, but rather to a characteristic of the sample examined. Moreover, it should be taken into account that the SF-36 is a tool developed to provide a rapid and comprehensive assessment of the patient's current health status, while a more detailed physical and mental examination could have identified more peculiar differences in the study population[41,42].

Moreover, when considering the scoring algorithm for PCS, we found a positive improvement trend in our sample. This confirms previously discussed results since PCS calculation includes positive weights for the physical functioning, role-physical, bodily pain, general health and vitality scales and negative weights for the social functioning, role-emotional and emotional well-being scales[43]. In our sample the PCS-36 total score improved (baseline 36.7 ± 11.1, follow-up 39.4 ± 10.4; p=0.339), becoming comparable with the population norms (baseline p=0.006; follow-up p=0.107). Therefore, the PCS-36 and MCS-36 and analysis, which represent two useful tools to validate SF-36 results in orthopedics[44,45], synthetize the overall positive therapeutic effect of denosumab, which has proved to be useful and effective in improving global health status and QoL in patients suffering from osteoporosis in middle-long term.

Limitations

Although this study evaluates the effectiveness of denosumab on the overall health of patients with osteoporosis for the first time, with a mean follow-up of 6 years and comparing

both the population longitudinally and with the normalized population, our results presented in this article should be interpretated in the light of some limitations. First, we reached a 56.4% drop-out rate for several reasons previously discussed, which drops to 43.6% if we exclude cases of death for causes unrelated to the study procedure. Although this data stand in line with similar studies, and although this confirms what normally happens in everyday clinical practice, this could certainly have influenced the results obtained. Therefore, future studies with low percentages of patients lost to follow-up would be desirable to increase the strength of the findings. Second, the self-administered assessments inherently present a certain amount of assessment bias. Also, in this case, our work does not differ from what is present in the literature on this topic[23,46], but in the future structured evaluations carried out by mental health care providers with more suitable and comprehensive assessments would increase the solidity of what we have found. Finally, the different duration of the follow-ups observation time of the patients included in the study led to different and not always overlapping surveillance periods. However, this limit was exceeded by using an average follow-up value and including both observation extremes in the analysis. For the future, a prospective design that includes an a priori defined observation time and with periodic and time-distributed observations is desirable.

Conclusions

Patients suffering from osteoporosis treated with denosumab reported a substantial improvement in health status and QoL at a mean follow-up of 6 years. The global health status that has been achieved is comparable to the population norms.

The analysis of the results presented in this study underlines the importance of considering the patient's health as a comprehensive condition, not exclusively linked to the primary physical, with repercussions in terms of personal, social and occupational functioning that must increasingly be considered in future studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Each author fulfils each of the authorship requirements. MM designed the study, performed data collection, statistical analysis and interpretation of data, wrote the paper, and drafted the final manuscript as submitted; FF contributed to the interpretation and analysis of data, and wrote the paper; RdF designed the study, performed data collection and interpretation, wrote the paper, and drafted the final manuscript as submitted; CV performed data collection and interpretation, and wrote the paper; FN performed data collection and interpretation, and wrote the paper; OG conceptualized and designed the study and critically reviewed the manuscript; GG conceptualized and designed the study, performed data interpretation, and critically revised the manuscript as submitted. All authors read and approved the final manuscript as submitted.

References

1) Haraldstad K, Wahl A, Andenæs R, Andersen JR, Andersen MH, Beisland E, Borge CR, Engebretsen E, Eisemann M, Halvorsrud L, Hanssen TA, Haugstvedt A, Haugland T, Johansen VA, Larsen MH, Løvereide L, Løyland B, Kvarme LG, Moons P, Norekvål TM, Ribu L, Rohde GE, Urstad KH, Helseth S; LIVSFORSK network. A systematic review of quality of life research in medicine and health sciences. Qual Life Res 2019; 28: 2641-2650.
2) Hamby S, Taylor E, Mitchell K, Jones L, Newlin C. Health-Related Quality of Life among Adolescents as a Function of Victimization, other Adversities, and Strengths. J Pediatr Nurs 2020; 50: 46-53.
3) Gomez LF, Soto-Salazar C, Guerrero J, Garcia M, Parra DC. Neighborhood environment, self-rated health and quality of life in Latin America. Health Promot Int 2020; 35: 196-204.
4) Andrei F, Mancini G, Agostini F, Epifanio MS, Piombo MA, Riolo M, Spicuzza V, Neri E, Lo Baido R, La Grutta S, Trombini E. Quality of Life and Job Loss during the COVID-19 Pandemic: Mediation by Hopelessness and Moderation by Trait Emotional Intelligence. Int J Environ Res Public Health 2022; 19: 2756.
5) Aloi M, de Filippis R, Grosso Lavalle F, Chiappetta E, Viganò C, Segura-Garcia C, De Fazio P. Effectiveness of integrated psychological therapy on clinical, neuropsychological, emotional and functional outcome in schizophrenia: a RCT study. J Ment Health 2020; 29: 524-531.

6) de Filippis R, Soldevila-Matías P, De Fazio P, Guinart D, Fuentes-Durá I, Rubio JM, Kane JM, Schoretsanitis G. Clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. Expert Rev Clin Pharmacol 2020; 13: 875-883.
7) Cugusi L, Prosperini L, Mura G. Exergaming for Quality of Life in Persons Living with Chronic Diseases: A Systematic Review and Meta-analysis. PM&R 2021; 13: 756-780.
8) Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos 2013; 8: 136.
9) Nawrat-Szołtysik A, Polak A, Małecki A, Piejko L, Grzybowska-Ganszczyk D, Kręcichwost M, Opara J. Effect of physical activity on the sequelae of osteoporosis in female residents of residential care facilities. Adv Clin Exp Med 2018; 27: 633-642.
10) Chiarella E, Aloisio A, Scicchitano S, Lucchino V, Montalcini Y, Galasso O, Greco M, Gasparini G, Mesuraca M, Bond H, Morrone G. ZNF521 Represses Osteoblastic Differentiation in Human Adipose-Derived Stem Cells. Int J Mol Sci 2018; 19: 4095.
11) Himmerich H, Kan C, Au K, Treasure J. Pharmacological treatment of eating disorders, comorbid mental health problems, malnutrition and physical health consequences. Pharmacol Ther 2021; 217: 107667.
12) de Filippis R, Mercurio M, Spina G, De Fazio P, Segura-Garcia C, Familiari F, Gasparini G, Galasso O. Antidepressants and Vertebral and Hip Risk Fracture: An Updated Systematic Review and Meta-Analysis. Healthcare 2022; 10: 803.
13) de Oliveira Ferreira N, Arthuso M, da Silva R, Pedro AO, Neto AMP, Costa-Paiva L. Quality of life in women with postmenopausal osteoporosis: Correlation between QUALEFFO 41 and SF-36. Maturitas 2009; 62: 85-90.
14) Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. N Engl J Med 2009; 361: 756-765.
15) Petranova T, Sheytanov I, Monov S, Nestorova R, Rashkov R. Denosumab improves bone mineral density and microarchitecture and reduces bone pain in women with osteoporosis with and without glucocorticoid treatment. Biotechnol Biotechnol Equip 2014; 28: 1127-1137.
16) Migliore A, Broccoli S, Massafra U, Cassol M, Frediani B. Ranking antireabsorptive agents to prevent vertebral fractures in postmenopausal osteoporosis by mixed treatment comparison meta-analysis. Eur Rev Med Pharmacol Sci 2013; 17: 658-667.
17) Scaturro D, Rizzo S, Sanfilippo V, Giustino V, Messina G, Martines F, Falco V, Cuntrera D, Moretti A, Iolascon G, Letizia Mauro G. Effectiveness of Rehabilitative Intervention on Pain, Postural Balance, and Quality of Life in Women with Multiple Vertebral Fragility Fractures: A Prospective Cohort Study. J Funct Morphol Kinesiol 2021; 6: 24.
18) World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191.
19) Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 2009; 8: 1137-1148.
20) Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive Summary of the 2013 International Society for Clinical Densitometry Position Development Conference on Bone Densitometry. J Clin Densitom 2013; 16: 455-466.
21) Moretti A, de Sire A, Curci C, Toro G, Gimigliano F, Iolascon G. Effectiveness of denosumab on back pain-related disability and quality-of-life in patients with vertebral fragility fractures. Curr Med Res Opin 2019; 35: 151-155.
22) Apolone G, Mosconi P. The Italian SF-36 Health Survey. J Clin Epidemiol 1998; 51: 1025-1036.
23) Lix LM, Acan Osman B, Adachi JD, Towheed T, Hopman W, Davison KS, Leslie WD. Measurement equivalence of the SF-36 in the canadian multicentre osteoporosis study. Health Qual Life Outcomes 2012; 10: 29.
24) Fanelli D, Mercurio M, Castioni D, Sanzo V, Gasparini G, Galasso O. End-stage ankle osteoarthritis: arthroplasty offers better quality of life than arthrodesis with similar complication and re-operation rates—an updated meta-analysis of comparative studies. Int Orthop 2021; 45: 2177-2191.
25) Castioni D, Galasso O, Iannò B, Mercurio M, Gasparini G. Posterior versus lateral surgical approach: functionality and quality of life after total hip arthroplasty in a matched cohort study. BMC Musculoskelet Disord 2021; 22: 932.
26) Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17: 45-56.
27) Compston J. Safety of long-term denosumab therapy for osteoporosis. Lancet Diabetes Endocrinol 2017; 5: 485-487.
28) Brown JP, Roux C, Törring O, Ho PR, Beck Jensen JE, Gilchrist N, Recknor C, Austin M, Wang A, Grauer A, Wagman RB. Discontinuation of denosumab and associated fracture incidence: Analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial. J Bone Miner Res 2013; 28: 746-752.
29) Tański W, Kosiorowska J, Szymańska-Chabowska A. Osteoporosis - risk factors, pharmaceutical

and non-pharmaceutical treatment. Eur Rev Med Pharmacol Sci 2021; 25: 3557-3566.

30) Alswat KA. Gender Disparities in Osteoporosis. J Clin Med Res 2017; 9: 382-387.

31) Testini V, Paparella MT, Gangai I, Guglielmi G. Postmenopausal osteoporosis: current status of bone densitometry. Minerva Obstet Gynecol 2021; 73: 730-743.

32) Johnston CB, Dagar M. Osteoporosis in Older Adults. Med Clin North Am 2020; 104: 873-884.

33) Fan Z, Li X, Zhang X, Yang Y, Fei Q, Guo A. Comparison of OSTA, FRAX and BMI for Predicting Postmenopausal Osteoporosis in a Han Population in Beijing: A Cross Sectional Study. Clin Interv Aging 2020; 15: 1171-1180.

34) Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, Niepel D, Van den Wyngaert T. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol 2019; 127: 117-135.

35) Hildebrand GK, Kasi A. Denosumab. StatPearls Publishing 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK535388/.

36) Yang L, Kang N, Yang J-C, Su Q-J, Liu Y-Z, Guan L, Liu T, Meng X-L, Wang Y, Hai Y. Drug efficacies on bone mineral density and fracture rate for the treatment of postmenopausal osteoporosis: a network meta-analysis. Eur Rev Med Pharmacol Sci 2019; 23: 2640-2668.

37) Zurita-Cruz JN, Manuel-Apolinar L, Arellano-Flores ML, Gutierrez-Gonzalez A, Najera-Ahumada AG, Cisneros-González N. Health and quality of life outcomes impairment of quality of life in type 2 diabetes mellitus: a cross-sectional study. Health Qual Life Outcomes 2018; 16: 94.

38) Gavala-González J, Torres-Pérez A, Fernández-García JC. Impact of Rowing Training on Quality of Life and Physical Activity Levels in Female Breast Cancer Survivors. Int J Environ Res Public Health 2021; 18: 7188.

39) Hayashi S, Fukuda K, Maeda T, Chinzei N, Kihara S, Miura Y, Sakai Y, Hashimoto S, Matsumoto T, Takayama K, Niikura T, Kuroda R. Denosumab Treatment Improved Health-Related Quality of Life in Osteoporosis: A Prospective Cohort Study. JBMR Plus 2019; 3: e10191.

40) Hendriks LEL, Hermans BCM, van den Beuken—van Everdingen MHJ, Hochstenbag MMH, Dingemans A-MC. Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non–Small Cell Lung Cancer and Bone Metastases: A Systematic Review. J Thorac Oncol 2016; 11: 155-173.

41) Matcham F, Norton S, Steer S, Hotopf M. Usefulness of the SF-36 Health Survey in screening for depressive and anxiety disorders in rheumatoid arthritis. BMC Musculoskelet Disord 2016; 17: 224.

42) van den Beukel TO, Siegert CEH, van Dijk S, Ter Wee PM, Dekker FW, Honig A. Comparison of the SF-36 Five-item Mental Health Inventory and Beck Depression Inventory for the screening of depressive symptoms in chronic dialysis patients. Nephrol Dial Transplant 2012; 27: 4453-4457.

43) Ware J, Kosinski M, Keller S. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

44) Farivar SS, Cunningham WE, Hays RD. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.1. Health Qual Life Outcomes 2007; 5: 54.

45) Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in Orthopaedics: A Brief Guide. J Bone Jt Surg 2015; 97: 1628-1634.

46) Stanghelle B, Bentzen H, Giangregorio L, Pripp AH, Bergland A. Associations between health-related quality of life, physical function and pain in older women with osteoporosis and vertebral fracture. BMC Geriatr 2019; 19: 298.