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Functional assessment measures in rheumatologic disorders

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Core tip: Health-related quality of life is an increasing important outcome in health care. This article presents an overview of the most important health-related quality of life and functional assessment measures, which have been commonly used in rheumatologic disorders.

Abstract

Rheumatologic disorders cause functional impairment and significantly affect health-related quality of life. Functional assessment and health-related quality of life scales are increasingly being used as outcome measures to assess the influence of the diseases and health outcome in clinical studies of patients with rheumatologic diseases. In this article, we review the functional assessment and health-related quality of life measures which have been commonly used as outcome measures in rheumatologic disorders. These measures are Short form-36 (SF-36), SF-12, Nottingham Health Profile, Sickness Impact Profile, EuroQol, SF-6D, Health Utilities Index mark 2 and 3, Stanford Health Assessment Questionnaire, Rheumatoid Arthritis Quality of Life Questionnaire, Arthritis Impact Measurement Scales, McMaster Toronto Arthritis Patient Preference Disability Questionnaire, Western Ontario and McMaster Universities Osteoarthritis Index, Lequesne Index, Knee Disability and Osteoarthritis Outcome Score, Knee Disability and Osteoarthritis Outcome Score-Physical Function Short-form, Hip Disability and Osteoarthritis Outcome Score, Hip Disability and Osteoarthritis Outcome Score-Physical Function SF, Fibromyalgia Impact Questionnaire, Psoriatic Arthritis Quality of Life Scale, Gout Assessment Questionnaires, Dougados Functional Index, Bath Ankylosing Spondylitis Functional Index, and Ankylosing Spondylitis Quality of Life Scale.

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INTRODUCTION

Millions of people around the world suffer from the effects of musculoskeletal disorders such as long-term pain and physical impairment^[1]. In a study from eight countries in Europe and America, musculoskeletal disorders were reported as one of the most frequently conditions among the chronic conditions^[2]. The financial costs of rheumatologic diseases including both direct costs of medical interventions and indirect costs of premature mortality and disability are estimated as 1%-2.5% of the gross national product of European countries^[3].

Rheumatologic disorders have negative influence on functional status and the health-related quality of life in terms of daily life activities, bodily pain, social and emotional functioning^[4].

Functional assessment

Functional assessment is defined as the measurement of the level of a patient's disability. Disability is a condition of having a physical limitation in individuals' body functions, which may cause personal and social challenges^[5].

Functional assessment is important in estimating burden of disease, monitoring outcomes in clinical practice, and as end points in clinical trials^[6].

Table 1 Overview of quality of life measures commonly used in rheumatologic disorders

Generic measures	Disease specific measures					
	Rheumatoid arthritis	Osteoarthritis	Fibromyalgia	Psoriatic arthritis	Ankylosing spondylitis	Gout
SF-36	HAQ	WOMAC	FIQ	PsAQoL	DFI	GAQ 1.0
SF-12	RAQoL	Lequesne			BASFI	GAQ 2.0
NHP	AIMS	KOOS			ASQoL	
SIP	AIMS-2	KOOS-PS				
EQ-5D	MACTAR	HOOS				
SF-6D		HOOS-PS				
HUI-2						
HUI-3						

SF: Short form; SIP: Sickness impact profile; EQ-5D: EuroQol; HUI-2: Health Utilities Index mark 2; HAQ: Health Assessment Questionnaire; RAQoL: Rheumatoid Arthritis Quality of Life Questionnaire; AIMS: Arthritis impact measurement scales; MACTAR: McMaster Toronto Arthritis Patient Preference Disability Questionnaire; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KOOS-PS: Knee Disability and Osteoarthritis Outcome Score-Physical Function Short-form; HOOS-PS: Hip Disability and Osteoarthritis Outcome Score-Physical Function Short-form; FIQ: Fibromyalgia Impact Questionnaire; PsAQoL: Psoriatic Arthritis Quality of Life; DFI: Dougados Functional Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; GAQ: Gout Assessment Questionnaire; NHP: Nottingham Health Profile.

Health-related quality of life

Quality of life is the subjective well-being and pleasure taken from life^[7]. World Health Organization defines health-related quality of life as individuals' perceptions of their conditions in life, with regard to their objectives, expectations, norms and concerns, within the context of their own cultural and value systems^[8]. Fitzpatrick has defined the dimensions of quality of life as physical, emotional and social functioning, role performance, pain and other symptoms including fatigue, nausea and disease specific symptoms^[9].

Health-related quality of life is an outcome measure that is increasingly used to assess health outcome in clinical studies of patients with rheumatologic diseases^[10].

Various generic and specific scales have been used to evaluate health-related quality of life. This paper provides an overview of functional assessment and health-related quality of life measures, commonly used in rheumatologic disorders.

FUNCTIONAL ASSESSMENT/HEALTH-RELATED QUALITY OF LIFE MEASURES USED IN RHEUMATOLOGIC DISORDERS

Generic scales are applicable for a wide range of populations and interventions-for example, Short form-36 (SF-36), which is the most widely used instrument for evaluating health-related quality of life. Specific scales are designed to be associated with specific health problems and can measure a few areas of interest-for example Fibromyalgia Impact Questionnaire^[11,12].

Health-related quality of life measures that are used in clinical practice ensure that the assessments and the treatment concentrate on the patient instead of the disease. Quality of life measures can be used: (1) in monitoring disease and response to treatment; (2) in clinical trials; (3) in evaluating psychosocial problems in individual patient care; (4) in clinical audit; and (5) in cost-utility analyses^[10,13]. Health-related quality of life measures which

are most commonly used in rheumatologic disorders are shown in Table 1.

GENERIC MEASURES: PROFILES

SF-36 (The Medical Outcomes Study 36-Item, Short-Form Health Survey)

The SF-36 is a self administered questionnaire including 36 items with eight dimensions, which assess: (1) limitations in physical functions; (2) limitations in social functions; (3) role limitations because of functional impairment; (4) role limitations because of psychological status; (5) bodily pain; (6) mental health; (7) energy; and (8) general health. It takes 5-10 min to complete. A specific advantage of SF-36 is that it also includes "energy" dimension, which is not included in the core set of outcome measures, but regarded as important by the patients^[14-17]. It has been commonly used as an outcome measure in various rheumatologic disorders including rheumatoid arthritis, connective tissue disorders, ankylosing spondylitis, osteoarthritis, and fibromyalgia^[17-21]. Also in a study of Andresen *et al*^[22], it was reported that it could be used as a health-related quality of life measure among patients with spinal cord injury. In some studies, SF-36 was found to be inadequate in evaluating health related quality of life of the elderly patients with comorbidities^[23,24].

Short form-12

The SF-12 is an abbreviated version of SF-36, developed by Ware *et al*^[25] in 1996 to be used in general and specific populations^[26]. In a study of Hurst *et al*^[27], it was found to be useful and valid measure, but slightly less reliable and less responsive than SF-36 in rheumatoid arthritis.

Nottingham Health Profile

The Nottingham Health Profile (NHP) is a 45-item generic questionnaire, designed to measure quality of life in terms of physical, psychological and social functions. It has two parts. First part has 38 questions that assess six components of health including sleep, energy, bodily

pain, and physical, social and emotional functioning. Second part includes seven aspects of daily life influenced by health status such as interests, personal relationships, social and sexual life and vacations. Scores range from 0 to 100. Higher scores indicate a poorer level of health status^[28,29]. The NHP has shown good construct validity, reliability and responsiveness^[30,31]. It was reported that it was a valid instrument as an outcome measure in rheumatoid arthritis^[32]. It has been also used for evaluating health-related quality of life of the patients with ankylosing spondylitis and osteoarthritis^[33,34].

Sickness Impact Profile

The Sickness Impact Profile is a generic health-related quality of life profile, developed in 1975. It consists of 189 items in 14 categories including social and family interaction, ambulation, mobility, sleeping and resting, nutrition, daily work, family administration, body motions, communicating, recreation and hobbies, intellectual and emotional functions, and hygiene. Its disadvantage is that it takes at least 35 min to complete^[35].

GENERIC MEASURES: UTILITY INSTRUMENTS

Utility instruments are measures that represent strength of an individual's preferences for various dimensions of health. The most important ones are EuroQol (EQ-5D), the SF-6D, and the Health Utilities Index (HUI)^[36].

EQ-5D

The EQ-5D is a generic utility instrument which is used in the clinical and economic assessment of health care and in clinical trials^[37]. The EQ-5D defines five components of health status as mobility, self-care, common activities, bodily pain and emotional status. It consists of 243 different health states^[5]. The EQ-5D has been commonly used in the studies of injury and diseases^[5,37]. It was reported that it was a valid instrument in measuring health-related quality of life of patients with rheumatoid arthritis^[38], while its reliability was fairly poor^[39].

SF-6D

The SF-6D is a six-dimensional utility instrument, revised from SF-36. It evaluates health status in terms of physical and social functions, role limitations, pain, mental status, and energy^[40]. The EQ-5D was found to be more responsive to deterioration and the SF-6D more responsive to improvement in early inflammatory disease, when compared^[41].

HUI mark 2 and 3

The HUI-2 and the HUI-3 are comprehensive, reliable, responsive and valid measures of health status and health-related quality of life. The HUI-2 comprises seven dimensions including sense, mobility, feeling, cognition, self-care, pain, and fertility. The HUI-3 includes eight di-

mensions: vision, hearing, speaking, ambulation, dexterity, emotion, cognition, and pain^[42].

DISEASE SPECIFIC MEASURES

Stanford Health Assessment Questionnaire

The Stanford Health Assessment Questionnaire (HAQ) is one of the most widely used instrument, developed in 1980 as an outcome measure in rheumatoid arthritis but has also been used in osteoarthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, spondyloarthritis, psoriatic arthritis, and systemic sclerosis. It is approved by the American College of Rheumatology for evaluating functional impairment in the patients with rheumatoid arthritis^[43,44]. The disability index of the scale includes 20 items and eight dimensions in terms of dressing, ascending, eating, walking, hygiene, reach, grip, and usual activities. It is commonly used as the HAQ scale, and sometimes as the HAQ disability index^[5,45].

A shortened version of the HAQ, modified HAQ (mHAQ) was developed by Pincus *et al*^[46] in 1983. It has eight items. Both the HAQ and the mHAQ are sensitive to change in clinical studies, but the HAQ was found to be more effective in determining alterations to the therapy, when compared with mHAQ^[47].

The Rheumatoid Arthritis Quality of Life Questionnaire

The Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) is a rheumatoid arthritis-specific measure that includes 30 questions about psychological state, public life, interests, daywork, personal and social relationships, and physical contact. The RAQoL has shown good construct validity, reliability, and responsiveness in rheumatoid arthritis^[39,45]. It was reported that the RAQoL was the most responsive instrument when compared with HAQ, EQ-5D, SF-6D, and HUI^[45].

HAQ and RAQoL have greater ability to assess functional status and detect smaller changes in rheumatoid arthritis, compared with generic measures^[48].

Arthritis impact measurement scales

The arthritis impact measurement scales (AIMS) was developed by Meenan *et al*^[49] in 1980 to measure disease-specific health-related quality of life in patients with arthritis. The AIMS consists of 45 items and nine dimensions including locomotion, physical activities, dexterity, family activities, social activities, daily living activities, pain, and psychological status^[49].

The expanded version of the AIMS (AIMS-2) was developed in 1992. It comprises 101 items and 12 dimensions including limb functions, social assistance, and work^[50].

Both AIMS and AIMS-2 were specifically developed for use among adults with rheumatoid arthritis and osteoarthritis, but they have been used in different conditions such as spondyloarthritis, psoriatic arthritis, fibromyalgia, and nerve entrapment syndromes^[23].

McMaster Toronto Arthritis Patient Preference Disability Questionnaire: The McMaster Toronto Arthritis Patient Preference Disability Questionnaire is a rheumatoid arthritis-specific questionnaire that assesses impairment in functional activities selected by the patient. It includes 5 items assessing the ability to perform the activities that have been affected by arthritis^[51]. It is valid and responsive instrument to evaluate change in functional status of the patients with early active rheumatoid arthritis, but its feasibility is limited^[52]. Evaluating each people according to different activities may be problematic. Also it was noted that the scoring system was complex and required amendments^[53].

Western Ontario and McMaster Universities Osteoarthritis Index: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a multi-dimensional, self-administered instrument that assesses health status in patients with hip and/or knee osteoarthritis. It includes 24 items and three dimensions including pain, stiffness and functional impairment^[54,55]. The WOMAC has been shown to be a reliable, valid and responsive outcome measure in the patients with hip and/or knee osteoarthritis^[56]. It was specifically developed for use among adults with knee or hip osteoarthritis, but it has been used among patients with rheumatoid arthritis^[57], and fibromyalgia^[58].

Lequesne Index: The Lequesne Index is a 10-item self-administered instrument, designed to evaluate health status in patients with knee and/or hip osteoarthritis. It includes three dimensions which assess pain, discomfort and morning stiffness; maximum distance walked and walking aid used; and activities of daily living. Total score ranges from 0 to 24^[59,60]. In a study of Theiler *et al*^[61], the Lequesne index was found to be less responsive than the WOMAC in patients with osteoarthritis of the lower limbs.

Knee Disability and Osteoarthritis Outcome Score: The Knee Disability and Osteoarthritis Outcome Score (KOOS) is a knee-specific functional assessment measure, developed by Roos *et al*^[62] in 1998. It has 42 items that assess five outcomes: pain, other symptoms, daily life activities, sport and recreational activities, and knee-related quality of life.

KOOS-Physical Function SF: The KOOS-Physical Function SF is a shortened version of KOOS, developed by Perruccio *et al*^[63] in 2008. It consists of seven questions about physical functions of knee^[64]. It was found to be responsive to medical treatment among participants with knee OA^[65].

Hip Disability and Osteoarthritis Outcome Score: The Hip Disability and Osteoarthritis Outcome Score (HOOS) is a hip osteoarthritis-specific functional assessment measure, developed by Klässbo *et al*^[66] in 2003. It

includes 40 items, which assess five dimensions: pain, other symptoms comprising stiffness and limitation of range of motion, daily life functions, sport and recreational activities, and hip-related quality of life. It was found to be more responsive than the WOMAC in total hip replacement^[67].

HOOS-Physical Function SF: It is the shortened version of HOOS, developed by Davis *et al*^[68] in 2008. It comprises five questions including climbing down the stairs, getting in or out of bath, sitting, running and twisting on loaded leg. The psychometric properties of the HOOS-Physical Function SF were found to be comparable to those of the WOMAC and Lequesne^[69].

Fibromyalgia Impact Questionnaire: The Fibromyalgia Impact Questionnaire (FIQ) is a 10-item, fibromyalgia-specific questionnaire that evaluates physical ability, work status, psychological status, sleeping, pain, stiffness, fatigue, and well-being in patients with fibromyalgia^[70]. The FIQ was found to be the optimal outcome measure in sensitivity to changes in perceived clinical enhancement in fibromyalgia^[71].

The Psoriatic Arthritis Quality of Life Scale: The Psoriatic Arthritis Quality of Life is the first patient reported, 20-item psoriatic arthritis-specific health-related quality of life instrument^[72]. It has shown reliability and construct validity^[73]. Its sensitivity to changes was demonstrated^[74].

Gout Assessment Questionnaire 1.0: The Gout Assessment Questionnaire 1.0 (GAQ 1.0) is a 21-item disease specific measure that collects information about gout impact on health-related quality of life in terms of pain, well-being, productivity, and treatment satisfaction. The GAQ 1.0 has acceptable psychometric properties^[75,76].

The expanded version of the GAQ (GAQ 2.0) was developed in 2008 by Hirsch *et al*^[77]. It has 24 items that evaluate the impact of acute and chronic gout on health-related quality of life. It has shown acceptable reliability and validity characteristics^[76,78].

Dougados Functional Index: The Dougados Functional Index (DFI) is an index of functional impairment in ankylosing spondylitis^[79]. It has 20 items about performing various daily living activities including dressing, getting in bath tub, standing for ten minutes, ascending one flight of steps, running, sitting down, getting up from a chair, getting into a car, bending over to pick up an object, crouching, lying down, turning in bed, getting out of bed, sleeping on their back and stomach, doing your daily activities, coughing or sneezing, and breathing deeply. Low responsiveness in the DFI scores was reported in clinical studies^[79,80].

Bath Ankylosing Spondylitis Functional Index: The Bath Ankylosing Spondylitis Functional Index (BASFI) is a 10-item questionnaire that evaluates functional status

in patients with ankylosing spondylitis^[81]. Patients define their ability to put on their clothes, to bend forward from the waist to pick up an object from the floor, to reach up to a high shelf, to get up out of an armless chair, to get up off the floor from lying on their back, to stand for ten minutes without any difficulty, to ascend the stairs, to look over their shoulder without turning their body, to perform physical activities, and to perform daily activities. Total score ranges from 0 to 10^[80,81]. It was reported that the BASFI performed better than the DFI in symptom modifying antirheumatic drug and disease controlling antirheumatic therapy clinical trials^[82].

Ankylosing Spondylitis Quality of Life Scale: The Ankylosing Spondylitis Quality of Life is an ankylosing spondylitis-specific health-related quality of life instrument, developed by Doward *et al*^[83]. It has 18 questions that evaluate impact of ankylosing spondylitis on the health-related quality of life. It has shown reliability and construct validity.

CONCLUSION

Musculoskeletal diseases have negative impact on functional status and health-related quality of life in terms of daily life activities, bodily pain, and social and emotional functioning. Functional assessment and health-related quality of life measures are increasingly being used to evaluate health outcome in clinical studies of patients with rheumatologic diseases.

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Monitoring osteoporosis therapy: Can FRAX help assessing success or failure in achieving treatment goals?

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or sustain any fracture within the first 2-year, had their osteoporosis treatment changed. Outcome measures included BMD and FRAX assessment calculated 3-year after commencing new osteoporosis treatment.

RESULTS: There was a significant negative correlation between 10-year probability of major osteoporotic and hip fractures and BMD at the total proximal femur at 2-year of treatment ($R = -0.449$ and -0.479 respectively), and at 5-year ($R = -0.489$ and -0.594 respectively). At both 2 years and 5 years of treatment, the 10-year fracture probability showed significant correlation with the incidence of fracture ($P < 0.01$). On comparing fracture probability, there was a significant difference ($P < 0.05$) between the responders and non-responders to osteoporosis treatment.

CONCLUSION: In women currently or previously treated for osteoporosis, the FRAX tool can be used to predict fracture probability. Osteoporosis treatment does not annul prediction of fractures. FRAX tool may be of value in guiding clinicians towards the need for continuation or withdrawal of treatment.

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Key words: The World Health Organization fracture risk assessment tool; Osteoporosis; Fracture; Dual-energy X-ray absorptiometry

Abstract

AIM: To assess: (1) Whether the World Health Organization fracture risk assessment tool (FRAX) can be used for monitoring osteoporosis patients receiving treatment as well as its clinical implications; and (2) The relation between fracture incidence and post-treatment FRAX.

METHODS: Five hundred and seventy-nine osteoporotic women known to be adherent to the prescribed osteoporosis medication, had dual-energy X-ray absorptiometry scan and fracture probability calculated at baseline, 2 and 5-year of osteoporosis treatment. Those patients who responded to treatment and did not sustain a new low trauma fracture during the first 2 years, continued their treatment and were re-assessed 3-year later. The patient subgroup who did not achieve an improvement in their bone mineral density (BMD)

Core tip: Treatment of osteoporosis should assure that the patient benefits from the treatment without experiencing undue harm. Monitoring of patients treated for osteoporosis has been recommended and so far dual-energy X-ray absorptiometry has been recognized as the tool to monitor osteoporosis therapy by several clinical practice guidelines. Recently, the duration of osteoporosis therapy became a research question with the possibility of having a drug holiday. However, more research is still needed to adequately assess when to stop the osteoporosis therapy and what is the optimal

duration of the drug holiday. This work was carried out aiming at determining whether the World Health Organization fracture risk assessment tool can be used as a tool to monitor patients receiving osteoporosis treatment and to evaluate its ability to predict new low trauma fractures.

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INTRODUCTION

Osteoporosis is a prevalent condition that may exist in a silent form, in which increased fracture risk can be detected by measurement of bone mineral density (BMD), or as a symptomatic condition after fragility fracture has occurred^[1]. In standard clinical practice, bone mineral density measured by dual-energy X-ray absorptiometry (DXA) is used to diagnose osteoporosis, assess fracture risk, and provide input for the World Health Organization (WHO) fracture risk assessment tool (FRAX)^[2]. The conventional wisdom is that patients should be screened for risk factors and those who are at high risk for fracture should be identified by means of BMD testing. Consequently, those who are at sufficiently high risk of fracture should receive pharmacological therapy to reduce the risk of fractures. This has been reported to be the most cost-effective strategy to reduce the huge personal and economic burden of osteoporosis^[3]. Treatment of osteoporosis should assure that the patient benefits from the treatment without experiencing undue harm. Monitoring of patients treated for osteoporosis has been also recommended and so far DXA has been recognized as the tool to monitor osteoporosis therapy by several clinical practice guidelines. Recently, the duration of osteoporosis therapy became a research question with the possibility of having a drug holiday. However, more research is still needed to adequately assess when to stop the osteoporosis therapy and what is the optimal duration of the drug holiday.

The FRAX, a diagnostic tool used to evaluate the 10-year probability of bone fracture risk based on the individual's risk factor profile, was developed by the WHO Collaborating Centre for Metabolic Bone Diseases^[4]. FRAX proved to be of great benefit, not only in patients whose DXA revealed osteoporosis, but also in the osteopenic patients. The implementation of 10-year fracture risk probability assessment in day to day clinical practice impacted positively on the physicians' prescribing pattern^[5]. However, when first implemented, it has been recommended that FRAX should be used only for osteoporosis therapy naïve patients and not to be applied

for the assessment of the change in fracture risk in individuals who received osteoporosis treatment. This was attributed to the earlier clinical trials' findings suggesting that the positive anti-fracture effect from osteoporosis therapy is constantly greater than what can be elucidated from the increase in BMD only (which accounts for only a fraction of the anti-fracture effect)^[6-8]. On the other hand, in most of the patients, bone mineral density is the only risk factor amongst those encompassed in the FRAX model expected to show a response to treatment. Therefore, the notion of using FRAX as a tool to assess the impact of osteoporosis therapy on fracture prediction might sound logic.

This work was carried out aiming at determining whether FRAX can be used for monitoring patients receiving osteoporosis therapy and to evaluate its ability to predict new low trauma fractures.

MATERIALS AND METHODS

Study

This was a retrospective 5-year follow up study of a patients cohort diagnosed to have osteoporosis based on DXA scan measurement of their BMD and having a T-score of ≤ 2.5 at either neck of the femur or spine.

Ethics

Local ethical and methodological protocols for approval of the study were followed. The study was approved by Ain Shams University research ethics committee. All patients who shared in the study signed an informed consent in keeping with the World Medical Association's declaration of Helsinki.

Patients

Data from consecutive female patients referred for osteoporosis assessment and management were recorded. Inclusion criteria included: time since menopause at least 6 mo and lumbar spine and/or neck of the femur BMD equal to or more than 2.5 SD below the mean for a normal population. Exclusion criteria were: (1) All women younger than 50 years as individuals referred for BMD testing are less representative of the general population; lack of agreed treatment protocols, and treatment rates are usually low; (2) Any patient suffering from diseases, other than primary osteoporosis known to affect bone metabolism; (3) History of hormone replacement therapy, or bisphosphonate therapy within the 6 mo prior to the start of the study; and (4) Low or non-adherent patients to osteoporosis therapy.

Study design

The study cohort available for analysis at the time of baseline assessment was 1026 women. All the patients, aged ≥ 50 years were assessed for baseline risk factors as well as BMD measurement and were considered for inclusion in this study. All patients included in this work were treated following the National Osteoporosis Foun-

dation recommendations^[9] and screened for adherence to therapy 1-year after commencing their medication. Only the patients who adhered to the prescribed osteoporosis treatment, had 10-year fracture probability calculated and their data recorded for the purpose of this work. At 2 and 5-year of osteoporosis therapy, a follow-up DXA scan was carried out for every patient. On both occasions, risk factors were reassessed and 10-year fracture probabilities were calculated using FRAX. Those patients who did not achieve any improvement in neck of the femur BMD measurement or had a new low trauma fracture within the first 2-year of management, changed had their osteoporosis treatment. BMD and FRAX measurements were carried out after 3-year of commencing new osteoporosis therapy. The patient cohort who showed good response well to treatment and had not sustained any new low trauma fracture within the first 2 years, had their treatment continued with a further assessment at 3-year.

Risk factors assessment

History of previous low trauma fractures as well as other osteoporosis risk factors, necessary for calculating fracture probability with FRAX, were assessed using a new DXA scan referral form^[10] completed for every patient before every bone mineral density assessment. The form also included assessment for falls risk using the "Falls Risk Assessment Score (FRAS)" score^[11], recent history of low trauma fractures or change in medications. Patients with high falls risk were referred to the local falls clinic. In addition, history of past osteoporosis therapy as well as current medications was included in the referral form. For purposes of the FRAX calculation, prior fragility fracture was considered if it was one of the major osteoporotic fractures (vertebral, hip forearm, or humerus fracture) and was not associated with severe trauma. The patients' records and radiology investigations were checked to confirm the history of any of these major osteoporotic fractures as well as history of site specific fracture reduction to enhance the diagnostic and temporal specificity of the fracture event. The diagnosis of rheumatoid arthritis and/or smoking over the past 3-year period before DXA scanning as well as prolonged steroid use (regardless of the dose) for more than 3-mo period in the year before the BMD measurement were cross-checked with the patients' notes.

Measurements

BMD was measured using a Hologic DXA machine (Hologic Inc., MA, United States). Every patient had a baseline BMD assessment as well as repeat DXA scan at 2 and 5 years post treatment. All the scans were analysed and the femoral neck, total proximal femur and spine BMD. The T scores were calculated using the equation: $T \text{ score} = (\text{BMD value of osteoporotic patient} - \text{BMD of healthy premenopausal population}) / \text{SD of the premenopausal healthy population}$. According to WHO classification: Osteoporosis was diagnosed at $T\text{-score} \leq -2.5$,

osteopenia at $T\text{-score} < -1$ to $T\text{-score} < -2.5$, whereas normal BMD was considered at $T\text{-score} \geq -1$. A quality control program including daily quality controls was conducted throughout the study^[12]. The Densitometer showed stable long-term performance (coefficient of variation $< 0.5\%$) and satisfactory *in vivo* precision. For each subject, the 10-year major osteoporosis as well as the hip fracture probability was calculated for each subject by the WHO Collaborating Centre (<http://www.shef.ac.uk/FRAX/tool.aspx?country=21>) using the previously defined variables without knowledge of the fracture outcomes. Prior to every DXA assessment every patient had a blood check for bone profile [serum calcium, phosphorus, alkaline phosphatase and 25 (OH) vitamin D] as well as liver and kidney function tests. Patients who had vitamin D deficiency were treated with high vitamin D therapy. FRAX estimated fracture risk probability was categorized based on fixed cut off points. For major osteoporotic fracture probability cut-off point was $> 20\%$ whereas for hip fracture it was $> 3\%$. The patients whose falls risk score was ≥ 3.5 on the FRAS score, were considered at high risk of falls and were referred to specialized falls clinic for further assessment and management.

Osteoporosis medication use

Osteoporosis therapy was selected from bisphosphonate (oral alendronate/risedronate; intravenous zoledronate), raloxifene, or salmon calcitonin. None of the patients was taking systemic hormone replacement therapy following the Women's Health Initiative Study^[8]. Strontium, Denosumab as well as anabolic therapies were not available at the start of the study, and their use was limited to the patients who did not respond or were intolerant to bisphosphonate therapy. Adherence, as defined by Cramer *et al.*^[13], was evaluated using the parameters of compliance and persistence. Compliance was estimated by the medication possession ratio (MPR) and persistence by the time from treatment initiation to discontinuation with no medication refill gap for a period of 30 d or more during the period of interest. MPR was defined as the ratio of actually available doses against the expected doses that the patient should possess over a fixed period of time. Study patients were rated as having good compliance if the annual MPR $\geq 80\%$. The MPR was calculated in the first year after BMD testing, and medication swapping was considered. Medication use was categorized as: (1) Untreated: no use in the year before or after BMD testing, and < 6 -mo lifetime use in earlier years; (2) Low adherence (current user): MPR $< 80\%$ in the year following BMD testing; (3) High adherence (current user): MPR $\geq 80\%$ in the year following BMD testing; (4) Past user: any use in the year preceding BMD testing or at least 6 mo lifetime use in earlier years, with no use in the year following BMD testing.

Statistical analysis

Descriptive analysis was performed using frequency distribution in categorical variables and mean and standard

Table 1 Mean of the proximal femur bone mineral density, predicted 10-year major osteoporotic fracture and hip fracture probability estimated for all patients at baseline, 2-year and 5-year

	At baseline mean \pm SD	2-yr of treatment mean \pm SD	5-yr of treatment mean \pm SD
Total proximal femur BMD	0.553 \pm 0.69	0.574 \pm 0.06	0.579 \pm 0.04
T-score	-2.75 \pm 0.61	-2.32 \pm 0.45	-1.46 \pm 0.35
FRAX 10-yr major osteoporosis fracture risk	21.43 \pm 7.56	14.81 \pm 4.79	9.67 \pm 2.92
FRAX 10-yr hip fracture risk	7.11 \pm 4.55	4.4 \pm 2.62	4.11 \pm 4.55

BMD: Bone mineral density; FRAX: The World Health Organization fracture risk assessment tool.

deviation in case of normally distributed continuous variables. Spearman Rank order correlation was used for non-parametric data. Paired student-*t* test was used for comparing dependent parametric data. For inferential statistics *P* value was always set at 0.05.

RESULTS

The patients' age range was from 50 to 79 years (mean 64.3 \pm 9.4 years). During mean 5.3 years of observation, there were 44/1026 (4.3 %) deaths and 28/1026 (2.7%) changed their address. 376/1026 (36.6%) were excluded as they did not adhere to therapy, therefore, in total 579 women out of 1026 (56.4%) were included in this cohort. Table 1 shows the mean (\pm SD) proximal femur BMD as well as the mean predicted 10-year major osteoporotic fracture and hip fracture probability estimated for all patients at baseline, 2-year and 5-year of observation. At baseline 49.6% of the patients had documented history of low trauma fracture. In the initial 2-year of the observation period 16.9% individuals had a new major osteoporotic fracture whereas in the following 3 years of observation period, 4.7% of the patients sustained a new low trauma fracture (Table 2). Hip fractures represented 48% of the total low trauma fractures occurring over the 5.3 years study period whereas the remaining 52% had one of the major osteoporosis fractures (spine, forearm or shoulder).

The FRAX stratified major osteoporotic and hip fracture 10-year probability had significant negative correlation with total proximal femur BMD measurement at 2-year as well as at 5-year of therapy (Table 3). After 2 years and 5 years of treatment (Figure 1), there was a significant relation between estimated 10-year predicted fracture probability for major osteoporosis fracture with both femur BMD as well as the fracture ($P < 0.01$) regardless of the medication used. Similarly, there was a significant relation between the fracture incidence and 10-year predicted fracture probability for hip fracture ($P < 0.01$) (Figure 2). On assessment of major fracture probability using BMD, there was a significant ($P < 0.05$)

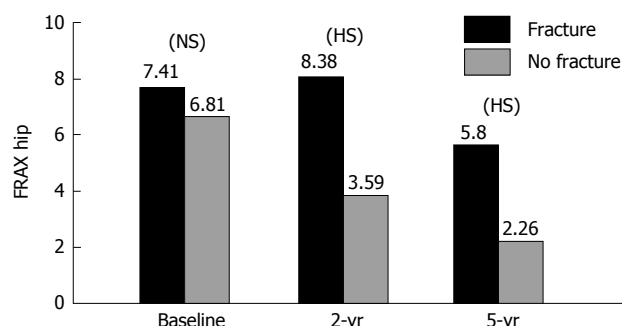


Figure 1 The 10-year hip fracture probability (the World Health Organization fracture risk assessment tool) in relation to incident fracture groups at baseline, 2 and 5-year. (Mean 10-year fracture risk probability are shown on top of each column). NS: Not significant; HS: Highly significant, $P < 0.01$ vs baseline.

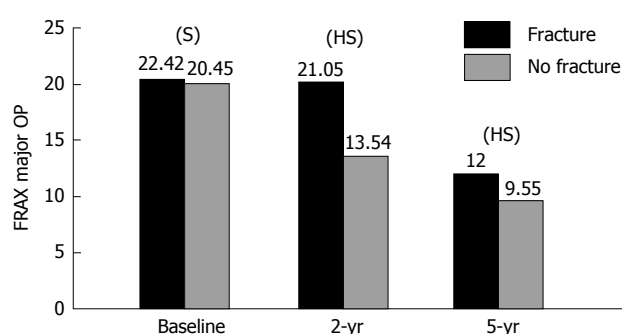


Figure 2 The 10-year major osteoporosis fracture probability (the World Health Organization fracture risk assessment tool) in relation to incident fracture groups at baseline, 2 and 5-year. (Mean 10-year fracture risk probability is shown on top of each column). S: Significant; HS: Highly significant, $P < 0.01$ vs baseline.

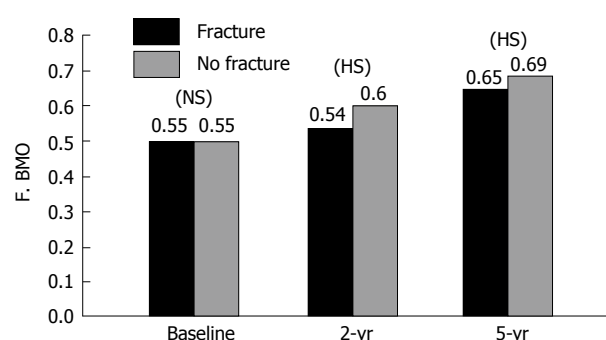


Figure 3 Total proximal femur bone mineral density in relation to the incidence of major osteoporosis fractures (mean bone mineral content are shown on top of each column). F: BMD: Femur bone mineral density; NS: Not significant; HS: Highly significant.

less fracture probability among responders in comparison to non-responders to osteoporosis treatment. Figure 3 shows that, the total proximal femur BMD was a strong predictor to both hip as well as major osteoporotic fractures; this was not affected by medication use ($P < 0.05$).

The patients who experienced an increase in femoral neck or total proximal femur BMD (expressed as a percentage difference from the baseline BMD) at 2-year treatment had a lower incidence rate of fracture (frac-

Table 2 Prevalence of low trauma fractures at baseline in comparison to its incidence at 2-year and 5-year of observation

	At baseline		At 2-yr		At 5 yr	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
No fracture	292	50.4	481	83.1	552	95.3
Low trauma fracture	287	49.36	98	16.9	27	4.7

Table 3 Correlation of the World Health Organization fracture risk assessment tool stratified major osteoporotic and hip fracture 10-year probability with the total proximal femur bone mineral density measurement

	BMD total proximal femur at baseline	BMD total proximal femur at 2-yr	BMD total proximal femur at 5-yr
FRAX 10-yr major osteoporosis fracture risk probability	-0.551 ^b	-0.449 ^b	-0.479 ^b
FRAX 10-yr hip fracture risk probability	-0.741 ^b	-0.547 ^b	-0.584 ^b
Change in FRAX 10-yr major osteoporosis fracture probability at 2-yr		-0.459 ^b	
Change in FRAX 10-yr hip fracture probability at 2-yr		-0.557 ^b	
Major osteoporosis fracture probability at 5-yr			-0.489 ^b
Change in FRAX 10-yr hip fracture probability at 5-yr			-0.594 ^b

^b*P* < 0.01, BMD total proximal femur at 2-yr and 5-yr *vs* BMD total proximal femur at baseline. BMD: Bone mineral density; FRAX: The World Health Organization fracture risk assessment tool.

ture incidence was 2.5%), compared to treated patients who experienced reduced BMD (fracture incidence was 19%). After controlling for covariates (namely age, steroids intake, smoking), patients with an improvement of at least 3% in femoral neck BMD at 2-year of therapy, were at a lower risk of new fractures development [OR = 0.63 (95%CI: 0.41-0.82)] than patients without such improvement. The results were in the same range when considering changes in total proximal femur BMD [OR = 0.64 (95%CI: 0.48-0.88)]. Changes in spine BMD were not statistically associated with the incidence of vertebral fracture (*P* = 0.10). For each percentage point increase in femoral neck and total proximal femur BMD observed after 2-year, the risk of sustaining a new vertebral fracture after 2-year decreased by 2.7% (95%CI: 1%-5%) and 1.8% (1%-4%), respectively.

Bisphosphonates were the most common medication used (553/579 patients, 95.5%). Treatment effects were assessed in the 579 patients who showed high adherence to therapy (MPR 0.80) over at least 5 years of bisphosphonate use. The subgroup of patients who did not respond to the treatment and re-measuring of their BMD, at 2-year time, did not reveal significant improvement, had higher incidence of fractures which was significantly higher than predicted. Figure 4A and B is the receiver operating characteristic (ROC) curve is for FRAX major osteoporosis and hip fracture probability at 2 years, whereas Figure 4C is the ROC curve for the 10-year fracture probability both sides at 5-year.

DISCUSSION

Monitoring the effects of osteoporosis therapy can inform the patient and physician that the drug is having its expected skeletal response. So far, there is no consensus about methods of re-assessment or identifying treatment failures in osteoporosis. Questions have been raised

whether the 10-year FRAX can be used to guide treatment decisions. Despite the scientific basis of FRAX and its strengths, the recommendation to the clinicians was not to use the tool in monitoring patients receiving osteoporosis treatment. That was based on the fact that treatment effects were not considered in the model. In turn, this would limit the value of using FRAX to a subgroup of patients whose BMD assessment revealed osteopenia in the presence of other risk factors. This work was carried out aiming at determining whether FRAX can be used as a tool to monitor those patients receiving osteoporosis treatment as well as its clinical implications.

Results of this study revealed that FRAX can be used as a predictor of new post-treatment fracture probability and assess the reduction in the fracture risk in women currently on osteoporosis therapy. FRAX probabilities showed significant correlation with the change in the neck of femur BMD in response to therapy. Besides, FRAX showed a relatively high predicting ability of the incidence of new low trauma fractures. Therefore, FRAX might have a role in guiding the requirement of treatment continuation or withdrawal. These findings are in agreement with the results of a recently published work^[14] assessing whether osteoporosis pharmacotherapy invalidates fracture predictions using FRAX. Results of that study^[14] revealed that FRAX, showed similar response pattern in untreated, currently treated and previously treated osteoporosis women. In the cohort of women who had high fracture risk with high adherence to at least 5 years of bisphosphonates, hip fracture risk was significantly less than predicted, with a treatment effect that approximated fracture risk reduction reported in bisphosphonates clinical trials^[15-18]. Furthermore, in concordance with the results of this work, there was significant agreement between predicted fracture probability and observed fracture incidence indicating that osteoporosis therapy does not annul using FRAX for fracture

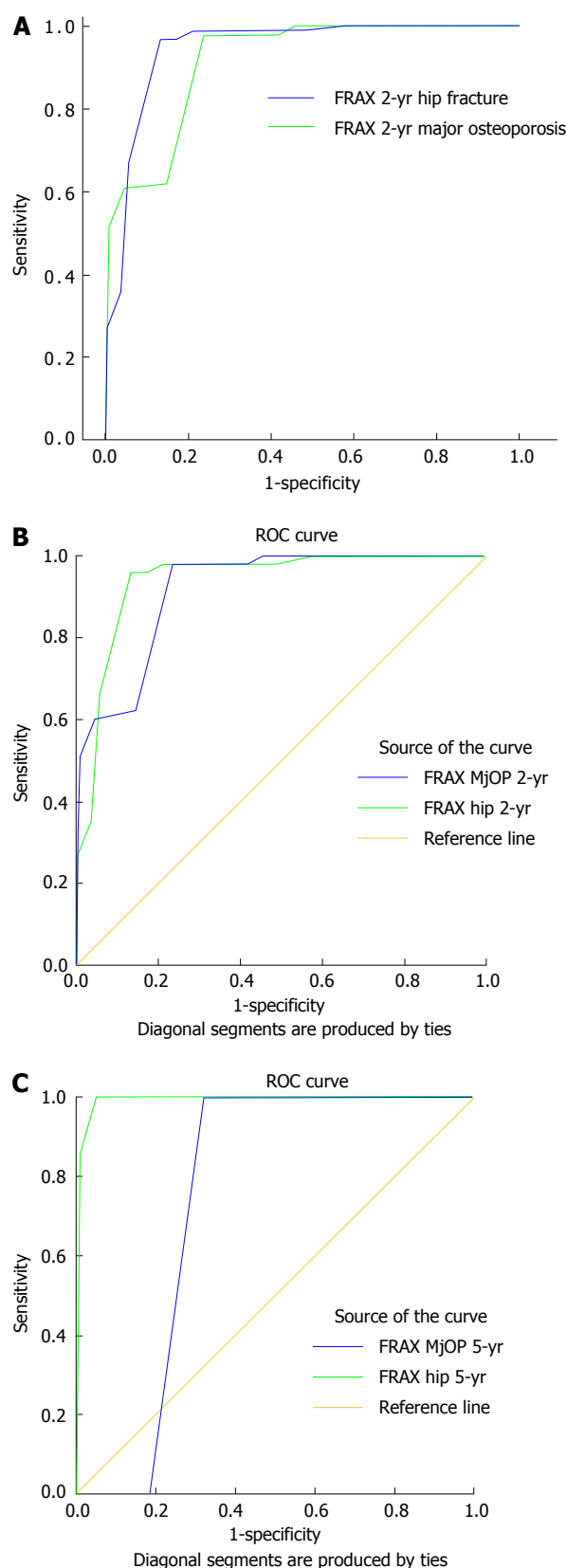


Figure 4 ROC curve displaying discriminating ability of 10 years the World Health Organization fracture risk assessment tool major osteoporosis and hip fracture probability at 2 years in prediction of fracture. A and B: At 2 years [The AUC for the World Health Organization fracture risk assessment tool (FRAX) major osteoporosis fracture: 0.916 and FRAX hip fracture 0.94]; C: At 5 years [The AUC for the World Health Organization fracture risk assessment tool (FRAX) major osteoporosis fracture: 0.748 and FRAX hip fracture 0.992]. AUC: Area under the curve; ROC: Receiver operating characteristic; MjOP: Major osteoporosis fracture.

prediction. This potentially expands the FRAX clinical role as a tool for persuading patients on their requirement for continued treatment, and whether treatment could possibly be stopped.

So far, BMD measurement using DXA scanning has been a surrogate marker for bone strength and fracture risk. Earlier results showed that stability or a significant increase in BMD is an acceptable response to therapy and is associated with a reduction in fracture risk^[3]. Similarly, a significant decrease in BMD suggests a suboptimal response to therapy and may require evaluation for factors contributing to bone loss and possibly changing the osteoporosis medication. In clinical practice, a valid quantitative comparison of BMD measurements requires that measurements be made on the same DXA machine (or different machines that have been cross-calibrated) according to well-established quality standards that include precision assessment and calculation of the least BMD statistically significant change^[19]. Results of this study revealed that a statistically significant BMD loss was positively correlated with increased fracture risk probability and a significant predictor of fracture incidence. Furthermore, the timing of follow up BMD testing to monitor osteoporosis treatment has been a matter of debate. In a post-hoc analysis of two randomized, placebo-controlled clinical trials, the concept of regression to the mean was invoked to suggest that treatment should not be changed before one year of therapy^[20]. In another post-hoc analysis of a single randomized controlled trial, it was concluded that BMD monitoring is unnecessary in the first three years after starting a potent bisphosphonate^[21]. However, the conclusions of both analyses have been challenged^[22,23]. Although regression to the mean is a valid statistical concept that is helpful in understanding apparent BMD changes in groups of patients in clinical trials, it does not indicate that serial BMD testing in clinical practice is useless^[24]. Results of this study revealed that re-measuring BMD after 2-year of osteoporosis treatment initiation is a valid time interval for BMD changes monitoring.

There are no data providing information on how to monitor osteoporosis patients or guide decision-making about the initiation and termination of “drug holiday”. In the absence of guidance from clinical trials, empiric approaches are necessary. Results of this study highlighted the value of FRAX and BMD measurement in the guidance for the continuation or withdrawal of treatment. Assessment of BMD changes and fracture risk probability 2-year after commencing osteoporosis drug therapy was helpful to identify the non-responders who warranted a change of their medication. Further assessment should be carried out after 5 years of treatment. Persistence of low BMD measures or high fracture risk probability suggests that the patient should continue the osteoporosis medication. On the other hand, drug holiday can be considered for patients whose follow-up BMD reveal normal or osteopenic levels with low fracture risk probability. It can also be suggested that repeat BMD measurement as well as 10-year fracture risk probability assessment be

carried out 3-5 years of osteoporosis drug holiday.

Long-term compliance and adherence to osteoporosis therapy has been repeatedly reported as relatively poor. Results of this study revealed that only 56.4% (579/1026) of the patients continued to take their osteoporosis therapy in the first year of management. This agrees with earlier data revealing that only about 50% of patients who begin an osteoporosis drug continue therapy for at least one year^[25]. These data, not only highlight the importance of checking the patient's adherence to therapy in the first year of osteoporosis management, but also stresses on the importance of patient education. Patients should be aware of the relationship between reduction in fracture risk with pharmacologic therapy and BMD increase measured by DXA, and that a combination of BMD and clinical risk factors assessment predict fracture more accurately than BMD or clinical risk factors alone.

A limitation of this study, is the number of osteoporosis therapy agents included in this work. Though the majority of the patients were treated with bisphosphonates, other forms of osteoporosis treatment were also included. These different osteoporosis therapy modalities differ in terms of vertebral and non-vertebral fracture prevention as well as FRAX probability dependency^[15,26-28].

In conclusion, this study highlighted the importance of monitoring osteoporosis treatment and its value to the treating clinician in early identification early of non-responders to treatment. This work suggests that the FRAX can be used as a predictor of fracture probability in those women on treatment for osteoporosis, at least on the short term, for guiding the need for continuation, modification or withdrawal of treatment. In general treatment decisions need to be tailored to the patient's BMD status, fracture risk as well as predisposing risk factors.

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COMMENTS

Background

Ten-year fracture risk assessment using the World Health Organization (WHO) fracture risk assessment tool (FRAX) is increasingly used as a guide to osteoporosis management and treatment decisions. However, using FRAX for estimation of fracture probability was recommended for treatment naïve patients only as there was no data published on whether osteoporosis therapy annuls fracture predictions with FRAX. The question of whether FRAX can be used in treated osteoporosis patients is addressed in this study.

Research frontiers

There are many differences between subjects in clinical trials and patients being treated in clinical practice. Defining a clinical practice patient as a "non-responder" or "suboptimal responder" to treatment remains a difficult question to answer. Therefore, a pragmatic approach has been suggested considering the evaluation of contributing risk factors and possible treatment changes in patients who have a significant decrease in bone mineral density, or have high fracture risk probability.

Innovations and breakthroughs

This work was carried out aiming at determining whether FRAX can be used as

a tool to monitor osteoporotic patients on treatment and to evaluate its ability to predict new low trauma fractures.

Applications

This study has positive therapeutic implications as it helps answering the question of whether FRAX works in osteoporotic patients currently on therapy. This work suggests that the FRAX can be used as a predictor of fracture probability in women currently receiving osteoporosis therapy.

Terminology

The WHO FRAX calculator is one of the most thoroughly studied and widely used tools of fracture risk assessment which gained momentum in the past decade. FRAX is mainly used as a guide for clinical decision-making in the patient's management.

Peer review

This is a retrospective clinical study to investigate the use of FRAX to monitor the patients receiving osteoporosis therapy and to study the relationship between the post-treatment FRAX and the occurrence of new low trauma fractures.

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Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 $\mu\text{g/L}$; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantum numbers can be found at: http://www.wjgnet.com/2220-3214/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: <http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15>

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