UROONCOLOGY

Invited Review

Implications of the Fracture Risk Assessment Algorithm for the assessment and improvement of bone health in patients with prostate cancer: A comprehensive review

Ashish Sharma, Rahul Janak Sinha, Vishwajeet Singh, Gaurav Garg, Samarth Agarwal, Siddharth Pandey

Cite this article as: Sharma A, Sinha RJ, Singh V, Garg G, Agarwal S, Pandey S. Implications of the Fracture Risk Assessment Algorithm for the assessment and improvement of bone health in patients with prostate cancer: A comprehensive review. Turk J Urol 2019; 45(4): 245-53.

ABSTRACT

Objective: Maintaining the optimum bone health is one of the important concerns in patients with prostate cancer, but it usually remains neglected. Failure to screen these patients is detrimental to both the length and the quality of life. The estimation of bone mineral density (BMD) and more recently the World Health Organization's fracture risk assessment (FRAX) algorithm in appropriate patients is recommended by several specialty organizations/associations at the time of instituting androgen deprivation therapy (ADT) for metastatic and high-risk individuals. It provides a 10-year risk evaluation of hip and major osteoporotic fractures (MOF). Using this web-based new investigating tool, candidates at high risk of fractures can be predicted more accurately according to clinical risk factors (CRF) alone or in combination with the femoral neck BMD. The FRAX application for senile osteoporosis has been studied and reviewed extensively, but no systematic review has ever been conducted for assessing the implication of FRAX in prostate cancer. This review article will give insight about the validity, role, and utility of this investigating tool in clinical practice for fracture risk assessment in these individuals.

Material and methods: This systematic review was carried out as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and Cochrane review principles. We searched the PubMed, Cochrane database of systematic reviews, and the EMBASE electronic database until December 2018 using the medical subject heading terms prostate cancer and FRAX.

Results: A total of nine studies meet the inclusion criteria and were included in the review. These studies enrolled a total of 3704 patients (sample size range, 78–1220) of localized, metastatic, castration resistant prostate cancer with or without ADT and/or on photon or radiotherapy. The factors that influenced FRAX included age, ethnicity, baseline BMD, duration of ADT, presence of CRF, and measurement methods (CRF, with/without BMD, computed tomography based). An advanced age and duration of ADT were the most robust risk factors. A 10-year MOF and hip fracture risk estimation was higher when the femoral neck BMD was not incorporated in the FRAX measurement. Despite several well-known strengths of using FRAX in the fracture risk assessment of suitable candidates with prostate cancer, several risk factors such as the mode/duration of ADT, mode of radiotherapy, Vitamin D levels, bone remodeling markers, and recent/recurrent fractures need to be incorporated in the FRAX calculator for improving the predictive ability. In contrast to senile osteoporosis with a longer life expectancy, the fracture risk in patients with prostate cancer need to be measured more frequently and for a shorter time. Therefore, models like Garvan calculator with both 5- and 10-year risk estimates have to be developed for these patients. Additionally, its utilization is of limited value in the presence of recurrent fractures or falls.

Conclusion: The FRAX algorithm is beneficial in identifying patients who require early intervention or bone-directed therapy as an early step to decrease skeletal-related events and other morbidity. Several risk factors need to be added for improving the FRAX predictive value. This model is still underutilized in the clinical practice and increasing the awareness among treating physicians will help in optimizing the bone health and the quality of life of this important population subgroup.

Keywords: Androgen deprivation therapy; bone health; bone-directed therapy; fracture risk assessment tool; FRAX algorithm; prostate cancer; skeletal-related events.

ORCID IDs of the authors:
A.S. 0000-0002-6337-8401;
R.J.S. 0000-0003-1658-8550;
V.S. 0000-0002-3230-416X;
G.G. 0000-0001-5198-8934;
S.A. 0000-0003-1390-6488;
S.P. 0000-0003-3314-1347

King George Medical University (KGMU), Lucknow, India

Submitted:
14.01.2019

Accepted:
05.02.2019

Available Online Date:
20.02.2019

Corresponding Author:
Rahul Janak Sinha
E-mail:
rahuljanaksinhakgmu@gmail.com

Available online at
www.turkishjournalofurology.com

Turk J Urol 2019; 45(4): 245–53
DOI:10.5152/tud.2019.11736

Introduction

Prostate cancer is one of the major global health concerns accounting for approximately 240,000 deaths annually with diverse biological and clinical behavior.[1,2] It has the highest incidence of bone metastases among all urological malignancies.[2] The bone involvement in the advanced stage of cancer causes some of the most distressing symptoms: 22% of patients require treatment for pathological fractures, 7% for spinal-cord compression, and 34% for paresis or hemiparesis.[2,3] Maintaining the optimum bone health is one of the important concern in these patients but it usually remains neglected even today.[3-5] Failure to properly screen these patients is detrimental to both the length and the quality of life, given the consistent increase in life expectancy of men with prostate cancer.[6-8]

Prostate cancer usually occurs in elderly population in which the prevalence of osteoporosis is already common, and further use of androgen deprivation therapy (ADT) as a treatment modality has cumulative deleterious results on the bone mineral density (BMD), leading to an increase in the incidence of osteoporosis and skeletal fracture risk.[8-11] Patients on ADT have a four times more likely probability of developing a significant BMD loss, and up to 20% of localized prostate cancer cases will develop fracture within 5 years of the ADT initiation.[12] Cancer-treatment-induced bone loss is a major cause of bone loss and bone-related morbidity in these patients.

An estimation of BMD at the time of instituting ADT for metastatic prostate cancer is recommended by several specialty groups and expert panels.[9-11] Using a new computer-based investigating fracture risk assessment (FRAX) model, candidates at high risk of fractures can be predicted more accurately, and appropriate treatment can be initiated as an early step to prevent skeletal-related events and to improve the quality of life in these patients.[12,13] An appropriate use of imaging modalities such as the Dual Energy X-ray Absorptiometry (DEXA) scan can help detect osteoporosis at an early stage. However, an estimated fracture risk prediction is not so accurate with this modality alone. Until recently, majority of clinical guidelines for the management of osteoporosis was predominantly based on the BMD and T-score alone. Now, more robust and valid models are available for detecting osteoporosis and predicting fracture risks such as FRAX. The FRAX algorithm is recommended by the World Health Organization (WHO) for prediction of the fracture risk according to the clinical risk factors alone or in combination with femoral neck BMD (gm/cm^2).[13-15] This is a web-based algorithm (available at www.shef.ac.uk/FRAX), which provides a 10-year probability of hip and major osteoporotic fractures (composite of hip, clinical spine, wrist, and humerus) according to age, gender, body mass index, and clinical risk factors.[13-16] The factors that may affects the FRAX score include age, ethnicity, type and duration of ADT, the mode of radiotherapy, and CRF.[14-17] The following dichotomized risk variables (CRF) were used for FRAX calculation: i) previous fragility fracture, ii) current smoking, iii) history of parental hip fracture, iv) prolonged use of oral steroids (>3 months), v) presence of other causes of secondary osteoporosis, vi) daily alcohol consumption of three or more units, and vii) presence of rheumatoid arthritis.

The National Osteoporosis Foundation (NOF) guidelines[9] recommend the initiation of therapy for prevention of fractures in patients with a T-score ≤2.5, a history of hip or vertebral fracture, and a 10-year hip fracture risk ≥3%, or the major osteoporotic fracture (MOF) ≥20% by the FRAX model (Table 1). Although the application of the FRAX model in the management of senile osteoporosis has been studied and reviewed extensively,[16,18] there has been no comprehensive review ever conducted for assessing the implication of FRAX in prostate cancer. This review article will give insight about the validity, role, and utility in current clinical practice of this investigating tool for FRAX in this important population. To the best of our knowledge, the present study is the first systemic review related to the implication of the FRAX algorithm for the prediction of the 10-year MOF and the hip fracture risk in patients with prostate cancer.

Material and methods

The current systematic literature review was carried out as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[19] and Cochrane review principles.[20] We searched the PubMed, the Cochrane database of system-

Table 1. National Guideline Recommendations (NOF & NCCN) for osteoporosis, BMD changes, and FRAX risk

Patient counseling
Smoking cessation
Limiting alcohol consumption
Weight-bearing exercise
BMD testing
Men 50–69 based on risk factors
All men >70 years old
Calcium and vitamin D supplementations
Men>50 years calcium: 1200 mg per day
Men>50 years vitamin D: 800–1000 IU per day
Bisphosphate therapy
FRAX risk >3% for hip fracture
FRAX risk >20% for major osteoporotic fracture
Osteopenia or osteoporosis on BMD

NOF: National Osteoporosis Foundation; NCCN: National Comprehensive Cancer Network; FRAX: fracture risk assessment; BMD: bone mineral density

Table 2. Summary of previous studies related to use of FRAX tool in prostate cancer

S. No.	Study author (Year)	Nation	Study type	Study duration	Sample size	Avg. Age (Yrs)
1.	Saylor et al.[22] (2010)	USA	Cross-sectional	4 months	363	72
2.	Adler et al.[14] (2010)	USA	Retrospective	1 year	115	77
3.	Neubecker et al.[25] (2011)	USA	Retrospective	NA	78	77
4.	Dhanapal et al.[24] (2011)	USA	Retrospective	1 year	174	65.5
5.	James et al.[13] (2013)	USA	Retrospective	NA	613	75
6.	Valery et al.[26] (2013)	USA	Prospective	2 years	382	N.A
7.	McDonald et al.[27] (2016)	USA	Retrospective	11 years	609	64.9
8.	Kawahara et al.[23] (2016)	Japan	Retrospective	NA	1220	74
9.	Ojeda et al.[17] (2017)	Spain	Prospective	Two-phase study Max. follow-up of 11 years	150	67.4

FRAX: fracture risk assessment; NA: not available

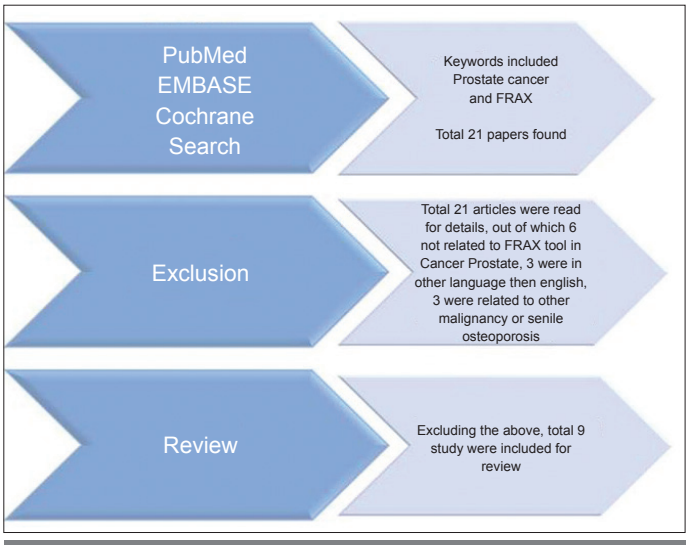

Figure 1. Flowchart of materials and methods for inclusion of studies in a systematic review

atic reviews, and the EMBASE electronic database extensively until December 2018 using the medical subject heading terms *prostate cancer* and *FRAX*. A total of 21 articles were found. On reviewing these articles, we found that six articles were not related to the FRAX implication in prostate cancer, while three were published in a language other than English. Three articles were related to the application of FRAX tool in other malignancies or in senile osteoporosis. Therefore, after excluding all these we had a total of nine studies for review (Figure 1). Quality assessment of these studies was performed using the New Castle Ottawa Scale tool.[21] In addition, articles published on the pathogenesis and management of the ADT-related bone loss as well as due to metastatic prostate cancer were extensively read and interpreted, and related information is included in the present review.

Study identification

Nine studies that met the inclusion criteria were identified and reviewed. These studies included a total of 3704 patients with the individual study sample size that ranged from 78 to 1220 and were published between 2010 and 2017 (Table 2).[13,14,17,22-27] Six studies were retrospective, two were prospective, and one was a cross-sectional study. Seven studies were carried out in the United States except one study in Japan and other one in Spain. The patient selection among these studies varied in respect to enrollment of localized, metastatic, castration resistant prostate cancer (CRPC), with or without ADT and patients on photon therapy or radiotherapy (Table 3). Adler et al.[14] and McDonald et al.[27] included 115 and 609 localized prostate cancer patients without bony metastases. Kawahara et al.[23] studied 1220 prostate cancer patients excluding CRPC, while Valery et al.[26] enrolled 382 patients on photon radiotherapy with or without ADT. The average duration of study was about 1 to 2 years with a range of 4 months–11 years. The range of the mean/median age of patients in these studies was 64.9–77 years.

Discussion

Cancer treatment-induced bone loss

Two complementary processes of the bone remodeling (i.e., bone formation and bone resorption) maintain the normal structural integrity of the healthy bone.[28] This delicate balance is disrupted by estrogen deprivation caused by cancer treatment, resulting in the bone net loss. Androgen deprivation with GnRH analogs or antagonists or surgical castration reduces serum testosterone to <20 ng/mL and estrogen levels by blocking the production of androgens (e.g., testosterone), which are precursors for estrogen biosynthesis via the aromatase pathway. The dysregulation in the RANK ligand pathway causes a subsequent increase in the osteoclast activity and bone resorption, as well as reduced osteoblast activity and bone formation.[28,29] Osteoclast

Turk J Urol 2019; 45(4): 245–53
DOI:10.5152/tud.2019.11736

Table 3. Therapeutic characteristics and methods of FRAX score measuring in previous studies

S. No.	Study	Type of patients	Type of treatment modality	Mean ADT duration	Measurement methods for FRAX or bone health
1.	Saylor et al.[22]	On ADT	GnRH agonist	1.6 Yrs (0–17)	FRAX with CRF FRAX with BMD by DEXA Scan
2.	Adler et al.[14]	Localized prostate cancer	Orchidectomy GnRH agonist and antagonist Androgen antagonist	3.6±3.3 Yrs	T-score versus FRAX
3.	Neubecker et al.[25]	With/without ADT	Orchidectomy GnRH agonist and antagonist Androgen antagonist	16.5 Months	BMD/T-Score/FRAX
4.	Dhanapal et al.[24]	On ADT	LHRH agonists	13.8+18 Months	DEXA Scan
5.	James et al.[13]	On ADT	Orchidectomy GnRH agonist and antagonist Androgen antagonist CYP 17 inhibitor	13 Months	FRAX with BMD, FRAX without BMD, T-Score alone
6.	Valery et al.[26]	On photon radio therapy with/without ADT	ADT and/or EBRT	NA	FRAX using CRF
7.	McDonald et al.[27]	Localized prostate cancer	EBRT	NA	CT-based bone density assessment without BMD
8.	Kawahara et al.[23]	All patients with prostate cancer, excluding CRPC	Brachytherapy Radical prostatectomy EBRT ADT monotherapy Active surveillance	NA	DEXA scan using BMD
9.	Ojeda et al.[17]	High-risk localized prostate cancer	ADT zolendronic acid alendronate	24+6 months	Hologic QDR-4500 DEXA scan using BMD and CRF

FRAX: fracture risk assessment; ADT: androgen deprivation therapy; CRF: clinical risk factors; BMD: bone mineral density; EBRT: external beam radiotherapy; NA: not available; CT: computed tomography

cells erode the trabecular bones, while osteoblast cells form the sclerotic woven bones. Although these generated woven bones appear dense on radiography, these are structurally weak and are associated with more risk of fracture.[28]

Bone metastases manifestations

The most common symptom of skeletal metastases from prostate cancer is pain. The most common site for metastasis is vertebral bodies. Other sites include the pelvis, rib, and long bones.[3] Fracture risk is particularly problematical in these patients given that ADT is the primary modality for metastatic prostate cancer. Optimal bone health is an important consideration and needs widespread awareness among treating urologist. With an increased detection of prostate cancer at an early age and improved longevity of these patients, prevention and management strategies of their skeletal-related complications have become all the more important aspect.[5,10]

Role of BMD (DEXA) in bone health evaluation

Early detection of bone loss in men on ADT helps to select the patients for lifestyle modifications, dietary adaptations, and medical treatment.[30] DEXA scans are usually employed to measure BMD. They use lesser radiation doses than conventional X-ray.[31] In this technology, two X-ray beams are used, which are attenuated differently by bones and soft tissues. Bones are imaged with a high degree of accuracy in the DEXA scan, and thus obtained X-ray images determine the bone mineral content in gm/cm^2 to calculate BMD. The femoral neck BMD is currently recommended as the reference standard bone site for precise BMD measurement because this has been the most widely validated bone site, and it provides a gradient of fracture risk higher than that of several other techniques.[32] BMD measurements are reported as T-score, i.e., the number of standard deviations by which patient's estimated bone loss deviates from the mean of normal population of the same gender at the given site.[33] A T-score of –1 is an indicator of 10%–20% bone loss and increases the relative risk of fracture by 1.5–2 times.

The European Association of Urology (EAU) guidelines recommend that before starting long-term androgen deprivation therapy in patients with prostate cancer, a baseline evaluation of BMD should be performed using a DEXA scan and a deci-

Table 4. Result and conclusion of previous studies related to FRAX in prostate cancer

S. No.	Study	10-year risk of MOF (%)	10-year risk of hip fracture (%)	Comments/conclusion
1.	Saylor et al.[22]	• FRAX using CRF including ADT as secondary osteoporosis-12% • FRAX using CRF excluding ADT as secondary osteoporosis-8.4% • FRAX calculation using femoral neck BMD (with DEXA- 7.0%, without DEXA- 11%)	• FRAX using CRF including ADT as secondary osteoporosis - 3.1% • FRAX using CRF excluding ADT as secondary osteoporosis-1.8% • FRAX calculation using femoral neck BMD (with DEXA- 0.9%, without DEXA- 2.4%)	• The FRAX algorithm identifies greater proportion of candidates for treatment than the T-score alone. • Prevalence of the fracture risk and need for treatment was strongly influenced by advancing age.
2.	Adler et al.[14]	• FRAX with BMD- 8.0±4.9% • FRAX without BMD- 12.3±6.7%	• FRAX with BMD- 1.6±1.7% • FRAX without BMD- 3.8±2.7%	The DEXA and FRAX algorithm identified different populations of men on ADT needing treatment.
3.	Neubecker et al.[25]	• FRAX without BMD-10.8% • FRAX with BMD- 9.5%	• FRAX without BMD- 5.5% • FRAX with BMD- 4.5%	Inclusion of BMD in the FRAX calculation did not affect the predictive ability of FRAX
4.	Dhanapal et al.[24]	MOF-5.6%	Hip fracture risk—2.2%	ADT increases chances of fracture risks, including both MOF and hip fractures.
5.	James et al.[13]	10.0% (Range, 1.7%–24.0%)	4.0% (Range, 0.2%–22.8%)	Prediction of the bone fracture risk: FRAX without BMD > FRAX with BMD > T-score alone
6.	Valery et al.[26]	NA	0.13% (Range, 0%–1.6%)	Photon therapy for prostate cancers did not influence FRAX score or hip fracture risk
7.	McDonald et al.[27]	Not mentioned	1.3% (Range, 0%–22%)	Use of CT-based FRAX may identify additional subjects for pharmacotherapy
8.	Kawahara et al.[23]	7.9% (8.8%±4.3%)	2.7% (Range, 3.5%±3.1%)	Duration-dependent worsening of FRAX scores was seen with ADT.
9.	Ojeda et al.[17]	2.4%±1%	0.7%±1%	The greatest loss of BMD occurred during the 1st year of ADT and was stabilized in the 2nd year.

FRAX: fracture risk assessment; MOF: major osteoporotic fracture; ADT: androgen deprivation therapy; CRF: clinical risk factors; BMD: bone mineral density; NA: not available; CT: computed tomography

sion for follow-up BMD measurements should be based on the value of the initial T-score. For an initial T-score <1.0, the BMD assessments is needed every 2 years. The annual BMD measurement should be done for T-scores between –1.0 and –2.5 in the absence of associated risk factors.[30]

National comprehensive cancer network guidelines for men on ADT

A baseline BMD assessment is done before the initiation of ADT. The 10-year fracture risk is calculated using the FRAX tool; ADT-related osteoporosis is considered secondary under the FRAX algorithm. Recommendations for men with a 10-year absolute risk of ≥3% for hip fracture or 20% or greater for any major osteoporotic fracture are oral calcium (1200 mg) plus vitamin D3 (800–1000 IU) and an antiresorptive therapy, which may include subcutaneous denosumab (60 mg) every 6 months or intravenous zoledronic acid (4 mg) annually, or oral alendronate (70 mg) weekly.[34]

Different methods for assessing the fracture risk

Various methods have been described in literature to assess the fracture risk, and many comparative studies have been conducted with this regard. Even FRAX scores are also calculated into different ways. The following methods can be used to assess the risk of bone fracture:

a) BMD using DEXA,
b) T-score,
c) FRAX using CRF without BMD,
d) FRAX using BMD or T-score,
e) Garvan fracture risk calculator,
f) Computer tomography (CT)-assisted screening,

Role of FRAX and other calculators

Current literature shows that fractures are not unusual in candidates whose BMD or T-score does not suggest the indication for osteoporosis treatment.[9] The FRAX calculator was introduced

Turk J Urol 2019; 45(4): 245–53
DOI:10.5152/tud.2019.11736

by WHO in February 2008 for better predication of the fracture risk by accounting for additional patient characteristics with or without the use of BMD. Currently, this is the most commonly used fracture assessment tool worldwide.[18,22] The application of the FRAX algorithm has been further supported by several associations/foundations including the NOF, International Osteoporosis Foundation, American Society for Bone and Mineral Research, and International Society for Clinical Densitometry.[9,18,22]

Saylor et al.[22] showed that the FRAX model detected a greater number of individuals with prostate cancer at risk for fracture than the BMD alone. They also found an advanced age as one of the most robust risk factors and almost all patients with more than 80 years of age were suitable for treatment. Another study by Adler et al.[14] demonstrated that the FRAX calculation using the femur neck BMD or without BMD detected different populations at risk of fracture. Additionally, low BMD including wrist identified a population that did not overlap well with population found by the FRAX algorithm. One of the explanations for this difference may be that many African-Americans men were included in this cohort, and there is some concern that the FRAX prediction is not so appropriate for men, particularly for African-Americans.[14]

A Garvan-nomogram-based fracture risk calculator (www.fracturerisk calculator.com) is also in common use in the fracture risk assessment in clinical practice. It also incorporates presence of a recent fracture/fall event and total episodes of fractures for risk assessment. While the FRAX algorithm is recommended as the primary tool that can calculate a 10-year fracture risk, the Garvan fracture risk tool calculates both the 5- and 10-year fracture risk probability and has additional benefits in patients with recurrent fractures and falls.[18] However, the CRF for FRAX algorithms are not included in the Garvan risk calculation, so the risk estimate may be low when compared to FRAX in the presence of multiple CRF, and the Garvan calculator is considered to be suitable for patients older than 60 years of age.

Factors affecting FRAX

Advancing age has a deleterious impact on the bone health. The osteoporosis incidence is 13% in Western males >50 years of age and 35% in otherwise healthy males in developing nations.[9] The current literature shows that a total duration of ADT affects the BMD and therefore the FRAX score, while controversies exist about the effect of the mode and type of ADT on FRAX.[23-27] Adler et al.[14] showed that the DEXA and FRAX score identify different candidates that require treatment among patients with prostate cancer on ADT. Neubecker et al.[25] suggested that the inclusion of the BMD for FRAX measurement did not influence the predictive value of the FRAX. James et al.[13] demonstrated that the prediction gradient for fracture risk assessment by various methods in descending order were FRAX without BMD, FRAX with BMD, and T-score alone. Valery et al.[26] in their prospective study found that the photon therapy for prostate cancers did not influence the FRAX score or a hip fracture risk. In summary, the following factors may influence the FRAX scores (Table 4):

- Age, ethnicity, and region,
- Baseline BMD,
- Duration and type of ADT,
- Mode of radiotherapy (brachytherapy/EBRT/proton therapy),
- Presence of CRF,
- Measurement methods: With/without BMD, CT-based.

Clinical risk factors

Large prospective observational studies have identified that the inclusion of both CRF and BMD in the FRAX calculation has a better predictability for a fracture risk than the CRF or BMD alone.[13,22] Advancing age and a previous fragility fracture are the most robust risk factors influencing the FRAX scores.[14,22] These CRF were originally described for postmenopausal osteoporosis FRAX calculation but are now also validated by various studies in patients with prostate cancer. ADT, being an organ transplant recipient, and prolonged immobility are counted as causes of secondary osteoporosis in the FRAX calculation.[13,14,22-27]

Four studies mentioned CRF and their impact on the FRAX score in patients with prostate cancer.[13,17,22,23] Saylor et al.[22] showed that excessive alcohol consumption (11.6%) was the most prevalent CRF in their study cohort followed by a long-term glucocorticoids use (8.3%), parental history of hip fracture (7.4%), smoking (4.7%), and personal history of fracture (2.5%). The prevalence of CRF other than excessive alcohol consumption was less than 10%. Kawahara et al.[23] also demonstrated that daily alcohol consumption of ≥3 units was the most common CRF (31.1%) in their study. Other CRF, in a decreasing order, were a previous fracture (20.9%), current smoking (11.3%), secondary osteoporosis (8.9%), parental history of hip fracture (7.4%), glucocorticoids (3.1%), and rheumatoid arthritis (1.1%). James et al.[13] reported that 7.3% and 16.3% of patients in the study subjects were consuming oral glucosteroids and tobacco, respectively.

Androgen Deprivation Therapy-Mode and Duration

An approximate BMD loss of 2%–8% in the lumbar spine and 1.5%–6.5% in the hip bone within the first year of ADT has been demonstrated by Diamond et al.[31] The average duration of ADT of the included studies in this review was 13 months to 3.6 years (Table 2). The type (medical or surgical), mode (continuous or intermittent and monotherapy or combination therapy) and total duration of ADT and type of radiotherapy (external beam radiotherapy or brachytherapy) may influence bone health and the FRAX score.[32-41] There are inconsistencies in the literature with

this regard. Both intermittent and continuous ADT have an equal impact on the bone loss, and none of them has been found to be superior in one study. Similarly, GnRH agonists with or without anti-androgens use have comparable BMD losses in the same study.[35]

Implication of FRAX in Prostate Cancer

The FRAX score measurement can be performed with CRF alone and with or without the inclusion of the femoral neck BMD or T-score. James et al.[13] performed a study that included 613 patients with prostate cancer on ADT to compare the osteoporotic risk by using the FRAX model with and without BMD and with T-Score. The median duration of androgen deprivation was 13 months (1–72 months). The FRAX score was measured for all subjects without the use of BMD. They found that 61.6% and 2.0% of patients met or exceeded the established treatment risk threshold of 3% for hip fracture and of 20% for MOF without the use of BMD, respectively. The median 10-year hip fracture risk and MOF were 4.0% (0.2%–22.8%) and 10.0% (1.7%–24.0%). The BMD measurement was available for 94 patients with a median T-score of 1.6 (0.3–4.7). When T-score was used alone, 19.1% patients were eligible for bone-tropic therapy. In the same patients, the FRAX model with the use of BMD detected 46.8% of patients eligible for treatment and 69.1% of patients without the use of BMD. Overall, the median 10-year hip FRAX score for all patients measured without the use of BMD was 4.1% (0.1%–19.0%). Therefore, the FRAX algorithm identified more candidates at risk of fracture without BMD than with BMD inclusion. A moderate positive correlation was found between the FRAX score for all patients with and without BMD. The FRAX risk calculation without BMD was most affected by advancing age, followed by FRAX with BMD, and then by T-score (Table 4).[13]

Adler et al.[14] conducted a study of 115 patients with localized prostate cancer on ADT for evaluating the efficacy of T-score versus FRAX score for the fracture risk assessment and showed that when the FRAX calculation incorporated the femoral neck BMD, the mean 10-year hip fracture risk was 1.6%. However, when the FRAX score was measured without the femoral neck BMD, it was 3.8% (i.e., above the 3% treatment threshold). The MOF risk estimation also increased when the femoral neck BMD was not incorporated into the FRAX calculation; however, it did not rise above the 20% risk threshold for hip fracture.

In a cross-sectional study of 363 patients with prostate cancer on ADT by Saylor et al.[22] the median age was 72 years, and the median duration of ADT was 1.6 years (range, 0–17 years). The prevalence of CRFs was <10% in the study subjects, with a 30.8% prevalence of bone metastasis. When the FRAX calculator used clinical information alone (without BMD), the median 10-year risk of the hip fracture was 3.1%, and 51% of patients exceeded the 3% risk threshold for treatment. The median major osteoporotic fracture risk was 12%. A risk of hip fracture accounted for larger number of patients reaching the treatment thresholds than did the major osteoporotic risk (51.2% versus 10.2%). When ADT was excluded as a risk factor for secondary osteoporosis, the estimated median hip fracture risk was 1.8%, and 32.8% of patients still exceeded the 3% risk threshold, while the FRAX algorithm using the BMD data showed that the median hip fracture risk was 0.9% with 15% of subjects exceeding the treatment threshold value. In contrast, the median 10-year risk of hip fracture without using BMD was 2.4%, and 44.1% subjects exceeded the 3% risk threshold. Fracture risk estimates with and without BMD were highly correlated in the study ($r=0.81$; $p<0.0001$). However, the estimated fracture risks were consistently lower when FRAX incorporated BMD data as compared to clinical information alone.

Ojeda et al.[17] conducted a two-phase prospective longitudinal study in 150 high-risk patients with prostate cancer on ADT to evaluate the rate of bone loss and fracture risk prediction with FRAX (Hologic DEXA Scan QDR-4500) at the baseline, 1, 2, and 3 years. Baseline osteoporosis was seen in 41% of patients. The mean duration of ADT was 2 years. The most common CRF were smoking and excessive alcohol consumption. The mean baseline 10-year MOF and hip fracture risk were 2.4% and 0.7%. Approximately, 4% of patients exceeded the risk threshold of 3% for hip fracture and none for MOF. The mean BMD deterioration after the 1st year of ADT was 3.7% and 2.1% in the lumbar spine and femur neck. However, the absolute fracture risk remains low if the androgen deprivation period does not exceed 2 years. Age, FRAX MOF, and hip fracture risk were found to be the independent predictors of bone loss in the lumbar spine in the linear regression model but Gleason score, baseline BMD, serum PSA, and duration of ADT were not found to be the independent predictors of the BMD loss. In this study, bone remodeling serum markers including amino-terminal propeptide of Type I collagen and beta carboxy-terminal telopeptide of collagen I were also evaluated. A significant elevation in markers of bone remodeling were observed after 1 year of treatment and a subsequent decrease after the 2nd year.

CT-based bone density assessment with FRAX screening

CT attenuation values of trabecular bones within the vertebral bodies of the lumbar spines have been illustrated as a method for the bone density assessment. Comparison of the CT attenuation threshold values with DEXA scan as the reference standard for osteoporosis prediction has yielded sensitivities and specificities above 90%.[27] Since CT scans are routinely obtained in men with prostate cancer for making planning of the external beam radiotherapy process, this may serve as an efficient alternative method for screening of osteoporosis without obtaining additional testing.

Turk J Urol 2019; 45(4): 245-53
DOI:10.5152/tud.2019.11736

McDonald et al.[27] performed a retrospective study of 609 patients with localized cancer prostate undergoing external beam radiotherapy. They evaluated the efficiency of a CT-based method of osteoporosis screening to the FRAX without incorporating BMD. The CT attenuation value of the L5 trabecular bone (L5CT) was assessed by contouring the trabecular bone on a single CT section at the mid-vertebral body level and by getting the average in the Hounsfield units (HU) of all included voxels. The L5CT attenuation values of 105 and 130 HU were employed as screening thresholds. The clinical characteristics of additional patients identified by each L5CT screening threshold were compared to patients whose estimated 10-year probability of hip fracture was more than 3% by the FRAX algorithm without using BMD. 74 patients (12.2%) exceeded the estimated 10-year hip fracture risk ≥3%. 22 (3.6%) and 71 (11.6%) additional patients were identified by CT screening methods when 105 HU and 130 HU thresholds were used, respectively. These additional patients identified by CT screening methods were more likely to be African-American, younger, obese, and without ADT. Thus, adding the CT-based screening methods to the FRAX without BMD identifies additional patients with different clinical characteristics.

After reviewing current literature, it can be summarized that despite several well-known strengths and advantages of using FRAX algorithms in the fracture risk assessment in a selected population of patients with prostate cancer, there are several limitations as well. The role of FRAX has not been established in randomized-controlled intervention trials with objectives of fractures prevention in these patients. FRAX does not incorporate several other probable risk factors such as the dose and duration of steroid use, total number and duration of causes of secondary osteoporosis, mode of ADT, vitamin D deficiency, and previous episodes of skeletal-related events. It calculates only the 10-year probability of fracture, while models such as the Garvan additionally calculate the 5-year fracture risk as well. In addition, fall-related risks are excluded explicitly from the FRAX risk measurement. Its utilization is of limited value in the presence of recurrent fractures or falls. Several risk factors that are unique and have significant impact on the bone loss or fracture risk in patients with prostate cancer include the mode and duration of ADT, mode of radiotherapy, vitamin D levels, bone remodeling markers, and recent or recurrent fractures. These factors can be added in FRAX algorithm calculations for a better prediction in prostate cancer patients. Still, the FRAX tool is not widely used by clinical practitioners for prostate cancer management, and further awareness about its role and implications will help in optimizing the bone health and the quality of life.

In conclusion, a prolonged ADT in patients with prostate cancer leads to suboptimal bone health and an increased risk of osteoporosis or fractures and therefore, FRAX. The FRAX algorithm can identify candidates with a high risk of fracture so that an appropriate treatment can be initiated at an early stage. The FRAX score is mostly influenced by an advanced age, ethnicity, duration and the mode of ADT, mode of radiotherapy, and presence of clinical risk factors. Several risk factors need to be added in the future for the FRAX calculation in patients with prostate cancer for a better risk prediction. The FRAX model is still an underutilized modality in clinical practice for prostate cancer management, especially in underdeveloped and developing nations, and further awareness about its role and implication will help in optimizing the bone health and quality of life of this population subgroup.

Peer-review: This manuscript was prepared by the invitation of the Editorial Board and its scientific evaluation was carried out by the Editorial Board.

Author Contributions: Concept – A.S., R.J.S., V.S., G.G.; Design – A.S., R.J.S., V.S., G.G., S.A., S.P.; Supervision – A.S., R.J.S., V.S., G.G., S.A., S.P.; Data Collection and/or Processing – A.S., R.J.S., V.S., G.G., S.A., S.P.; Writing Manuscript – A.S., R.J.S.; Critical Review – A.S., R.J.S., V.S., G.G., S.A., S.P.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Scardino PT. The Gordon Wilson Lecture. Natural history and treatment of early stage prostate cancer. Trans Am Clin Climatol Assoc 2000;111:201-41.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108. [CrossRef]
3. Smith MR, Brown GA, Saad F. New opportunities in the management of prostate cancer related bone complications. Urologic Oncology: Seminars and Original Investigations 2009;27:S1-20.
4. Diefenbach MA, Dorsey J, Uzzo RG, Hanks GE, Greenberg RE, Horwitz E, et al. Decision-making strategies for patients with localized prostate cancer. Semin Urol Oncol 2002;20:55-62. [CrossRef]
5. Pradhan M, Mandhani A, Chipde S, Kumar J, Ansari MS, Srivastava A, et al. Bone mineral densitometry at the time of instituting androgen deprivation therapy in metastatic prostate cancer: Does practice pattern match the guidelines? Indian J Urol 2012:S72.
6. Resnick MJ, Lacchetti C, Bergman J, Hauke RJ, Hoffman KE, Kungel TM, et al. Prostate cancer survivorship care guideline: American Society of Clinical Oncology Clinical Practice Guideline endorsement. J Clin Oncol 2015;33:1078-85. [CrossRef]
7. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc 2006;54:85-90. [CrossRef]
8. Green HJ, Pakenham KI, Headley BC, Gardiner RA. Coping and health-related quality of life in men with prostate cancer ran-

domly assigned to hormonal medication or close monitoring. Psychooncology 2002;11:401-14. [CrossRef]
9. Physician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation; Washington D.C.: 2008.
10. Saylor PJ, Smith MR. Bone health and prostate cancer. Prostate Cancer Prostatic Dis 2010;13:20-7. [CrossRef]
11. Prakash G, Gautam G. Optimal bone health management strategies in patients with prostate cancer. Indian J Urol 2013;29:89-99. [CrossRef]
12. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-64. [CrossRef]
13. James H 3rd, Aleksic I, Bienz MN, Pieczonka C, Iannotta P, Albala D, et al. Comparison of fracture risk assessment tool score to bone mineral density for estimating fracture risk in patients with advanced prostate cancer on androgen deprivation therapy. Urology 2014;84:164-8. [CrossRef]
14. Adler RA, Hastings FW, Petkov VI. Treatment thresholds for osteoporosis in men on androgen deprivation therapy: T-score versus FRAX. Osteoporos Int 2010;21:647-53. [CrossRef]
15. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology 2007;69:500-4. [CrossRef]
16. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581-9 [CrossRef].
17. Ojeda S, Lloret M, Naranjo A, Déniz F, Chesa N, Domínguez C, Lara PC. Androgen deprivation in prostate cancer and the long-term risk of fracture. Actas Urol Esp 2017;41:491-6. [CrossRef]
18. Van den Bergh JP, van Geel TA, Lems WF, Geusens PP. Assessment of individual fracture risk: FRAX and beyond. Curr Osteoporos Rep 2010;8:131-7. [CrossRef]
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
20. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
22. Saylor PJ, Kaufman DS, Michaelson MD, Lee RJ, Smith MR. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. J Urol 2010;183:2200-5. [CrossRef]
23. Kawahara T, Fusayasu S, Izumi K, Yokomizo Y, Ito H, Ito Y, et al. Bone management in Japanese patients with prostate cancer: hormonal therapy leads to an increase in the FRAX score. BMC Urol 2016;16:32. [CrossRef]
24. Dhanapal V, Reeves DJ. Bone health management in prostate cancer patients receiving androgen deprivation therapy. J Oncol Pharm Pract 2012;18:84-90. [CrossRef]
25. Neubecker K, Adams-Huet B, Farukhi IM, Delapena RC, Gruntmanis U. Predictors of fracture risk and bone mineral density in men with prostate cancer on androgen deprivation therapy. J Osteoporos 2011;2011:924595. [CrossRef]
26. Valery R, Mendenhall NP, Nichols RC Jr, Henderson R, Morris CG, Su Z, et al. Hip fractures and pain following proton therapy for management of prostate cancer. Acta Oncol 2013;52:486-91. [CrossRef]
27. McDonald AM, Jones JA, Cardan RA, Saag KS, Mayhew DL, Fiveash JB. Combining computed tomography-based bone density assessment with FRAX screening in men with prostate cancer. J Clin Densitom 2016;19:430-5. [CrossRef]
28. Clarke NW, McClure J, George NJ. Osteoblast function and osteomalacia in metastatic prostate cancer. Eur Urol 1993;24:286-90. [CrossRef]
29. Ibrahim T, Flamini E, Mercatali L, Sacanna E, Serra P, Amadori D. Pathogenesis of osteoblastic bone metastases from prostate cancer. Cancer 2010;116:1406-18. [CrossRef]
30. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Actas Urol Esp 2011;35:565-79. [CrossRef]
31. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer 2004;100:892-9. [CrossRef]
32. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone 2008;42:467-75. [CrossRef]
33. Garg MK, Kharb S. Dual energy X-ray absorptiometry: Pitfalls in measurement and interpretation of bone mineral density. Indian J Endocrinol Metab 2013;17:203-10. [CrossRef]
34. Yu EY, Gillessen S, Mottet N. What Do the Guidelines Say for Metastatic Prostate Cancer Starting Androgen Deprivation Therapy? National Comprehensive Cancer Network, European Society for Medical Oncology, and European Association of Urology recommendations. Eur Urol Focus 2018; pii:S2405-4569(18)30287-6.
35. Kiratli BJ, Srinivas S, Perkash I, Terris MK. Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. Urology 2001;57:127-32. [CrossRef]
36. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol 2017;71:630-42. [CrossRef]
37. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-55. [CrossRef]
38. Gillessen S, Omlin A, Attard G, de Bono JS, Efstathiou E, Fizazi K, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol 2016;pii: mdw180.
39. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-68. [CrossRef]
40. Kapoor A, Gupta A, Desai N, Ahn H. Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog. Prostate Cancer 2011;2011:176164. [CrossRef]
41. Schulman C, Irani J, Aapro M. Improving the management of patients with prostate cancer receiving long-term androgen deprivation therapy. BJU Int 2012;109(Suppl 6):13-21.