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Results of Genetic Diagnosis and FRAX Model *vs* Results of DEXA (1-0)

Eiman Shahrour[1*], Bassel Al-Halabi[2], Walid Al-Achkar[2], Abd Alrazak Hassan[3] and Haissam Yazigi[4]

[1]Department of Biochemistry and Microbiology, Faculty of Pharmacy, Tishreen University, Ministry of High Education, Lattakia, Syria

[2]Department of Molecular Biology and Biotechnology, Human Genetics Division, Atomic Energy Commission, Damascus, Syria

[3]Department of Internal Medicine, Faculty of Medicine, Tishreen University, Ministry of High Education, Lattakia, Syria

[4]Department of Laboratory Diagnosis, Faculty of Medicine, Tishreen University, Ministry of High Education, Lattakia, Syria

[*]**Corresponding author:** Eiman Shahrour, Department of Biochemistry and Microbiology, Faculty of Pharmacy, Tishreen University, Ministry of High Education, Lattakia, Syria. E-mail: eimanm.shahrour@gmail.com

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Abstract

Objectives: The definition, diagnosis and treatment plans for osteoporosis and osteopenia are defined on the basis of assessment of bone mineral density by dual-band X-ray absorptiometry. However, this method faces many limitations and challenges. The main difficulty in assessing fracture risk is that while this threshold is High passivity, but low sensitivity, so that the majority of fragility fractures occur in individuals with BMD values above the osteoporotic threshold. These limitations necessitated the search for alternative solutions of better quality, including radiological, genetic, and applications of more risk factors in the fracture risk assessment (FRAX). In fact, FRAX was more consistent with the clinical diagnosis than DEXA. Genetic diagnosis has not been decided yet, but it has a clear role. But the matter is not settled so far, and the clinical diagnosis remains the reference standard for diagnosis and therapeutic intervention, and FRAX is an aid to confirm this diagnosis. The genetic factor is an important factor.

Methods: This study includes two clinical cases from Tishreen University Hospital patients. Clinical history was taken. DEXA imaging, genetic diagnosis-LRP5rs121908669, COL1A2rs72658152 mutations were analyzed by RFLP, DNA sequencing-, FRAX application were applied.

Results: The results of DEXA conflict with the clinical diagnosis, while the results of FRAX agree with the clinical diagnosis. This requires more studies for comparing the results of FRAX with the results of DEXA on a larger scale of samples. Genotypes of LRP5G171R agree with the FRAX results but vary with DEXA radiographic findings.

Conclusion: FRAX application results are more compatible with genetic and clinical diagnosis than radiographic diagnosis DEXA.

Keywords: FRAX; DEXA; T-score; Challenges of assessment osteoporosis; Genetics in osteoporosis; LR5G171R genotypes

Introduction

Assessment of Bone Quantity: Bone Mineral Density and T-score:

In 1994, the World Health Organization (WHO) developed a definition of osteoporosis on the basis of studies of women of various ages [1,2]. Bone mineral density (BMD), measured with dual x-ray absorptiometry (DEXA), is expressed in absolute terms as grams of mineral per square centimeter scanned (g/cm2). A patient's bone mineral density can also be related to a reference value for young normal adults of the same sex by using the T-score. The T-score is reported as the number of standard deviations that a patient's bone mineral density value is above or below the reference value for a healthy thirty-year-old adult. This definition became widely used, and osteoporosis was subsequently defined by the standard deviation rather than by an absolute value of bone mineral density. The World Health Organization T-score cutoff value for osteoporosis is -2.5. Fracture risk increases approximately twofold for every standard deviation below the mean for a young adult [1,3,4]. Therefore, low bone mineral density remains a strong predictor of future fracture risk. Although measurement of bone mineral density with dual x-ray absorptiometry is the so-called gold standard for diagnosis of osteoporosis, it has some limitations. First, dual x-ray absorptiometry provides a two-dimensional projection of a three-dimensional structure and cannot capture three-dimensional bone geometry or microarchitecture. Thus, the bone mineral density values obtained with dual x-ray absorptiometry do not represent true volumetric bone mineral density but rather a projected areal bone mineral density. Second, Increased bone mineral density due to thickening of the bones (geometrical change) and those resulting from increased tissue mineral density (material change) cannot be distinguished from each other using DEXA because dual X-ray absorptiometry does not take into account the differences in bone volume between individuals. Third, Soft tissue calcifications may affect the scans used. Fourth, BMD is not successful in monitoring treatment because changes in BMD are slow. The differences resulting from the use of medications may not be revealed until several years after the treatment of osteoporosis [1,5,6]. Fifth, T-scores are not reliable indicators of fracture risk in premenopausal women, younger men, and children. Sixth, Bone strength is now understood to depend on factors besides bone mineral density, sometimes causing discordance between DEXA results and true fracture risk [7]. Seventh, the major problem in DEXA is that BMD gives only an idea about the strength of the bone by measuring the density of mineral components especially CaCO3 and Ca3(po4)2. But BMD gives no idea about collagen which is the main responsible for bone flexibility. So, BMD and T-score give us an incomplete picture about the safety of the bone. And that can be a justification for conflicting cases with WHO osteoporosis definition especially It is axiomatic that we need a tool give us a whole look for strength and flexibility of the bone which are responsible for bones 'integrity as the same importance [8].

While DEXA is the gold standard test for measuring bone density, clinical judgment should take precedence if results contradict clinical information, especially with these challenges facing DEXA [7]. The aim is to provide threshold values for these screening indices to help health care providers refer patients for DEXA scans so that osteoporosis can be detected efficiently and early [9].

The Fracture Risk Assessment Tool (FRAX):

The principal aim of treatments for osteoporosis is to decrease the risk of fragility fractures. Thus, the ability to assess fracture risk is critical in identifying patients who are eligible for therapeutic intervention [10-12].

Several clinical factors are associated with a fracture risk that is greater than what can be accounted for by bone mineral density alone [1,13]. Fracture risk assessment, therefore, they should employ specific risk factors in addition to bone mineral density. For example, age is a powerful independent risk factor that has largely been ignored in previous clinical guidelines. In women with a T-score of -2.5, the probability of hip fracture is five times greater at the age of eighty years than it is at the age of fifty years [1,14]. Thus, fracture risk can be assessed more accurately by considering Age and BMD together can give us a more accurate result than a BMD in case of an assessment of fracture risk [1,15].

Because of the limitations of dual x-ray absorptiometry, efforts have been made to formulate a system to better predict fracture risk. On the basis of a series of meta-analyses undertaken to identify clinical risk factors for osteoporosis, the Fracture Risk Assessment Tool (FRAX) was developed [1,16,17]. FRAX, released in 2008 by the World Health Organization, was developed and validated under the direction of Professor John Kanis, Sheffield University, with the support of many individuals and organizations including the American Society for Bone and Mineral Research, the National Osteoporosis Foundation, the International Society for Clinical Densitometry, and the International Osteoporosis Foundation. FRAX is currently available online at www.shef.ac.uk/ FRAX [1,16,18] (Figure 1). The aim of FRAX is to provide an assessment tool for the prediction of fractures in men and women with use of clinical risk factors with or without femoral neck bone mineral density. These clinical risk factors include age, sex, race, height, weight, body mass index, a history of fragility fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake of three or more units daily [1,14,19-21].

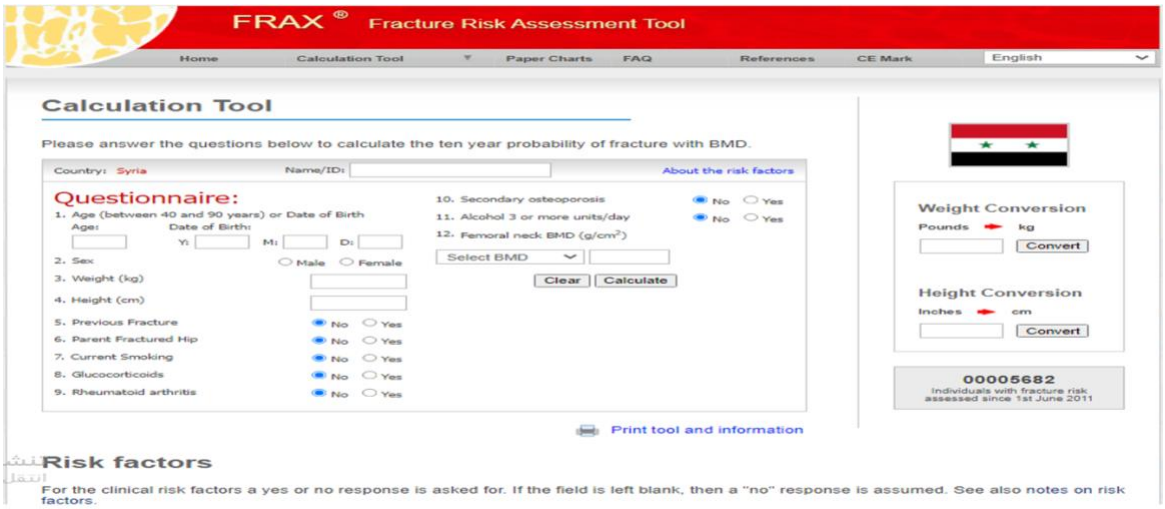

Figure 1: Image of FRAX_ web page (http://www.shef.ac.uk/FRAX) showing the chart for input of data and format of results in the Syrian version of the FRAX_ tool. (Printed with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. FRAX_ is registered to Professor J.A. Kanis, University of Sheffield).

FRAX calculates the ten-year probability of a major osteoporotic fracture (in the proximal part of the humerus, the wrist, or the hip or a clinical vertebral fracture) and of a hip fracture calibrated to the fracture and death hazards [1,14,19]. The initial FRAX model required a T-score calculated by means of a so-called FRAX patch [1,22]; however, in February 2009, FRAX was revised so that clinicians could either enter T-scores or select the manufacturer of the densitometry equipment (such as Hologic, GE Lunar, or Norland) and enter the femoral neck bone mineral density in grams per square centimeter. It is not possible to neglect the geographical area of the individual, as the probability of the fracture is noticeable between the different regions of the world [1,23].

Fracture probability differs markedly within and across regions of the world [10,24,25], and thus FRAX models are calibrated to the epidemiology of fracture and mortality in individual countries. Models are currently available for 73 nations or territories, covering more than 80% of the world population included Syria [26]. The FRAX website (http://www.shef.ac.uk/FRAX) receives approximately 3million visits annually, and the tool is available in 35 languages. Website usage markedly underestimates the uptake of FRAX since this is not the sole portal for the calculation of fracture probabilities using the FRAX tool. For example, FRAX is available in BMD equipment, on smartphones and, in some countries, through hand-held calculators. However, access to the website provides a good overview of global usage of the tool [27,28]. The use of FRAX in assessment guidelines FRAX has been incorporated into more than 80 guidelines worldwide [29], although the nature of this application has been heterogeneous. Several guidelines have adopted FRAX into pre-existing guidelines [30,31].

The latest international guidelines in the management of osteoporosis, which integrates the results of DEXA and FRAX to reach the best diagnosis and the best therapeutic plans. However, it is not yet approved by the World Health Organization [32].
Bone strength is now understood to depend on factors besides bone mineral density, sometimes causing discordance between DEXA results and true fracture risk. The Fracture Risk Assessment Tool incorporates clinical factors and can help guide treatment decisions. New technologies directed at bone microarchitecture may one day improve risk analysis [7]. Indeed, there are limitations to FRAX, but it is a state-of-the-art method for evaluating osteoporosis. Therefore, the clinical diagnosis remains crucial [1,10].

Genetic Assessment in Osteoporosis:

Genetic diagnosis of osteoporosis is a real scientific revolution. There are thousands of point mutations implicated in osteoporosis. The future hope is to find a genetic diagnostic method for osteoporosis. This is very necessary because the treatments currently used are to delay the progression of osteoporosis, and therefore an earlier intervention will be effective. In addition, it serves the future prospects for gene therapy for osteoporosis [33]. Abnormal genotyes of LRP5G171R are risk factors related to osteoporosis and osteopenia. Normal genotype GG increase the likelihood of normal femur BMD. homozygous genotype CC and heterozygous GC genotype increase the likelihood of osteoporosis or osteopenia in femur bone. There are often associations in the distribution between carriers of GC or CC and carriers with osteoporosis or osteopenia in femur bone [34].

Aim of the Study:

The aim of the study is a local medical service goal to keep pace with developments regarding the assessment of fracture risk using FRAX -Especially this application has a special tool for Syria. Study the relationship between FRAX results,DEXA results, results of genetic analysis, clinical study results. The genetic factor may be added as a risk factor in the FRAX application questionnaire after conducting confirmed studies on a larger scale, who know?

Materials and Methods:

The study included 2 participant cases who visited rheumatology clinic at Tishreen University Hospital, Lattakia, Syria. The work was approved by the Ethics Committee in Syrian Ministry of High Education and written informed consent was obtained from the participants. The participants were interviewed with a structured questionnaire. The contents of the questionnaire included socio-demographic characteristics, work habits, physical activity, and medication history, as well as starting and onset of menstrual, pregnancy and number of children, History of family orthopedic complaint. Height and weight were measured by the investigator using professional medical scales, body mass index (kg/m2) was calculated. The participants were women with per-menopause or post-menopause. They were from different families. Blood phosphorous and calcium analyzes were measured. LRP5rs121908669, COL1A2rs72658152 mutations were analyzed by RFLP, DNA sequencing. The bone mineral density (BMD; g/cm2) of the lumbar spine (L1-L4) and left femur as measured by dual energy X-ray absorptiometry (DEXA) (Medix DR, france), in the Department of Radiology, Tishreen University Hospital. The DEXA scans were conducted by a specially trained specialist. BMD Results were converted to age- and gender-specific Z-score matched normal Caucasians. The samples were classified according to the World Health Organization classification of T-score values.

Participants were assessed using the FRAX questionnaire for age, race, sex, history of previous fractures, family history of hip fracture in a parent, glucocorticoid use (equivalent to ≥5mg of prednisolone for ≥3 months), current smoking, rheumatoid arthritis, risk for secondary osteoporosis (history of type 1 diabetes mellitus, osteogenesis imperfecta, long-standing untreated hyperthyroidism, menopause at <45 years of age, chronic liver disease, long-standing malnutrition), and alcohol intake (≥3 units/ day).

DEXA Evaluation Standard WHO: Cases that are normal are T-SCORE ≥1 in femur or spine region, osteopenia -2.5 <T-SCORE <-1, osteoporosis ≥-2.5.

FRAX Evaluation Standard: Cases in risk of fractures and need treatment are with Major osteoporotic ≥20% Hip Fracture ≥3%.

Results and Discussion:

This is the first study of its kind with regard to comparing the evaluation of cases using DEXA and FRAX among the Syrian people. The following illustrated cases commonly encountered challenges if the DEXA data and clinical presentation are incongruous.

Case 1: A Postmenopausal Woman with Normal T-scores and Fractures

A 75-year-old woman. She is Caucasian. The complaint is a fracture of her wrist after a simple trauma. She suffered consecutive fractures after simple injuries. She has arterial hypertension. Her menstruation stopped at the age of 50 years old and started at the age of 14 years old. She has 5 children. She lives in the city and work as a housewife. She is 166 cm tall, weighs 70 kgs, and BMI is 25.40kg/m2. She is non-smoker and non-alcoholic. Her sisters have history of osteoporosis. She suffers untreated rheumatoid arthritis. She doesn`t have any cause for secondary osteoporosis. She is a carrier of the heterozygous GA and has normal genotype of COL1A2rs72658152*. Calcium and phosphorous in the blood are normal. Neck left femur T-score is -1.0 and -1.4 for total hip, L1-L4 T-score is -0.6 (Figure 2).

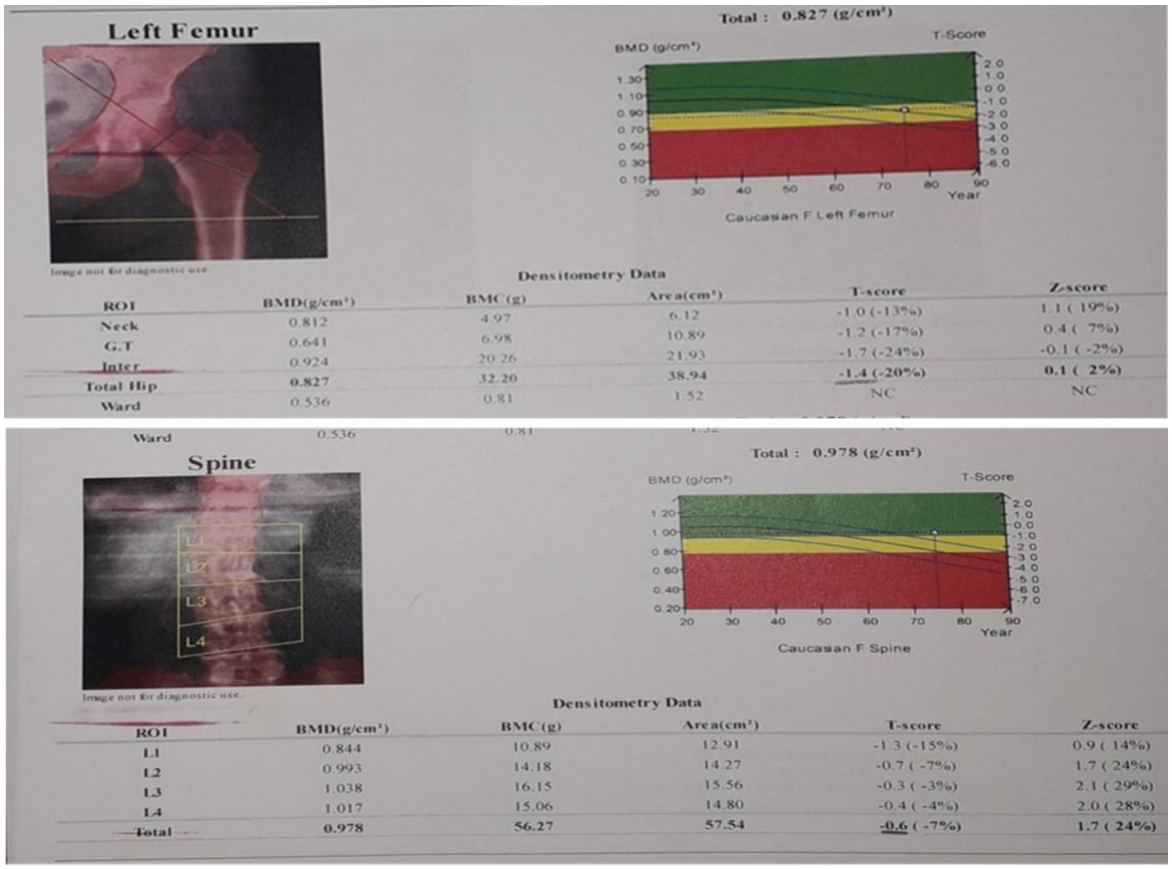

Figure 2: BMD profile of a 75-year-old woman with consecutive fractures disproportionate to near-normal T-score values.

Evaluation of the case according to the results of DEXA is, osteopenia in the femoral region and normal in the lumbar region. Clinical evaluation is done by an orthopedist with over 25 years of experience, based on clinical diagnosis. The case is diagnosed as hyperostosis and requires a different treatment intervention according to the results of DEXA, which is the same assessment according to the FRAX tool. Major osteoporotic is 20 and Hip Fracture is 9.7 (Figure 3).

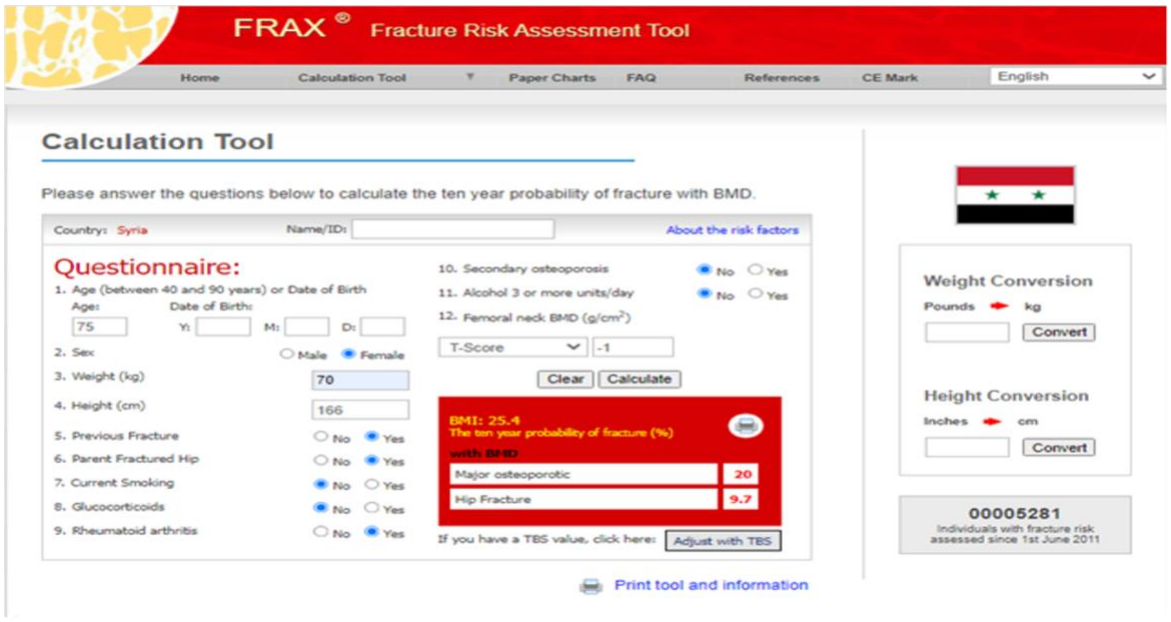

Figure 3: FRAX results with Major osteoporotic is 20 and Hip Fracture is 9.7 for a 75 year-old woman with consecutive fractures disproportionate to near-normal T-score values.

Case 2: A Young Woman with Osteoporosis According DEXA

A 45-year-old woman suffering from menstrual disorders. Joint pain is the reason to request a BMD scan. She is Cuacasian, Unmarried. Her menstrual period started at the age of 13. She lives in the city and works is an office. Its length is 160 cm, Weight 77kg. BMI is 30.08kg/m2. For the FRAX questions, there are no previous fractures, and no family history of osteoporosis. She does not take any glucocorticoid drugs. She is non-alcoholic, but a smoker. There is no cause for secondary osteoporosis. She does not suffer from rheumatoid arthritis. She is generally in good health and blood tests are normal. She has a normal genotype GG of LRP5rs121908669 and normal genotype of COL1A2rs72658152*. Calcium and phosphorous in blood are normal.*. The values of total femoral T-score is -0.1 and -0.5 for neck femoral T-score, total lumbar T-score is -2.9 (Figure 4). The values indicate that osteoporosis is present and requires treatment according to the DEXA results. The clinical diagnosis is that there is no osteoporosis. The results of FRAX also show that there is no osteoporosis. Major osteoporotic 0.4 Hip Fracture 0.0 (Figure 5).

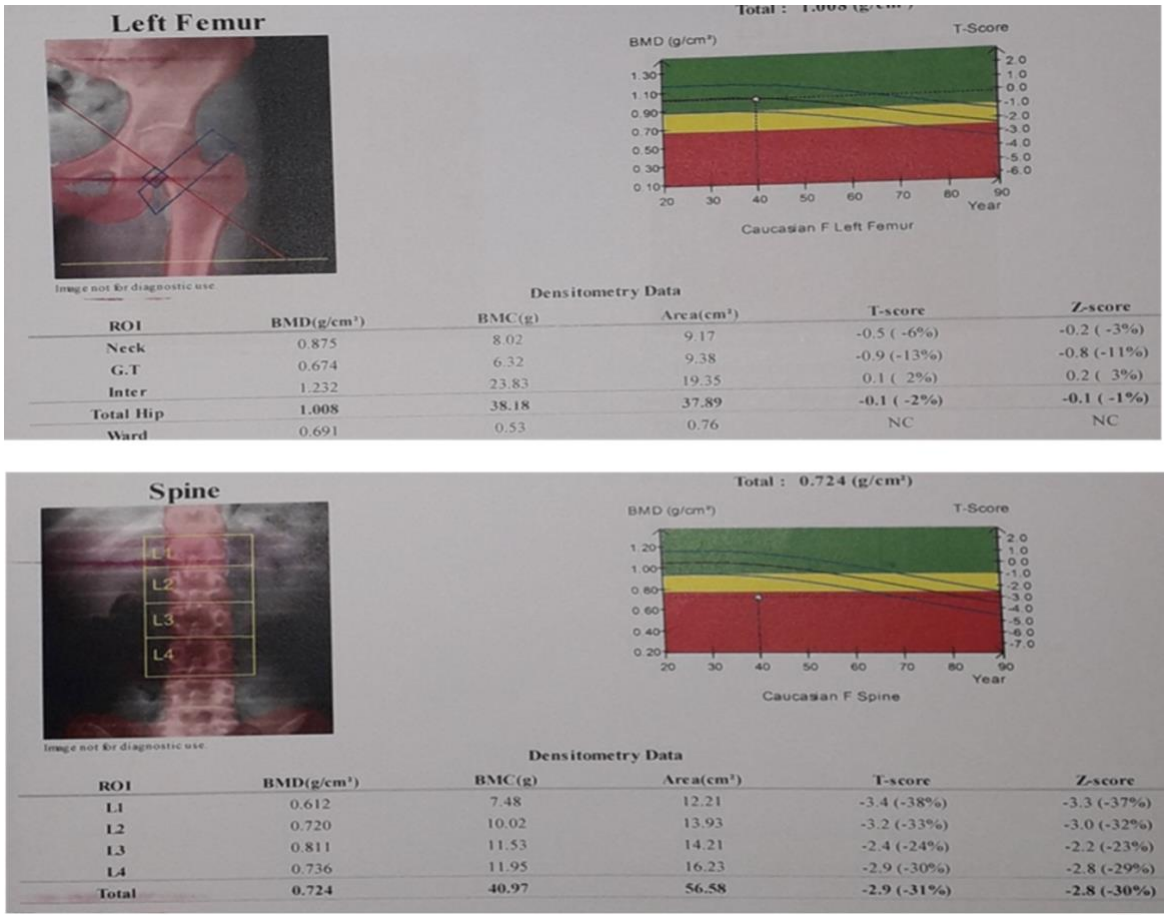

Figure 4: BMD profile of a 45-year-old fracture-free woman with T-score values in osteoporosis.

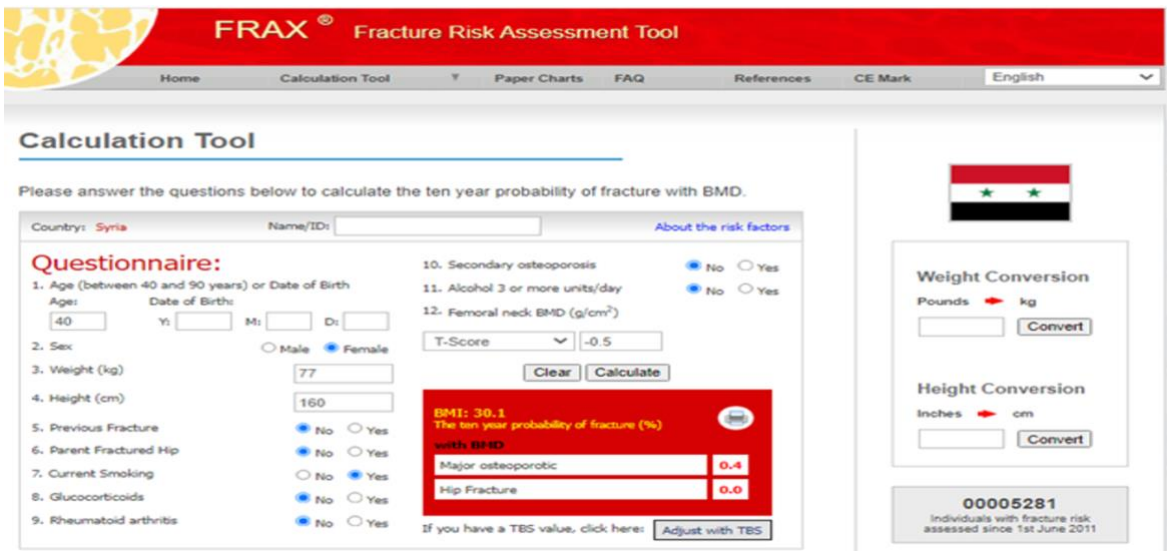

Figure 5: FRAX results with Major osteoporotic is 0.4 and Hip Fracture is 0.0 of a 45-year-old, fracture-free woman with T-score values in osteoporosis.

Scientific advances have brought about a more complex understanding of the relationships between fracture risk, bone strength, and bone density. T-scores do not always correlate with fracture risk or even with a patient's history of fracture and hence can be misinterpreted, leading to inappropriate treatment recommendations. A T-score should not solely determine diagnosis and treatment, and clinical data should appropriately modify the interpretation of results. Studies indicate that FRAX: The most important risk calculator is better than DEXA for assessing bone condition [7].

Bone mineral density cannot be used as the sole predictor of bone strength; <50% of the variation in whole-bone strength is attributable to variations in bone mineral density [35,36]. In fact, the majority of patients who sustain fragility fractures have a T-score above -2.5 [37,38]. The National Osteoporosis Risk Assessment study revealed that 82% (1852) of 2259 postmenopausal women with a fracture after one year of follow-up had a T-score above -2.5 and 67% (1514) had a T-score of greater than -2.0 as measured with peripheral densitometry [37]. Similarly, in a Rotterdam study of 7806 individuals fifty-five years of age or older, 56% (280 of 499) of the nonvertebral fractures in the women and 79% (115 of 145) in the men were in individuals with a T-score in the osteopenic range (between -1.0 and -2.5) [39].

Assess patients using DEXA and FRAX. These are still the major tools for assessing fracture risk. However, their results should not be regarded as absolute. The practitioner, not the technology, is the final arbiter for diagnosing disease [7].

Conclusions and Recommendations

LRP5G171R genotying agree with the FRAX results. FRAX model(https://www.sheffield.ac.uk/FRAX/) must be more active in the assessment of cases in orthopedic and rheumatology clinics in government and private hospitals and private clinics in Syria. Especially, there is a calculation tool for Syria within the application (Figure 1). It is also approved in all countries of the world and some Arab countries. More global attention to genetic diagnosis.

More studies are required as comparative studies between the results of DEXA and the results of FRAX on a larger scale than as clinical cases and link it with genetic and clinical diagnosis. Nowadays, Clinical diagnosis is the reference standard for the diagnosis of osteoporosis. The discrepancy between the results of DEXA and the results of FRAX requires observational studies of the same cases over a period of years to verify the validity of their results.

*This case is one of the participants in a genetic study on osteoporosis. During which two mutations proven pathogenic for osteoporosis were studied, one of them is LRP5rs121908669, which leads to osteoporosis associated with normal blood tests for calcium, phosphorus, high or normal T-score (HBM).

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Authors Contributions

Conceptualization: Eiman Shahrour, Haissam Yazigi and Abd Alrazak Hassan.

Methodology: Eiman Shahrour, Haissam Yazigi, Abd Alrazak Hassan, Walid Al-Achkar and Bassel Al-Halabi

Validation: Haissam Yazigi, Abd Alrazak Hassan, Walid Al-Achkar and Bassel Al-Halabi.

Investigation: Eiman Shahrour and Bassel Al-Halabi.

Writing-Review and Editing: Eiman Shahrour, Haissam Yazigi Abd Alrazak Hassan and Walid Al-Achkar.

Visualization: Haissam Yazigi and Abd Alrazak Hassan.

Supervision: Haissam Yazigi and Abd Alrazak Hassan

Project Administration: Walid Al-Achkar, Abd Alrazak Hassan and Haissam Yazigi.

Software, Formal Analysis, Resources, Data Curation, Writing-Original Draft Preparation, Funding Acquisition: Eiman Shahrour.

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