"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE –A HOSPITAL BASED CROSS SECTIONAL STUDY"

BY

REGISTRATION NO. BL0120010

Dissertation

Submitted to the

KLE ACADEMY OF HIGHER EDUCATION & RESEARCH

(Deemed-to-be-University)

Belagavi, Karnataka

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

ORTHOPAEDICS

DEPARTMENT OF ORTHOPAEDICS

J. N. MEDICAL COLLEGE

BELAGAVI- 590010. KARNATAKA

JUNE/JULY 2023

KLE Academy of Higher Education & Research

(Deemed-to-be-University)

Belagavi, Karnataka

Endorsement by the HOD/ Principal/ Head of the Institution

This is to certify that the dissertation entitled **"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE –A HOSPITAL BASED CROSS SECTIONAL STUDY"** is a bonafide research work done by **REGISTRATION NO. BL0120010** Department of Orthopedics, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi-590010

Dr. Ravi S. Jatti
M.S.(ORTHO)
Professor and Head,
Department of Orthopaedics,
KAHER, J. N. Medical College,
590010 Nehru Nagar, Belagavi – 590010

Date:

Place: Belagavi

KAHER BELAGAVI J.N. MEDICAL COLLEGE

Dr. N. S. Mahantashetti.
MD PEDIATRICS
Principal,
KAHER, J.N. Medical College,
Nehru Nagar, Belagavi,

PRINCIPAL
J.N. Medical College,
BELAGAVI- 590 010

Date:

Place: Belagavi

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 40 **Date: 25/01/2021**

To,

Dr. Subhash Bose S
PG student in Orthopaedics,
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE – A HOSPITAL BASED CROSS SECTIONAL STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH

JAWAHARLAL NEHRU MEDICAL COLLEGE

(Recognized by Medical Council of India, New Delhi)

Accredited 'A+' Grade by NAAC (3rd Cycle) **Placed in Category 'A' by MHRD (GoI)**

Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 13-12-2022.

ACCEPTANCE LETTER

The softcopy of thesis entitled: **"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE –A HOSPITAL BASED CROSS SECTIONAL STUDY"** has been submitted for Anti-Plagiarism check through Turnitin software. The scan has been carried out and the scanned output reveals a match percentage of **05%** which is within the acceptable limits of **10%** as per the guidelines given by UGC.

Guide.

KAHER BELAGAVI J. N. MEDICAL COLLEGE

Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BL0120010,
Postgraduate Student,
2020-21 Batch,
Department of Orthopaedics,
J. N. Medical College, Belagavi.

UNDERTAKING

[Reg No. BLO120010], hereby declare that the information and the data mentioned in my dissertation entitled **"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE –**
A HOSPITAL BASED CROSS SECTIONAL STUDY" belongs to me and is original. I am aware of the definition of plagiarism as detailed below.

- An act or instance of using or closely imitating the language and thoughts of another author without authorization and the representation of that authors works one's own, as by not crediting the original author.
- A piece of writing or other work reflecting such unauthorized use or imitation.
- The deliberate or reckless representation of another's words, thoughts or ideas as one's own without attribution in connection with submission of academic work, whether graded or otherwise.

I hereby declare that the dissertation prepared by me is original one and does not involve plagiarism anywhere. In case at a later stage, it is founded that I have indulged in plagiarism, than I am solely responsible for the same and the institution is at liberty to take any disciplinary action against me including cancellation of dissertation or any other penalties imposed by the university.

Date 03/01/2023

Place: Belagavi REG NO: BLO120010

LIST OF ABBREVIATIONS USED

Abbreviation	Expansion
ADOPT	A Diabetes Outcome Progression Trial
AGEs	Advanced Glycation End Products
AR	Absolute Risk
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed tomography
DEXA/ DXA	Dual-energy X-ray absorptiometry
DM	Diabetes Mellitus
HR	Hazard's Ratio
HR pQCT	High-Resolution Peripheral Quantitative Computed Tomography
IGF	Insulin like Growth Factor
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
QUS	Quantitative ultrasonography
RH	Relative Hazard
RR	Relative Risk
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
WHI	Women's Health Initiative
WHO	World Health Organisation

ABSTRACT

TITLE: "ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE –A HOSPITAL BASED CROSS SECTIONAL STUDY"

Introduction: The likelihood of fracture over a given time period can be expressed using a fracture risk assessment tool like FRAX. Type 2 diabetes mellitus (T2DM) constitutes more than 95% of all population with diabetes mellitus in India. Diabetes is not presently a risk factor in the FRAX algorithm. Diabetics certainly have a higher fracture risk, but there is still no risk categorization for these patients.

Objective: The present study was carried out with an aim to assess the use of WHO FRAX score in diabetic patients and to compare the fracture risk between diabetic and healthy population using FRAX score.

Methodology: The study was undertaken as a hospital based cross sectional study of 82 patients in either sex aged 40 to 80 years in a tertiary care teaching hospital in Belagavi, Karnataka during the period Jan 2021 to Oct 2022. Simple random sampling technique was used to select study part cipants. Patients were evaluated using DEXA scan. Statistical analysis: The chi square test was used to determine the statistical significance of the proportional difference. Statistics were considered significant at a p value of 0.05.

Results: Maximum of the study participants were in the age group of 61-70 years (37.8%) and females (80.5%). Maximum of the study participants had osteopenia (45.1%) and nearly one third had osteoporosis (29.3%) as per BMD T score classification at femoral neck. A

statistically significant association was observed between history of diabetes mellitus and history of previous fracture (p value <0.001), and history of parent hip fracture (p value -0.020). Higher proportion of patients in older age groups had osteoporosis, while higher proportions in the age group of 51-60 years had osteopenia (p value -0.026). Higher proportion of females had osteopenia and osteoporosis as compared to males (p value - 0.045). Significantly higher proportion of patients with history of diabetes mellitus had osteopenia and osteoporosis (p value <0.001), history of previous fracture (p value <0.001), and history of parent hip fracture (p value -0.043). Significant association was observed between FRAX score for hip fracture & osteoporotic fracture and presence of osteoporosis as per BMD T score classification (p values <0.001). Higher proportion of patients with history of diabetes mellitus had a very high risk of osteoporotic fracture and hip fracture as per FRAX classification (p values <0.001).

Conclusion: Significant association was observed between FRAX score for hip fracture & osteoporotic fracture and presence of osteoporosis. Diabetes mellitus was found to be a risk factor for osteoporosis and impacted the FRAX score of the patients.

KEYWORDS:

Osteoporosis, Type 2 Diabetes Mellitus, DEXA, FRAX

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

Diabetes Mellitus:

A clinical illness known as diabetes mellitus is defined by hyperglycemia brought on by an absolute or relative lack of insulin. Depending on the etiology of the Diabetes mellitus (DM), factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dys-regulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Changes in lifestyle, unhealthy habits of consumption of high energy foods, reduced physical activity and stress were considered to the important factors driving epidemic of diabetes mellitus worldwide. Type 2 diabetes mellitus constitutes more than 95% of all population with diabetes mellitus in India.

Bone Mineral Density:

Bone turnover is slowed down, and its material qualities and microstructure are modified; the latter is especially true in people with diabetes mellitus who have microvascular problems. The complex pathophysiological mechanisms underlying bone fragility in diabetes mellitus are complex, and include hyperglycemia, oxidative stress and the accumulation of advanced glycation end products that compromise collagen properties, increase marrow adiposity, release inflammatory factors and adipokines from visceral fat, and potentially alter the function of osteocytes. Additional factors contributing to reduced bone mineral density includes treatment-induced hypoglycemia, certain antidiabetic medications with a direct effect on bone and mineral metabolism such as thiazolidinedione), as well as an increased propensity for falls, all contribute to the increased fracture risk in patients with diabetes mellitus.

In 2000, there were 1.4 million clinical vertebral fractures, 1.6 million hip fractures, 1.7 million forearm fractures, and an approximated nine million osteoporotic fractures

globally.[3] The mortality rate is elevated by 10 to 20 percent in cases of hip and spine fractures.[4] Fractures can lead to persistent discomfort, sadness, loss of independence, as well as a restriction on mobility.[5,6]

Bone mineral density (BMD), bone geometry (shape and size of the bone), level of mineralization, microarchitecture, & bone turnover are factors that affect bone strength. Many patients have access to BMD measurements, and research has shown that when BMD declines, the risk of fracture rises.[7] Methodologies like double tetracycline-labeled transiliac bone biopsy with histomorphometry, high-resolution peripheral quantitative computed tomography (HR-pQCT), high-resolution magnetic resonance imaging (HR-MRI), or microMRI, which are not frequently used in clinical practice, are required for assessing bone microarchitecture.

Growing older, previous fractures, falls, glucocorticoid medication, a family history of hip fracture, and current smoking are non-BMD variables that raise the risk of fracture.[8,9] Incorporating risk factors that are independent of BMD increases the sensitivity of fracture risk assessment and thereby improves treatment intervention strategies.[10] Uni- and multivariate analyses suggest that age, prior fracture history, and BMD are the strongest predictors of fracture risk.[11]

Dual Energy X Ray Absorptiometry:

Although there are many methods available to measure body mass composition most of them are time consuming and invasive, while, dual-energy x-ray absorptiometry has emerged as one of the most commonly used clinical standards.[12] In Dual-energy X-ray absorptiometry, typically the energy source produces photons at two different energy levels, 40 and 70 kV, which pass through tissues and attenuate at rates related to its elemental composition.

Improvements have been achieved through advances in x-ray generation and detection technology, modification of data acquisition protocols, and implementation of more sophisticated image analysis algorithms. The comprehensive view of body composition provided by dual energy x-ray absorptiometry makes it an attractive technique for a variety of clinical applications.[13]

Bone is rich in highly attenuating various minerals, calcium and phosphorous, and it can be readily distinguished from soft tissues. The unique elemental profiles of bone, fat, and non-bone lean tissue allow for visualization and separate analysis of each tissue type by dual energy x ray absorptiometry.[14] Dual energy x-ray absorptiometry is also found to have higher degree of accuracy and precision in measuring body mass composition.[15]
The likelihood of fracture over a given time period can be expressed using a fracture risk assessment tool like FRAX. However, older persons with diabetes may have a higher risk of fracture for a given BMD T-score or FRAX score than those without diabetes.[16,17] Diabetes is not presently a risk factor in the FRAX algorithm. More research is required in collecting new population cohorts worldwide before this risk factor can be included. It has, however, been suggested that if a diabetic patient is just below the FRAX-based intervention threshold, the clinician may take into account the effect of diabetes on fracture risk and recommend treatment.[18]

AIMS AND OBJECTIVES

Aims:

- To assess the use of WHO FRAX score in diabetic patients and to compare the fracture risk between diabetic and healthy population using FRAX score.

Objectives:

- To evaluate the use of WHO FRAX score in diabetic patients and to compare with healthy population .
- To estimate the fracture risk between diabetic and healthy population using FRAX score.

REVIEW OF LITERATURE

It is still debatable if diabetes mellitus and osteoporosis are related.[19] Although it is possible that the metabolic abnormalities of diabetes impact bone metabolism, structure, and mineral density, it is still unclear to what extent they are responsible for the rise in fracture risk seen in people with type 1 and type 2 diabetes. Changes in the metabolism of the bones are not the only things that may be significant:

- The degree of bone loss varies between type 1 and type 2 diabetes, and it may happen as early as puberty if diabetes is diagnosed.
- Type 2 diabetes has been linked in certain studies to an increase in bone mineral density (BMD).[20]
- Bone fragility, especially in type 2 diabetes, may increase the risk of fractures without being reflected by BMD, and in certain people, BMD may not even be a reliable indicator of fracture risk.
- The late consequences of diabetes may have an impact on bone metabolism (eg, renal failure).
- Falling may result in a higher risk of fracture due to vision impairment, cerebrovascular disease, or neuropathy.
- Localized bone loss brought on by diabetic neuropathy may raise the possibility of ankle and foot fractures.
- Particular therapies might affect fracture rates.

Bone Metabolism in Diabetes Mellitus:

Studies on bone histomorphometry have generally, [19] but not always, revealed a low turnover of bone with a reduction in bone formation and, to a lesser extent, bone resorption. Reduced serum concentrations of indicators of bone turnover have been shown in various investigations to indicate low bone turnover. [21] For instance, indicators of both

bone production (osteocalcin) and resorption (C-telopeptide) were lower in patients with type 1 and type 2 diabetes compared to controls in a comprehensive review and meta-analysis of 66 studies examining bone metabolism in patients with diabetes. [21]
Patients with diabetes who develop end-stage renal disease have been seen to experience comparable alterations.

Diabetes patients have a higher risk of developing adynamic bone disease (including that linked to aluminium deposition) compared to healthy individuals, [22,23] but hyperparathyroid bone disease is uncommon, occurring in less than 10% of cases. [22-24]
Diabetes is likely the result of multiple factors, which contribute to the impaired bone turnover. Research on uremic rats suggests that low insulin levels may reduce bone turnover. [25] Since reduced bone formation can be seen in type 1 diabetics prior to the beginning of clinical renal impairment, insulin shortage may also be significant earlier. [19,24,26]

Low levels of insulin and IGF-1 in type 1 diabetes may impair osteoblast function and may mediate the anabolic effects of insulin through the insulin-like growth factor-1 (IGF-1) pathway.[27] Contrarily, type 2 diabetes caused by obesity-induced insulin resistance results in elevated levels of insulin and IGF-1, which may have anabolic effects on bone.

Reduced bone formation may also be caused by the build-up of advanced glycation end products (AGEs) in collagen as a result of hyperglycemia. Increased fragility of diabetic bone may be caused by low bone turnover, a decrease in unmineralized bone matrix, and increased collagen glycosylation.[19,28,29] The measurement of bone density might not be able to anticipate the rise in bone fragility.[30]

Hypercalciuria is another element that may impact bone metabolism in diabetics. Although the exact mechanism by which this happens is unknown, insulin can help.[31] Both bone mineral loss and functional hypoparathyroidism might be contributing factors.[32]

Bone Density:

Type 1 Diabetes:

BMD at the forearm and lumbar spine is present in children and adolescents with type 1 diabetes,[33-35] and it seems to be stable over time.[33]

Various results have been reported, ranging from decreases in trabecular BMD[36] but not cortical BMD to no deficit when BMD is weight-adjusted.[37] Any BMD deficit is thought to result from a failure to develop endosteal bone during growth.

Lumbar BMD is often normal in persons with type 1 diabetes,[38-40] while femoral BMD is decreased.[20,38-41] The majority of studies found no connection between BMD and either the length of diabetes or glycemic control.[33,35,37,39] However, these results have not consistently been found.[41,42] For instance, one research of premenopausal women discovered elevated lumbar BMD and normal femoral BMD.[42] Another study's low lumbar BMD and high prevalence of retinopathy and neuropathy patients raise the possibility that BMD can be affected by microvascular illness. Low femoral neck BMD and neuropathy have also been linked in studies.[39]

Type 2 Diabetes:

In the vast majority of type 2 diabetes investigations, BMD was discovered to be either normal or elevated at the lumbar spine, femoral neck, and mid & distal radius. Both men and women could benefit from these discoveries.[43-46] BMD correlated with body mass index as was predicted.[46] Increased BMD was independent of obesity in the studies that adjusted for BMI.[43-46]

In comparison to their suitable controls, older, functional patients with type 2 diabetes demonstrated better hip, total body, and volumetric spine BMD in both black and white men and women, while a lower spine bone volume was observed in the diabetes group, which may potentially reduce bone strength.[47]

Two key conclusions were drawn from a longitudinal 12-year study involving 109 patients with both type 1 and type 2 diabetes[29]:

- In both groups, baseline radial BMD was lower than in normal people.
- As a result, the initial deficit was restored. The rate of loss in radial BMD over time was comparable to that of normal patients with type 1 diabetes and lower than that of normal subjects with type 2 diabetes.

According to the scientists, the initial decline in BMD was caused by reduced osteoblast recruitment or function, and age-related bone loss in older individuals with type 2 diabetes was mitigated by low bone turnover. The fact that BMD could only be assessed in survivors, who made up little over half of the initial study population, is one limitation of our findings. High-resolution peripheral quantitative computed tomography (HR-pQCT) research has suggested that a deficiency in cortical bone, resulting in increased cortical porosity, may make a contribution to fracture risk in type 2 diabetes, partially explaining the decrease in bone strength that is undetectable by dual-energy x-ray absorptiometry (DXA).[48] Only the group with microvascular difficulties had cortical bone

abnormalities, according to a different study that used HR-pQCT to compare patients with type 2 diabetes (with and without microvascular issues) to controls.[49]

Women on thiazolidinediones appear to be one subset of type 2 diabetics who are more likely to experience bone loss. It is necessary to conduct more research to go deeper into this subject.

Fracture:

Increased risk: Despite the fact that some studies have not found a connection, [45,50,51] the majority of them have shown that patients with diabetes have an increased risk of fractures.[52-58]

- Women with type 2 diabetes (n = 5285) had a higher risk of fracture after seven years of follow-up compared to women without diabetes in the Women's Health Initiative (WHI) Observational Study, a prospective cohort study of 93,676 postmenopausal women (adjusted relative risk [RR] 1.20, 95% CI 1.11-1.30).[59]
- Patients with either type 1 diabetes (RRs 6.3 and 6.9, respectively) or type 2 diabetes (RRs 6.3 and 6.9, respectively) were found to have an increased risk of hip fracture (RRs 1.7 and 1.4, respectively).[60,61] The meta-analysis's findings also revealed that type 2 diabetics had higher hip and spine BMD than type 1 diabetics, who had lower BMD at both locations.[60] BMD was reduced and fracture risk was increased in people with diabetes comorbidities.

Population-based studies have shown a link between greater type 2 diabetes, diabetic retinopathy, developed cortical cataract, neuropathy, and insulin administration and the risk of fractures (proximal humerus, vertebral, and hip).[62,63] In one study, even after accounting for visual acuity, the link between retinopathy and fracture risk was still statistically significant, suggesting that retinopathy may serve as a stand-in for severe

diabetic microvascular disease.[62] Additionally, it has been noted that older diabetic women are more likely to fall.[64]

An increased incidence of foot fractures, primarily metatarsal, has also been noted in diabetic athletes in a retrospective analysis.[58] Men were more likely to sustain fractures, which were linked to chronic illness. Additionally, metatarsal fractures, osteopenia in the hands and feet, and an increased incidence of osteopathy have all been linked to diabetic neuropathy.[52]

A retrospective, population-based cohort research involving 82,000 persons with diabetes and approximately 236,000 matched nondiabetic controls also demonstrated the likelihood that fracture risk is related to the severity of the disease and the prevalence of long-term consequences.[65] Adults with long-term diabetes had an increased risk of osteoporotic fractures (RR 1.15, 95% CI 1.09-1.22) and hip fractures (RR 1.40, 95% CI 1.28-1.53), whereas those with newly diagnosed diabetes had a lower risk of fractures (RRs 0.91, 95% CI 0.86-0.95 and 0.83, 95% CI 0.75-0.92 for osteoporotic and hip fractures, respectively). Patients with type 2 diabetes under 65 have a higher risk of fracture when their glycemic control is subpar.[66]

Therapy may potentially have an impact on fracture risk. In comparison to metformin or glyburide, newly diagnosed women with diabetes who were randomly assigned to receive 4 years of rosiglitazone experienced a greater rate of fractures, according to the Diabetes Outcome Progression Trial (ADOPT).

Together, the data indicate that BMD is decreased in type 1 diabetic individuals and normal or enhanced in type 2 diabetic patients. However, fracture risk seems to be higher in both groups, which may be due to factors other than BMD such diabetes duration, comorbidities from diabetes, bone quality, therapy, and fall risk.

Clinical evaluation:

The examination of BMD and clinical risk factors is a component of the assessment of fracture risk in patients who have diabetes mellitus, just as it is for individuals without diabetes.

Fracture risk is enhanced by low bone mineral density (BMD). However, methods for quantifying fracture probability by combining clinical risk variables with BMD offer appealing alternatives to depending solely on BMD testing. Thus, evaluation of both should be included in the assessment of fracture risk.:

- BMD
- Clinical risk factors

Bone mineral density:

The standard deviation (SD) difference between a patient's BMD and that of a young-adult reference group was used by the World Health Organization (WHO) to classify BMD in 1994. These days, a "T-score" is a popular way to express this value. A T-score of -1.0 or above is considered normal, a T-score between -1.0 and -2.5 is categorized as low bone mass (osteopenia), and a T-score of -2.5 or less is consistent with an osteoporosis diagnosis.

Numerous studies have shown that a low BMD is linked to a higher risk of fracture.[11,67-69] Fracture risk is highest in people with T-scores of -2.5. The absolute frequency of fractures in subjects with T-scores in the osteopenia range, however, is higher than in patients with T-scores in the osteoporosis range because more people have osteopenia than osteoporosis.[8,9,70] Treatment methods focusing exclusively on BMD testing will miss many people at risk for fracture who could benefit from measures to minimize fracture risk because the majority of fractures occur in patients with T-scores better than -2.5.

Clinical risk factors:

For the purpose of predicting fractures, it is crucial to evaluate clinical risk variables that are not influenced by BMD. The risk variables that have been shown to be most indicative of fracture, in addition to BMD, include advanced age, a history of fragility fracture, chronic glucocorticoid usage, low body mass index (BMI), a family history of hip fracture, smoking, and excessive alcohol consumption.

In areas of the world without access to BMD measuring tools, clinical risk factor assessment alone may be taken into consideration for fracture prediction.[71] When BMD is unknown, the Fracture Risk Assessment Tool model enables estimation of the 10-year probability of hip fracture and major osteoporotic fracture using only clinical risk factors.[72,73]

Absolute risk should be used to describe fracture risk rather than relative risk. When determining which patients are most likely to benefit from therapy, absolute risk (AR) offers a more accurate evaluation of the likelihood of fracture. The likelihood of fracture during a given time period, usually 10 years, can be determined with the aid of a fracture risk prediction tool.

Fracture risk assessment tool:

In 2008, the University of Sheffield introduced the Fracture Risk Assessment Tool, which uses easily accessible clinical risk factors for fracture and, when available, femoral neck BMD (g/cm2, using dual-energy x-ray absorptiometry [DXA]) to estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for untreated patients between the ages of 40 and 90.[72] If DXA is not available, quantitative computed tomography (QCT) measurements of the femoral neck BMD that are equivalent to DXA may also be used with FRAX. However, this is not advised for use in clinical practice due to higher costs and radiation exposure.[74]

FRAX is based on information gathered from sizable, prospective, observational studies of both men and women from various ethnic backgrounds and geographical locations around the world, where clinical risk factors, BMD, and fractures were assessed.[75] FRAX has been tested in 11 separate cohorts, mostly made up of females. This enormous dataset's statistical power enables estimation of fracture likelihood from a person's set of risk factors. There are numerous countries for which the FRAX prediction algorithms are online. Additionally, the FRAX calculator is accessible through apps for smartphones and current DXA software versions.

According to findings from a sizable prospective cohort study, FRAX can predict fractures in women who are being treated for osteoporosis or who have already received treatment.[73] According to this data, there was agreement between the FRAX-predicted risk and the observed incidence of major osteoporotic fracture in both treated and untreated women. The observed hip fracture incidence was significantly lower than the expected risk only in the subset of women who were at the greatest risk for fracture and who adhered closely to their osteoporosis medication. Therefore, the use of FRAX for fracture prediction may not be prohibited by osteoporosis treatment. FRAX should not be used to track patients receiving therapy, however, as it does not seem to capture the change in fracture risk linked to therapy.[76]

There are other fracture risk assessment models, but they are not commonly used and most of them have not been validated in a variety of populations.[77,78]

Clinical application of fracture risk assessment

By using FRAX to calculate thresholds for cost-effective pharmacologic intervention, country-specific fracture data, life-expectancy data, and economic assumptions, clinicians can more accurately identify patients who will benefit from therapy than they can with currently used qualitative techniques.[79-81] According to

treatment recommendations based on FRAX, older patients with slightly low T-scores and high fracture risk would likely receive more medication treatment, while younger patients with low T-scores and low fracture risk will likely receive less drug treatment.

Based on country-specific health economic statistics, such as treatment costs for fractures and willingness-to-pay criteria, intervention thresholds differ.[72] In the majority of nations, the analysis is based on a five-year bisphosphonate treatment regimen. Based on the prevalence of hip fracture in Caucasian postmenopausal women and the anticipated cost of generic alendronate, the analysis was conducted in the United States.[81,82] The fracture probability at which this treatment is cost-effective is probably lower than what was calculated since the price of generic alendronate in the United States today is less than the estimated price. On the other hand, using more expensive nongenetic medications raises the likelihood of a fracture at which treatment is financially viable.

Limitations:

The clinical tool FRAX is helpful for determining fracture risk. There are some restrictions, nevertheless, just like with any therapeutic tools. There are a number of restrictions, including a lack of comprehensive validation in treated patients, a restriction to four ethnic groups in the United States (Caucasian, Black, Hispanic, and Asian), lack of certainty regarding the range of error with regard to fracture risk, and a lack of validation with BMD measurements by methods other than DXA83 and QCT.[74]

FRAX uses femoral neck BMD (g/cm2) to determine the likelihood of fracture in patients who are not receiving treatment. It is not advised to use BMD input from non-hip sites or other hip regions of interest because it has not been validated with FRAX.[83] FRAX is probably going to underestimate the fracture risk for people whose lumbar spine BMD is significantly lower than their femoral neck BMD. It is interesting that not all osteoporotic fractures are included in the FRAX estimation of major osteoporotic fracture,

given that many fragility fractures do not occur at the four "major" bone locations identified by the FRAX algorithm.[84] Additional limitations include dichotomous (yes or no) input for clinical risk factors that are associated with variable risk depending on dose and duration of exposure (e.g., glucocorticoids) and failure to take into account all risk factors, which may cause over- or underestimation of fracture risk in a specific patient (eg., multiple fractures, falls, bone turnover). Even while there is evidence that fractures at the hip, vertebra, and humerus seem to carry a higher risk of subsequent fracture than fractures at other sites, it is not possible to quantify this additive risk in FRAX.

Therefore, FRAX may understate the likelihood of fracture in people with[16,85]:

- Lumbar spine BMD much lower than femoral neck BMD
- High-dose glucocorticoid exposure (prednisolone >7.5 mg/day or equivalent)
- Multiple or recent fractures
- Prevalent, severe vertebral fractures
- Type II Diabetes mellitus
- A parental history of non-hip fragility fracture

Large population databases have been used to study the degree to which FRAX may overestimate or underestimate fracture risk, and methods for adjusting FRAX probability have been suggested.[86,87] The FRAX estimate for major osteoporotic fracture, for instance, may be increased or decreased by one-tenth for each rounded T-score difference or offset between the lumbar spine and femoral neck, according to an analysis of the Canadian Manitoba BMD database (eg., when the lumbar spine T-score is 1.0 less than the femoral neck T-score, the 10-year probability of major osteoporotic fracture can be increased by one-tenth).[87] Another analysis using the United Kingdom General Practice Research Database revealed that the 10-year probability of a major osteoporotic fracture

may increase by 15% and the 10-year probability of a hip fracture may increase by 20% for patients exposed to high dose glucocorticoids (prednisolone >7.5 mg/day or equivalent).[86] By selecting "yes" for rheumatoid arthritis in the FRAX algorithm, it may be possible to detect the increase in fracture risk related to type 2 diabetes mellitus.[88] The FRAX chance of fracture can be improved with changes like these. However, the bulk of the nations represented by FRAX have not had these adjustment factors calculated.

Clinical Risk Factor Assessment:

Patients who do not have osteoporosis as defined by the World Health Organization (WHO) based on a T-score of -2.5 or less tend to fracture more frequently. Although those with osteoporosis have the highest risk of fracture, those with low bone mass or osteopenia (T-score between -1.0 and -2.5) have a higher rate of fractures because there are so many more people in this category.[9,89,90] For fracture prediction, it is crucial to evaluate clinical risk variables that are not influenced by bone mineral density (BMD).

Ageing, prior fractures, glucocorticoid medication, a family history of hip fracture, poor vision, low body weight, neuromuscular problems, and smoking are a few of these risk factors for Caucasian women and men.[91,92] A prospective study of 1435 Chinese women found similar risk factors.[71]

Many of these risk factors can be quickly identified during a routine physical and history review; when considered collectively, they can predict the development of a hip fracture even in the absence of BMD measurements.[93,94] The two most significant BMD independent risk variables for fracture are increasing age and prior personal fracture history. For the purpose of fracture prediction in areas of the world without access to BMD technologies, clinical risk factor assessment alone may be taken into account. With the help of the femoral neck BMD and clinical risk factors, the Fracture Risk Assessment Tool

model can estimate the 10-year probability of hip fracture and major osteoporotic fractures.

Advanced age: The risk of fracture increases with age for any given T-score.[95]

Personal history of fracture as an adult: Another significant risk factor for a subsequent fracture in both men and women is a history of a fragility (low-trauma) fracture[96-99]:

- An increased risk of any fracture (relative risk [RR] 1.8, 95% confidence interval [CI] 1.6-1.9), osteoporotic fracture (RR 1.8, 95% CI 1.6-1.9), and hip fracture (RR 1.6, 95% CI 1.3-2.0) was found in both men and women, even after adjusting for BMD, in a meta-analysis of 11 prospective cohort studies of fracture risk in men or women with prior fracture.[100]
- The RR of subsequent fracture in women with any initial low-trauma fracture (after age 60 years) was 2.0 (95% CI 1.7-2.2) and for men was 3.5 (95% CI 2.7-4.5) in a prospective cohort study of 4005 Australian men and women followed for 16 years.[97]
- The absolute risk (AR) of a new vertebral fracture in women with a prior vertebral fracture ranged from 25 to 50%, depending on T-score, in a longitudinal study (Study of Osteoporotic Fractures [SOF]) of 9700 older (age >65 years at baseline) women, 2680 of whom were followed for an average of 15 years.[96] Women with a total hip T-score -2.5 and a prior vertebral fracture were most at risk for a new fracture (AR 56 percent, 95% CI 44-69).

A previous high-trauma fracture may also increase the risk of a subsequent fracture in women. Women having a prior history of both high and low-trauma, non-spine fractures showed a similarly higher risk of subsequent fracture compared to women who had not experienced such fractures in a nine-year study with 8022 SOF participants.[101] Women with a history of high- or low-trauma fracture were at an increased risk of subsequent fracture by 34% (95% CI 7-67) and 31% (95% CI 20-43) respectively.

Glucocorticoid therapy: In the United Kingdom General Practice Research Database, a retrospective cohort study of 244,235 oral glucocorticoid users revealed a dose-dependent relationship between chronic glucocorticoid use and fracture risk, with high doses (prednisolone 7.5 mg/day or greater) having the highest risk.[102] Low glucocorticoid dosages (prednisolone less than 2.5 mg/day) were also linked to an increased risk of fracture.

History of fragility fracture in a first-degree relative: Regardless of BMD, a woman's risk of hip fracture is doubled if her parents have had hip fractures.[93]

Low body weight: Less than 58 kg of body weight is linked to a higher risk of osteoporosis and fractures, possibly due to small bones.[103-105] Increased height and weight loss after the age of 50 in women both increase the risk of hip fracture, although weight gain lowers it.[104,106,107] The way you lose weight could have an impact on how your bones physiology change. In a single small randomized trial, participants who lost weight by restricting calories saw a reduction in their total hip BMD, but not those who lost the same amount of weight by exercising only as usual.[108]

Cigarette smoking: According to meta-analyses, smoking is linked to lower BMD and a higher risk of fracture.[109,110] Smoking history and current smoking both increased the risk of fracture, but current smokers had the highest risk.

Excessive alcohol consumption: With excessive alcohol consumption, there is a dose-dependent risk of fracture.[111] According to a meta-analysis of case-control and prospective cohort studies, drinking more than two drinks (or 28 g of pure alcohol) per day increases the risk of hip fracture (RR 1.39, 95% CI 1.08-1.79).[112]

Medical diseases: Low BMD and a higher risk of fracture are linked to numerous medical conditions, either as a result of underlying inflammation, malabsorption, renal calcium excretion, or drugs used to treat the conditions. As examples:

- Inflammatory bowel disease.
- Rheumatoid arthritis.
- Cystic fibrosis.
- Celiac disease.
- Renal disease.

An increased risk of fracture is linked to end-stage renal failure. A higher risk of fracture has also been linked in one study, but not in another, to moderate levels of renal insufficiency (as determined in patients with a stable serum creatinine).[113,114]

- Type 1 and 2 diabetes.
- Previous hyperthyroidism.
- Sickle cell disease.

Other risk factors: Risk factors in addition to those described above include the following:

- Vitamin D deficiency.
- Many drugs, including androgen deprivation agents, aromatase inhibitors, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), thiazolidinediones, and anticonvulsants.
- Reduced functional mobility, recurrent falls, or use of walking aids.
- Dementia.
- Previous fracture between the ages of 20 and 50 years.
- Poor health/frailty.
- A previous history of breast cancer.

Possible risk factors:

- In some studies, depression has been linked to a higher risk of fracture.[115] The link between sadness and fracture is probably complicated, though. Additionally, SSRI usage,

higher frequency of falling, hypercortisolism, and lifestyle choices all raise the risk of fracture in those with depression (smoking, alcohol).

- In a case-control study, mild asymptomatic hyponatremia (serum sodium 135 mEq/L) was linked to a higher risk of fractures from falls (adjusted odds ratio [OR] for fracture 4.2, 95% CI 2.2-7.7).[116] Hyponatremia was typically either a side effect of a drug (diuretics, SSRIs, and antiepileptic medications) or a result of the syndrome of inappropriate antidiuretic hormone secretion.
- Aortic calcification on computed tomography (CT) scan.[117]
- High dietary retinol intake, which some, but not all, studies suggest increases fracture risk.
- Elevated markers of inflammation.[118,119]
- Vitamin B12 deficiency (pernicious anemia).
- Sedentary lifestyle.[120]
- Consumption of large amounts of caffeine. The association between excess caffeine and increased fracture risk has been variably reported as a definite association,[93] no association,[121,122] and an association only if the patient does not drink milk.[123]
- High homocysteine levels, which, though not universally so, have been linked to a higher risk of fracture.[124-126]
- Although the impact on older women is unknown, carbonated beverages may have negative effects on skeletal development in adolescents due to the displacement of nutrient-dense foods and beverages. In one report, modest intake of carbonated beverages did not have adverse effects on BMD,[127] while in another, cola drinks (but not other carbonated beverages), were associated with lower bone density.[128]

Methods of measurement of BMD:

No matter how the bone mineral density (BMD) is measured, low BMD is linked to a higher risk of fracture.[68,69,75,129] The T-score values, however, vary depending on the bone site and the technology used. Depending on the technique utilized and the bone site assessed, the increase in fracture risk every 1.0 standard deviation (SD) reduction in BMD (fracture gradient) varies. T-scores obtained from various bone sites using various technologies are therefore not comparable.[91,130]

Dual-energy x-ray absorptiometry (DXA), the most effective method for tracking serial BMD changes, and the only one that can be used for diagnostic classification in clinical practice. However, alternative methods that gauge several skeletal locations have shown the capacity to forecast the likelihood of fractures. Therefore, fracture risk assessment may be conducted utilizing alternative technologies (measuring the lumbar spine, hip, or peripheral skeletal locations) in conjunction with taking clinical risk factors into account when BMD testing by DXA is not available.

Dual-energy x-ray absorptiometry (DXA):

DXA determines "areal" BMD (aBMD) in g/cm2 by dividing "bone mineral content" (BMC; measured in grams) by "bone area;" measured in square centimeters. Because it provides extremely accurate measurements at clinically significant skeletal sites (i.e., those with significant clinical consequences when a fracture occurs), as well as the ability to be used for diagnostic classification, input with FRAX, and monitoring the effectiveness of therapy, DXA is the most popular method for determining BMD. The main drawbacks of DXA are that it involves ionizing radiation, albeit at very low doses, and that it is a bulky (i.e., non-portable) apparatus that is more expensive than most ancillary technologies.

Fracture prediction: Numerous studies have shown that osteoporotic (fragility) fracture can be predicted by low BMD measured by DXA at any skeletal site (lumbar spine, hip,

or forearm).[68,69,129] For each SD decrease in BMD, there is an overall increase in the risk of these fractures of about two times. As examples:

- A prospective research of 9700 older women found an inverse relationship between bone density at all measurement sites and the incidence of vertebral fracture, with 2680 of those participants being followed for an average of 15 years.[96] The age-adjusted odds ratio (OR) of vertebral fracture was 2.1 (95% CI 1.8-2.3) and 1.8 (95% CI 1.6-2.0) for each SD decrease in DXA-measured BMD of the lumbar spine and total hip, respectively.
- Each SD decrease in DXA-measured BMD of the hip or lumbar spine was linked to an increased risk of osteoporotic fracture at any site in a historical cohort study (mean observation 3.21.5 years) of 16,505 Canadian women (hazard ratio 1.8 [95% CI 1.7-2.0] for total hip and 1.5 [95% CI 1.4-1.6] for spine).[67]

Despite the fact that osteoporotic fracture can be predicted by low BMD at any bone site, site-specific measures are often preferable for each site. For instance, hip BMD is more accurate at predicting hip fracture than BMD assessed at other bone locations.[67,68,75,131] Every 1 SD drop in BMD at the femoral neck in women was linked to a relative risk of 2.6 (95% CI 2.0-3.5) for hip fracture and 1.6 (95% CI 1.4-1.8) for all fractures, according to a meta-analysis of prospective cohort studies with over 90,000 person-years of observation. The relative risk (RR) for vertebral fracture was 2.3 (95% CI 1.9-2.8) and the RR for all fractures was 1.5 (95% CI 1.4-1.7) for lumbar spine BMD loss of 1 SD.[132] Between total fracture, hip fracture, and femoral neck BMD in both men and women, there is a similar association.[70,129]

Observational research and clinical osteoporosis trials have usually omitted high-trauma fractures (often referred to as fracture from motor vehicle crashes, sports accidents, or falls from ladders or other higher surfaces). The prevalent belief was that apparently normal bone would fracture under most high-trauma settings, despite the fact that the force

to which bone is subjected changes with the level of damage. As a result, high-trauma fracture have not been identified as an osteoporosis risk factor.[133]

Evidence, however, points to a link between low BMD and a higher risk of high-trauma fractures.[101,134] As an illustration, a 1 SD decrease in total hip BMD was linked to similarly elevated risks of high- or low-trauma fractures in two significant prospective cohort studies of older community-dwelling men and women (age-adjusted relative hazards [RH] 1.4 [95% CI 1.2-1.7] and 1.5 [95% CI 1.4-1.6] for high- and low-trauma fractures, respectively, in females and 1.5 [95% CI 1.2-2.0][101]

The studies are constrained by the broad definition of high-trauma fracture, despite the fact that the connection between BMD and fracture appears to be comparable regardless of the source of fracture.[133] Independent of BMD, there is a certain amount of force at which normal bone would fracture. It would be clear which patients with fractures need an osteoporosis assessment if it were possible to reliably classify traumatic fractures that are unlikely to be caused by low BMD. Osteoporosis testing is necessary for those who fracture from a degree of force that normal bone would not typically fracture. Further research is necessary to fully understand the connection between force and fracture.

Quantitative ultrasonography (QUS):

QUS examines the transmission of ultrasound waves through accessible limb bones or the reflectance of ultrasonic waves off the bone surface rather than bone mineral density (BMD). Broadband ultrasonic attenuation (BUA), speed of sound (SOS), and computed values like the quantitative ultrasound index (QUI) or stiffness index are among the parameters that transmission ultrasound may measure (SI). Ultrasound with reflection only transmits SOS.

QUS may be more advantageous than BMD measurement because it is less expensive, portable, and radiation-free. The calcaneus (heel), a skeletal region formed mostly of

cancellous bone, analogous to the spine, is the location where measurements are most frequently taken.

QUS is a good predictor of osteoporotic fracture risk.[135-137] As examples:

- QUS of the calcaneus predicted hip fracture as precisely as DXA of the calcaneus or femoral neck in a large, prospective trial involving 6189 postmenopausal women over the age of 65. Hip fracture risk increased by twofold for every SD decrease in calcaneal BUA (relative risk [RR], 2.0; 95% CI 1.5-2.7). [138]
- Calcaneal QUS also proved to be a reliable indicator of total and hip fracture risk in a larger trial involving 14,824 patients, which included younger women and men ages 42 to 82. BUA predicted fracture risk in all patient subgroups, with a relative risk comparable to the previous study.[136]

Other studies have discovered that QUS is at least as excellent as (and potentially better than) clinical risk variables for predicting women at risk for osteoporosis in addition to fracture risk.[139,140]

For identifying people at high risk for osteoporosis, QUS appears to be at least as effective as clinical risk variables in predicting fractures in both men and women. However, as the WHO criteria were developed based on BMD measurement by DXA and cannot be used with FRAX, QUS cannot be used for diagnostic classification. Additionally, because changes in QUS are too slow to be clinically relevant, QUS cannot be used to track a patient's response to therapy. There are no studies that demonstrate a decrease in fracture risk for patients chosen for therapy based on QUS measures.

Quantitative computed tomography:

At the hip and spine, quantitative computed tomography (QCT) assesses volumetric BMD (vBMD) in mg/cm^3. Contrary to DXA, QCT may separate trabecular bone from the cortical bone that surrounds it. According to certain studies, QCT of the

spine may be a marginally more accurate predictor of the risk of spinal fracture than anterior-posterior spine DXA,[141,142] possibly as a result of the significant role trabecular bone plays in the strength of the vertebral body.[143] However, according to a different study, QCT of the spine is not more accurate at predicting non-spine fractures than DXA of the hip.[144]

Due to the degree of radiation exposure and expense, it is not advised to utilize QCT-derived, DXA-equivalent T-scores of the hip in clinical practice unless DXA is not available for the diagnosis of osteoporosis and osteopenia using the WHO criteria for BMD categorization 74. For the purpose of calculating the fracture risk using FRAX, the computed aBMD of the hip acquired from QCT data may be employed.[145] For some patients with structural abnormalities of the spine that prevent the use of DXA, QCT may be clinically beneficial to track changes in BMD over time. It might be used to keep track of the therapeutic effects of anabolic steroids or other medications with cutting-edge mechanisms of action. Currently, QCT is largely utilised as a research tool and has greatly aided in our understanding of the pathophysiology of osteoporosis and the effects of medications used to treat it on the skeletal system. Compared to DXA, it is more expensive, less repeatable, and requires more radiation.

Prevention and Treatment of Osteoporosis:

There aren't many studies out there right now that exclusively deal with osteoporosis and diabetic patients. As examples:

- Three years of alendronate therapy led to comparable improvements in bone density in postmenopausal women with (n = 297) or without diabetes (n = 6161) diabetes in a subgroup analysis of a larger study, the Fracture Intervention Trial.[146]
- In a post hoc analysis of risedronate trials in Japan, risedronate was safe and effective in suppressing bone turnover and increasing bone mineral density (BMD) in

osteoporosis patients with coexistent diabetes (n = 53) compared with nondiabetics (n = 832).[147]

- In a large Danish cohort study, there was no difference in the effects of bisphosphonate treatment or raloxifene treatment in fracture reduction between women and men with type 1 and type 2 diabetes and women and men without diabetes receiving these treatments.[60] There were insufficient people receiving strontium in the cohort to allow analysis. Serious adverse events from bisphosphonate treatment do not seem to be increased in patients with diabetes. [146-148]

Both men and women who have diabetes who are postmenopausal can benefit from the general advice regarding leading a healthy lifestyle, getting enough exercise, and taking calcium and vitamin D supplements.[149,150] Since there aren't any studies explicitly addressing osteoporosis in diabetics, other suggestions for treatment, such those for postmenopausal men and women, should be used instead.

Diffuse Idiopathic Skeletal Hyperostosis:

Diabetes patients may experience diffuse idiopathic skeletal hyperostosis (DISH) more frequently than non-diabetics. DISH is a prevalent degenerative enthesopathy that affects both the axial and appendicular bones. The cause of DISH is unknown. The pathogenetic role of insulin, insulin-like growth factor (IGF), and growth hormone has been examined in light of its potential association with diabetes and obesity as well as its presence in acromegaly patients.

Other similar research works:

Kamalanathan S et al[151] assessed bone mineral density in 194 non-insulin-dependent diabetes mellitus patients. Results of the study indicated that bone mineral density was normal (Z score > -2) in 156 (80.5%) and low (Z score ≤ -2) in 38 (19.5%) patients in the

diabetes study group. Bone mineral density in the diabetes group was significantly higher than the control group in both sexes at the hip and spine.

Dutta MK et al[152] evaluated BMD in patients with type 2 diabetes mellitus. It was observed in the study that BMD was lower in diabetic patients as compared to controls (hip 0.962 ± 0.167 g/cm^2 vs 1.013 ± 0.184 g/cm^2, P = 0.05; spine 0.929 ± 0.214 g/cm^2 vs 1.113 ± 0.186 g/cm^2, P < 0.00001). The study also reported that BMD was significantly lower among female patients with non-insulin-dependent diabetes mellitus.

Chakrabarty N et al[153] studied bone mineral density in diabetes mellitus in among patients in Kolkata, eastern India among 138 cases of diabetes and 212 controls. There was no statistically significant correlation between BMD and diabetes in the study.

Mathen PG et al[154] carried out a prospective cross sectional study on 150 patients with type 2 diabetes mellitus and compared with an equal number of age and gender matched healthy controls in South India. Bone mineral density was measured at the femoral neck and lumbar spine (L2-L4) by dual energy absorptiometry in the study. The study findings were that the femoral neck and lumbar spine bone mineral density was significantly lower in cases compared to controls. Also the femoral neck and lumbar spine T-score was significantly lower in cases compared to controls.

Maisnam I et al[155] in their study conducted in eastern part of India reported that the bone mineral density of diabetic patients with normal body mass index were 0.95 ± 0.125, 0.97 ± 0.11 and 1.05 ± 0.12 g/cm^2 in right femur, left femur and lumbar spine respectively. Similarly bone mineral density was found to be significantly high among males as compared to females among the study participants with non-insulin-dependent diabetes mellitus.

Majima T et al[156] assessed bone mineral density at the sites with different cortical/ cancellous bone ratio (lumbar spine, femoral neck, and distal radius) using dual-energy X-

ray absorptiometry among patients with diabetes mellitus. According to the study, type 2 diabetic patients' bone mineral density and Z score at the distal radius were significantly lower than those in the control group. HbA1C values and bone mineral density were found to be negatively correlated in patients with non-insulin-dependent diabetes mellitus. Since Obesity is associated with diabetes mellitus in the western population and Higher BMD in those with non-insulin-dependent diabetes mellitus may be due in part to greater obesity associated with the disease.[157,158]

Sahin G et al[159] examined bone mineral density with the dual-energy X-ray absorptiometry technique at the lumbar and femoral regions and in a subgroup of patients and found significantly higher levels of bone mineral density at the lumbar and femoral levels in the non-insulin-dependent diabetes mellitus subjects compared with the control group.

MATERIALS & METHODOLOGY

Study setting:

The present study was carried out in a tertiary care teaching hospital in Belagavi, Karnataka. The hospital caters to population from Belagavi and neighboring districts belonging to different socio-economic classes.

Study Population:

Patients reporting to the study hospital in the age group of 40 -80 years with complaints of hip pain and low back pain comprised the study population.

Study design:

The present study was undertaken as a hospital based cross sectional comparative study.

Study sample:

82 Patients of either sex with 40-80 years of age complaining of hip and low back pain comprised the study sample.

Sample Size estimation:

The minimum sample required sample size was calculated based on the formula

$$n = \frac{(z_\alpha + z_\beta)^2 (s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

where Zα is linked with the level of significance and zβ is linked with the power of the test. For 5% level of the significance zα =1.96 and zβ =0.84 for 80% power of the test. Considering the prevalence of osteoporosis and osteopenia from the study by Kaushal N et al.[160]

Sampling technique:

Simple random sampling technique was used to select study participants from the study population.

1.1. Study Period:

The study was done during the period Jan 2021 to Oct 2022.

1.2. Inclusion Criteria:

- Patients aged from 40 to 80 years with complaints of hip and low back pain
- Patients of either sex

1.3. Exclusion Criteria:

- Osteoporotic patient on medication like bisphosphonates, teriparatide calcitonin and hormonal therapy were excluded.
- Secondary bony changes in the spine (L1 - L4) that produce false BMD measurements, such as degenerative sclerotic changes, the presence of osteophytes and collapsed compression fractures were discarded from the data.
- Patients with hip and spine implants.
- Patients with Skeletal anomalies.

Brief Procedure:

The patients with complaints of hip and low back pain reporting to the OPD or admitted in KLE'S Dr. Prabhakar Kore Hospital & Research Centre and Charitable Hospital, Belagavi were examined thoroughly and basic investigations were done. Then the patients who are being assessed were explained in detail about the study and informed written consent was taken for those who wish to participate. Diabetic profile of the patient were then sent and depending on the results, patient were sent for BMD screening or DEXA scan. The reports of all said investigations were then be documented, compiled and analyzed.

Statistical analysis:

For continuous and categorical variables, the corresponding means and proportions were calculated. The chi square test was used to determine the statistical significance of the proportional difference. Statistics were considered significant at a p value of 0.05. Data entry was carried out using MS Excel 2016 and data analysis was carried out using SPSS (Statistical Package for Social Sciences) version 22.0

Ethical Considerations:

Informed written consent was obtained from all patients before including them in the study. Institute ethical committee approval was obtained before the study was begun.

PROFORMA:

The patients were evaluated through a proforma & after ruling out the patients in the exclusion criteria, the rest were enrolled in the study.

OPD No:

Name: To identify the patient

Age: Age is an important factor to be noted, as the study was focused on patients aged more than or equal to years.

Sex: Both Male and female were included in the study

Address: Address was noted to communicate with the patient for treatment purposes if found osteoporotic & osteopenia.

Socioeconomic Status: Was classified into upper, middle and lower status based on income.

Questionnaire:

1. Occupation:

Occupation of the individual was asked and it was further classified into manual labor, sedentary work and other group. This was to assess the amount of physical activity a patient involves in as increased bone mass is seen with higher physical activity.

2. Complaints of the individual

To know the reason for attending the department of orthopedics or department of Endocrinology for evaluation & treatment.

3. Medication History.

To rule out all the exclusion criteria. To advice the patient to stop calcium supplementations 48 hours prior to the scan.

4. History suggestive of following chronic diseases.

a. Chronic liver disease b. Chronic kidney disease

c. Chronic skin disease d. Rheumatoid arthritis

e. Hypertension f. Malignant conditions

5. History of alcohol Consumption.

Alcohol consumption was asked as it leads to fall in bone mineral density. If the patient consumed alcohol, quantity of intake was assesed.

6. History of smoking cigarettes.

Cigarette smoking was asked as it leads to fall in bone mineral density. If the the patient smoked cigarettes, the number of cigarettes smoked per day was asked.

7. History of consumption of milk & milk products.

To assess whether the patient is on calcium rich diet as it leads to increase in BMD.

8. Diet

Patients diet was assessed whether the patient is a vegeterian or a non vegetarian.

9. Sunlight exposure

A history of exposure to sunlight (number of hours per day) was solicited. Exposure more than 1.5 hours per day to sunlight was considered adequate.

10. Family history of fractures

Family history of fractures after trivial fall or deformity of the back (Hunch Back was asked.

11. Body mass index was calculated after determining the Height & weight

BMI: - wt(kg)/Ht(m2)_____

12. Duration since suffering from diabetes .

To ascertain whether duration of diabetes has any relationship with osteoporosis

Investigations:

1. Blood sugar test.
2. BMD (Bone mineral density) measurement was done using DEXA Scan of make GE Wipro and 2008 Lunar model.

DEXA Scan Evaluation technique:

A dual energy X-ray absorptiometry (DEXA) scan uses X-ray equipment and a computer to measure bone density. Bone mineral density is the most important tool in the diagnosis of osteoporosis. It allows for accurate, precise and reproducible assessment of bone mineral density and enables the detection of osteoporosis before the occurrence of fractures. DEXA Scan is the gold standard in the assessment of BMD.

Pre-Scan Requisites

1. Completion of the questionnaire
2. Selection of the study group after ruling out the exclusion criteria
3. Filling of the informed consent.

Instructions prior to the scan

1. Stoppage of calcium supplements 48 hours before the scan.
2. Removal of clothes that have metal buttons or other metal accessories & change to a gown if necessary.
3. To remain still during the procedure.

Procedure:

The procedure was quick, painless and time taken was about 10 minutes. It involved exposing the body to a small dose of X-ray radiation. Patient was taken to the X-ray room and asked to lie down on an X-ray table. A radiographer operated the scanning equipment.

Scan was carried out at two sites the lumbar spine followed by the hip joint. Patient legs were flexed & placed over a large block for scanning of the lumbar spine. This was done to achieve straightening of the spine. For scanning of the hip joints patient was made to lie supine only. The scanning apparatus was then passed over the patient's lumbar spine & the hip joints respectively and it will project X rays beam. Some of this radiation travels straight through the bones and a certain amount is absorbed by them - how much depends on how dense the bones are.

A detector measured how much radiation passes through the bones and sends the information to a computer. A printed report was then obtained stating the BMD, 'T' & 'Z' scores.

Assessment of data:

The Bone Mineral Density (BMD in g/cm2) and 'T' and 'Z' scores was determined. 'T' score compares the BMD result with that of a young adult of the same gender with a peak bone mass while 'Z' score compares the BMD result with people of the same age group size and gender.

Data was analyzed as follows.

- Normal BMD: T scores not more than 1 SD below the adult mean.
- Osteopenia: T score between -1.0 and- 2.5.
- Osteoporosis: T score <- 2.5 with or without fragility fracture.

Data was collected and recorded and diagnosis based on the BMD score was done. BMD data was correlated with the data of various risk factors obtained through the questionnaire and correlations were derived.

RESULTS

Table 1. Distribution of study participants based on age (n=82)

Age (in years)	Numbers	Percentage
40-50	12	14.6
51-60	18	22
61-70	31	37.8
71-80	21	25.6
Total	82	100

Maximum of the study participants were in the age group of 61-70 years (37.8%). The mean age of the study participants was observed to be 62.3±10.3 years.

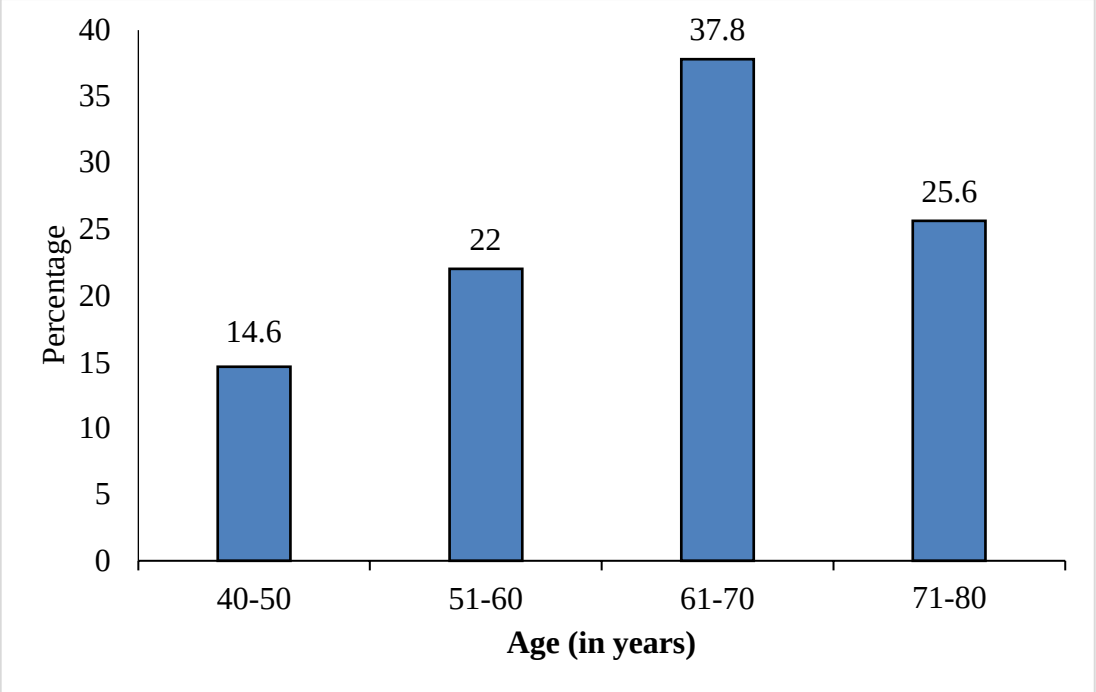


Figure 1. Distribution of study participants based on age (n=82)

Table 2. Distribution of study participants based on gender (n=82)		
Gender	**Numbers**	**Percentage**
Male	16	19.5
Female	66	80.5
Total	82	100.0

Majority of the study participants were females (80.5%), while 19.5% of them were males.

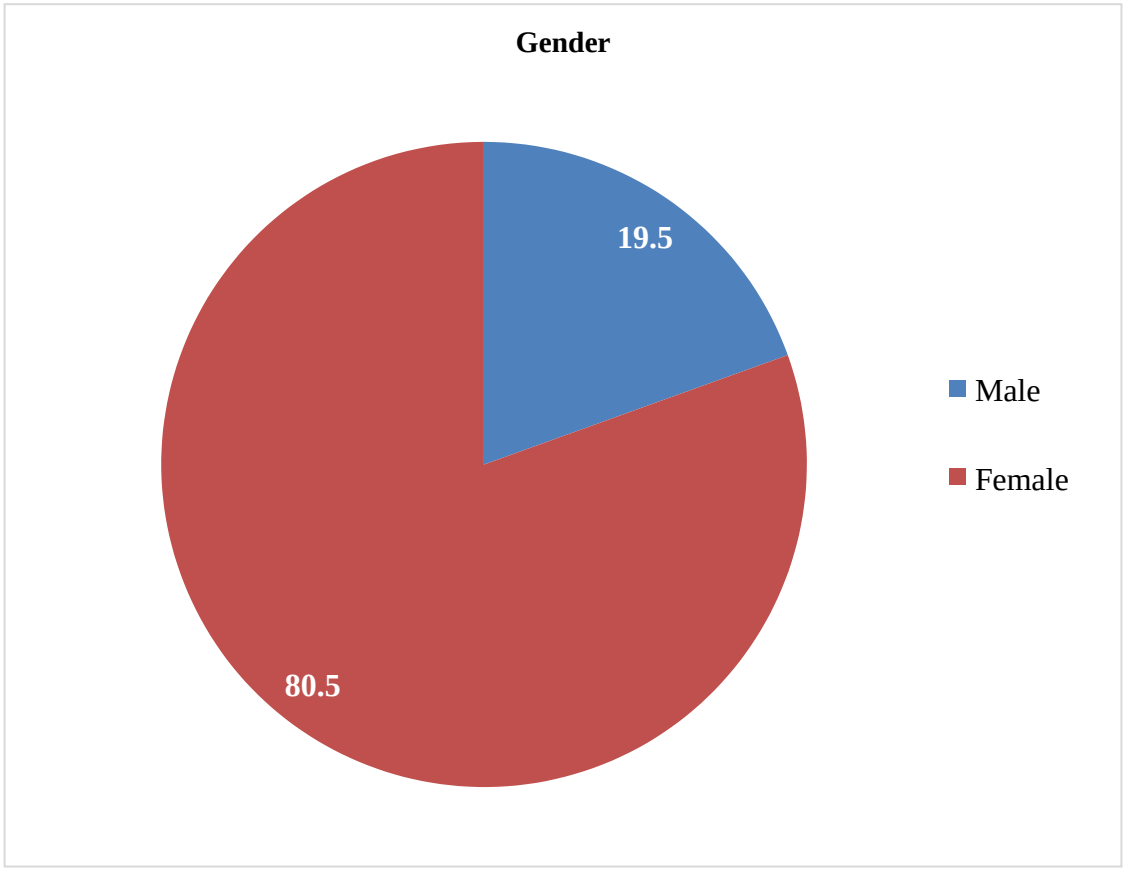


Figure 2. Distribution of study participants based on gender (n=82)

Table 3. Distribution of study participants based on BMI classification (n=82)

BMI Classification	Numbers	Percentage
Normal (<23.5)	14	17.1
Overweight (23.5-24.99)	9	11.0
Obese (25 and above)	59	72.0
Total	82	100

Majority of the study participants were obese (72%), while 11% were overweight.

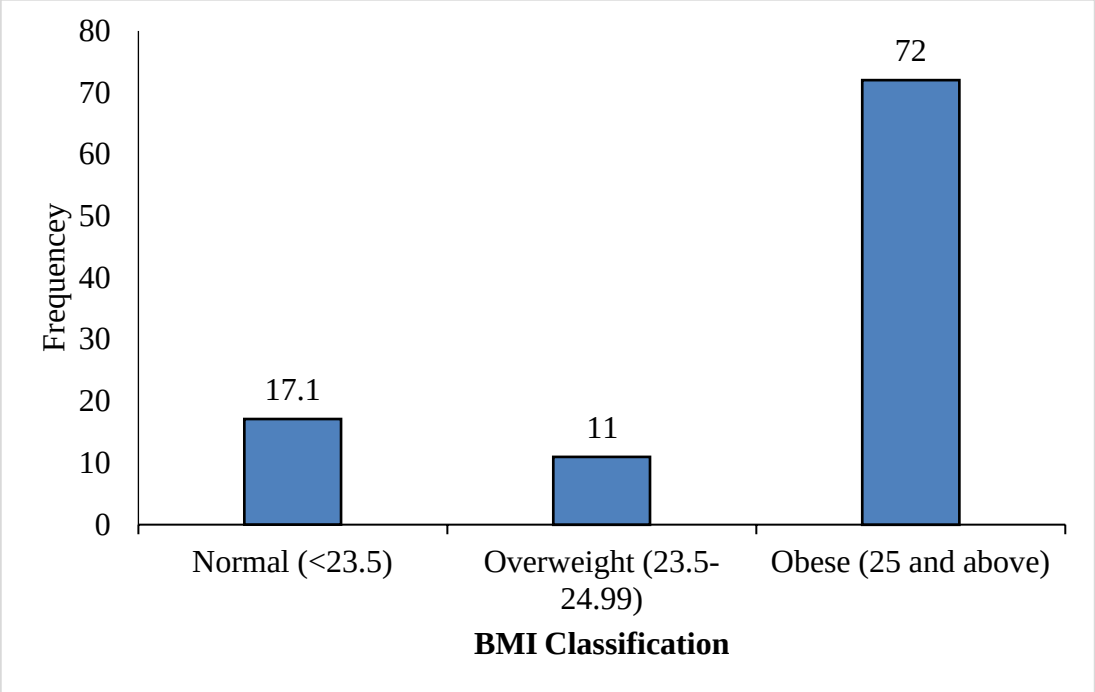


Figure 3. Distribution of study participants based on BMI Classification (n=82)

Table 4. Distribution of study participants based on H/o Diabetes Mellitus (n=82)		
H/o Diabetes Mellitus	**Numbers**	**Percentage**
Yes	38	46.3
No	44	53.7
Total	82	100.0

Nearly 46.3% of the patients were known case of diabetes mellitus.

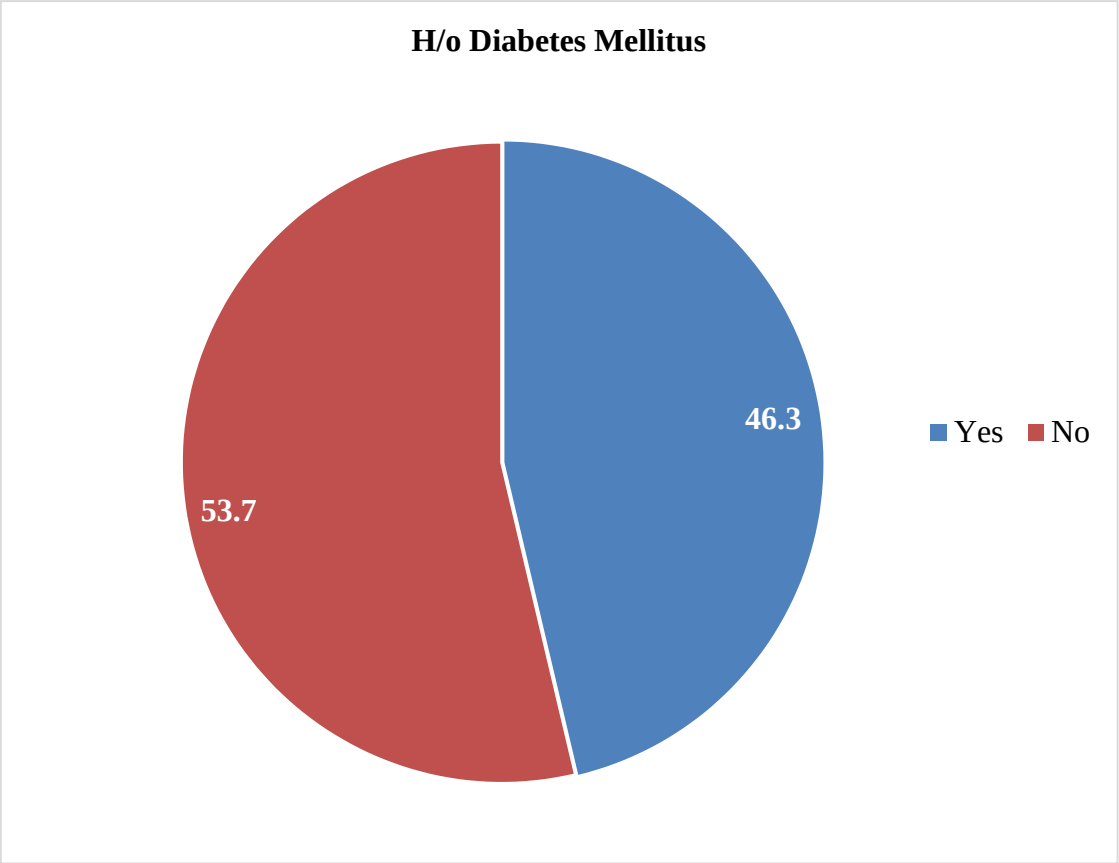


Figure 4. Distribution of study participants based on h/o diabetes mellitus (n=82)

Table 5. Distribution of study participants based on h/o previous fracture (n=82)		
H/o Previous Fracture	**Numbers**	**Percentage**
Yes	55	67.1
No	27	32.9
Total	82	100.0

A history of previous fracture was present in majority of the study participants (67.1%)

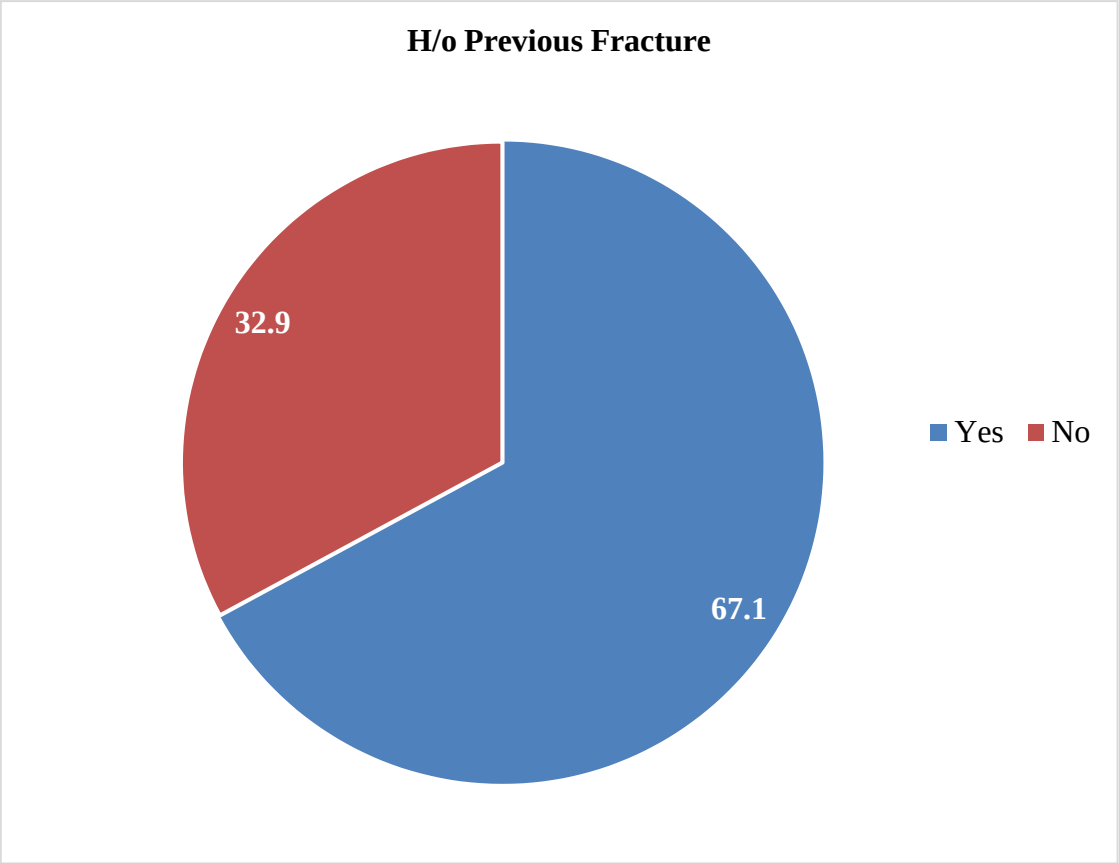


Figure 5. Distribution of study participants based on h/o Previous Fracture (n=82)

Table 6. Distribution of study participants based of h/o parent hip fracture (n=82)		
H/o Parent hip Fracture	**Numbers**	**Percentage**
Yes	15	18.3
No	67	81.7
Total	82	100.0

A history of parent hip fracture was present in nearly one fifth of the study participants (18.3%)

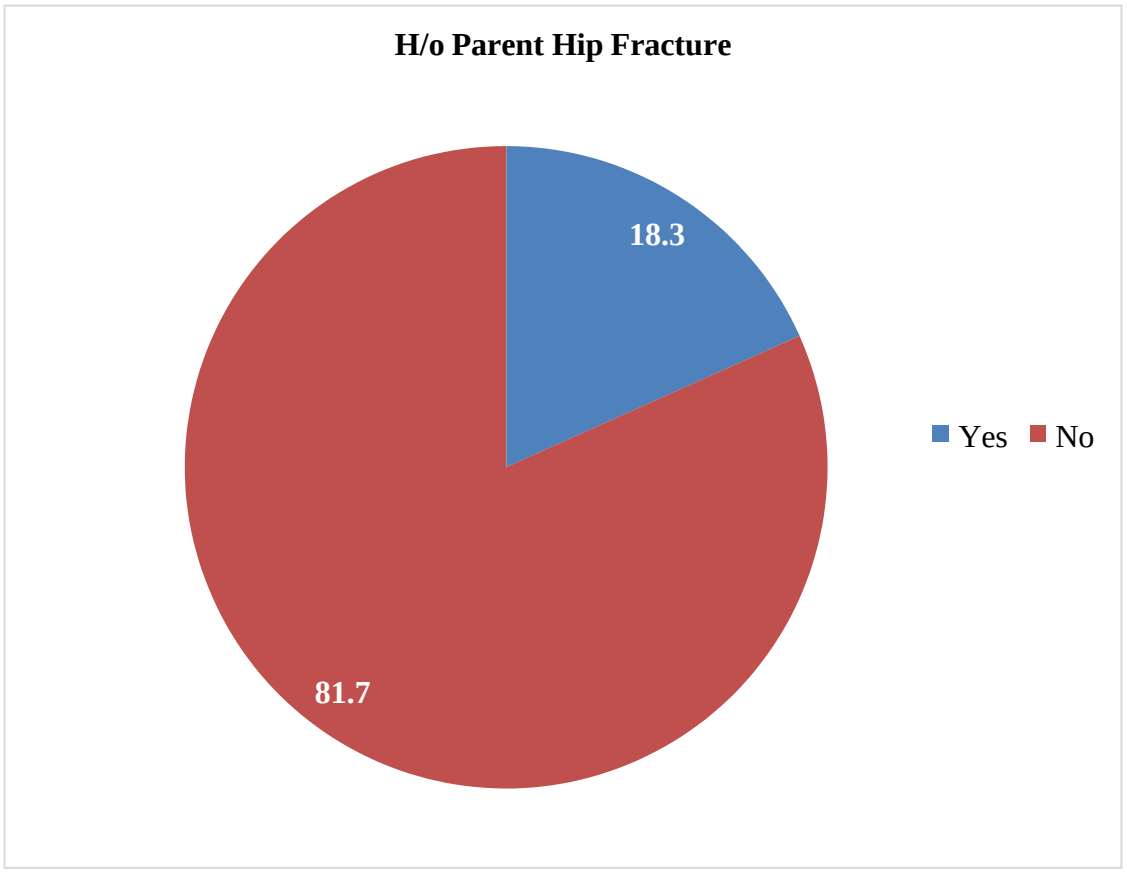


Figure 6. Distribution of study participants based on h/o Parent hip Fracture (n=82)

Table 7. Distribution of study participants based on Femoral Neck BMD T score classification (n=82)

Femoral Neck BMD T score classification	Numbers	Percentage
Normal	21	25.6
Osteopenia	37	45.1
Osteoporosis	24	29.3
Total	82	100

Maximum of the study participants had osteopenia (45.1%) and nearly one third had osteoporosis (29.3%) as per BMD T score classification at femoral neck.

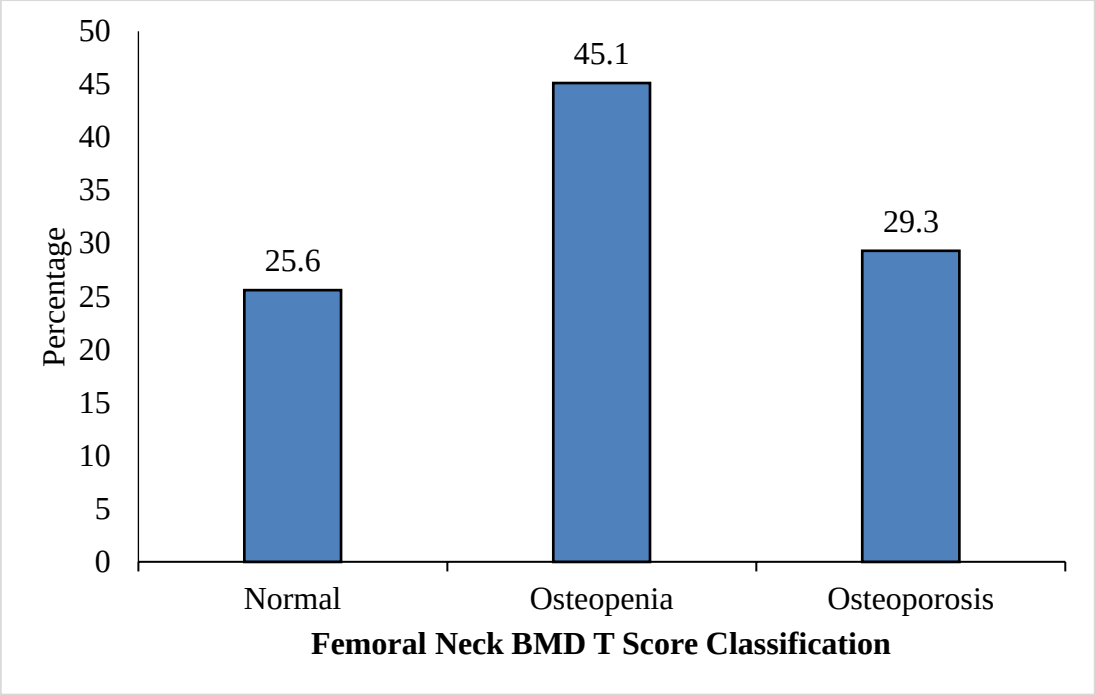


Figure 7. Distribution of study participants based on Femoral Neck BMD T score classification (n=82)

Table 8. Association between age and Diabetes Mellitus (n = 82)				
Age (in years)	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
40-50	3(25.0)	9(75.0)	12(100.0)	0.142
51-60	6(33.3)	12(66.7)	18(100.0)	
61-70	18(58.1)	13(41.9)	31(100.0)	
71-80	11(52.4)	10(47.6)	21(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of participants above 60 years of age had diabetes mellitus, however, this association was not statistically significant.

Figure 8. Association between age and Diabetes Mellitus (n = 82)

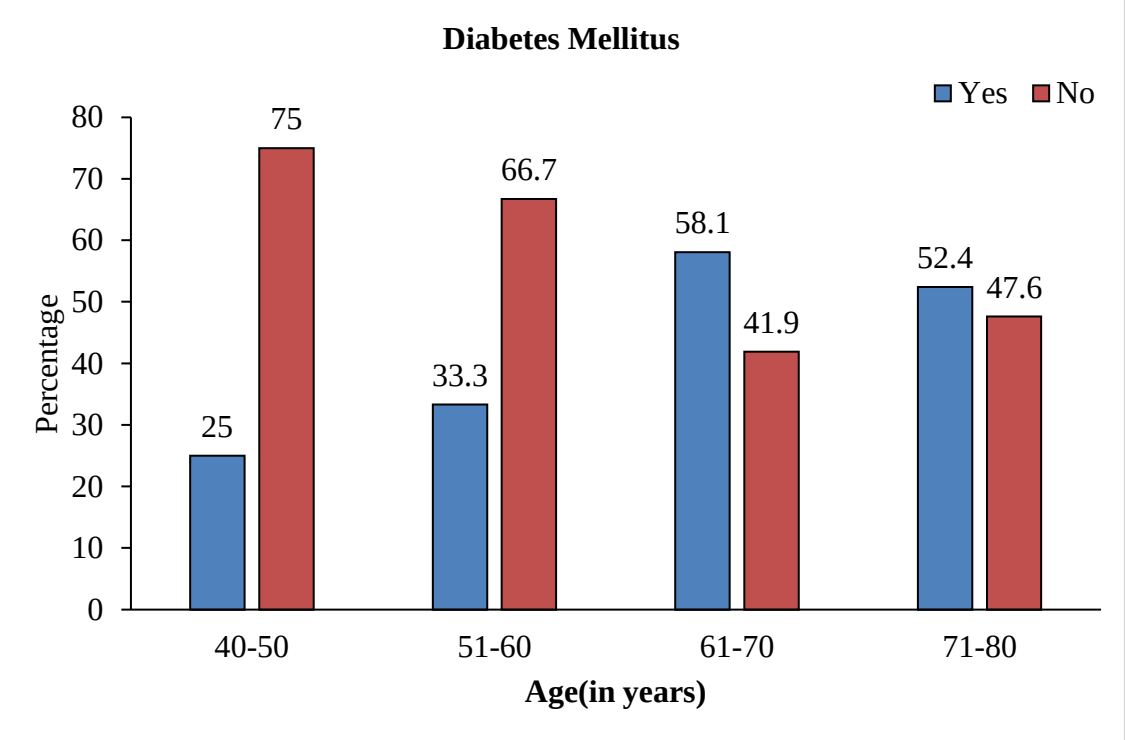


Table 9. Association between sex and Diabetes Mellitus (n = 82)				
Sex	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
Male	5(31.3)	11(68.8)	16(100.0)	0.177
Female	33(50.0)	33(50.0)	66(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of females had diabetes mellitus as compared to males, however, this association was not found to be statistically significant.

Figure 9. Association between sex and Diabetes Mellitus (n = 82)

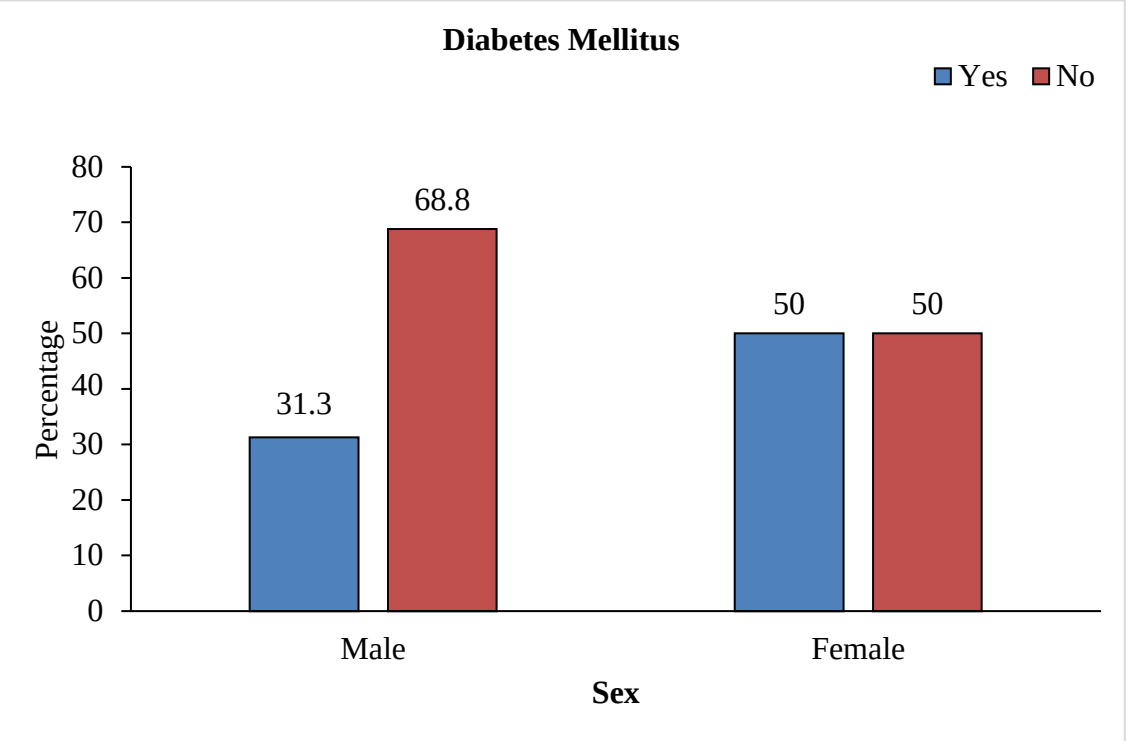


Table 10. Association between BMI and Diabetes Mellitus (n = 82)				
BMI	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
Normal (<23.5)	11(78.6)	3(21.4)	14(100.0)	0.027
Overweight (23.5-24.99)	3(33.3)	6(66.7)	9(100.0)	
Obese (25 and above)	24(40.7)	35(59.3)	59(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of patients with normal BMI had diabetes mellitus as compared to those who were overweight and obese. Also, this association was found to be statistically significant.

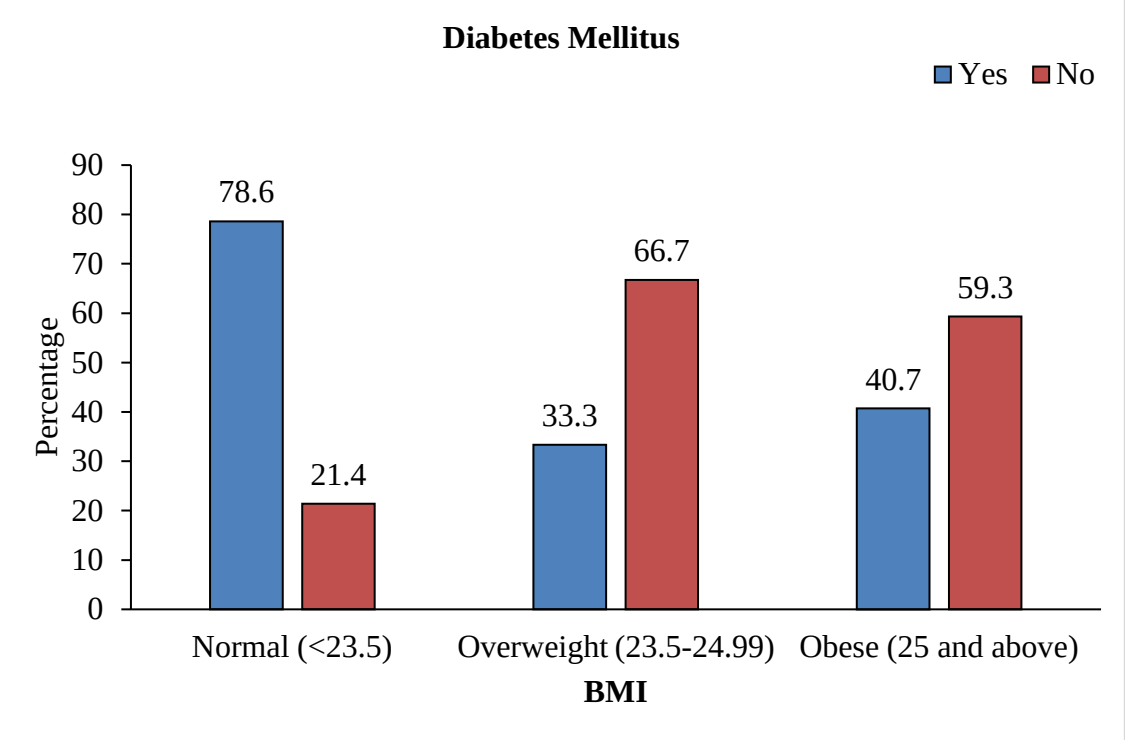


Figure 10. Association between BMI and Diabetes Mellitus (n = 82)

Table 11.	Association between previous fracture and Diabetes Mellitus (n = 82)			
Previous fracture	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
Present	34(61.8)	21(38.2)	55(100.0)	<0.001
Absent	4(14.8)	23(85.2)	27(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

A statistically significant association was observed between history of previous fracture and history of diabetes mellitus.

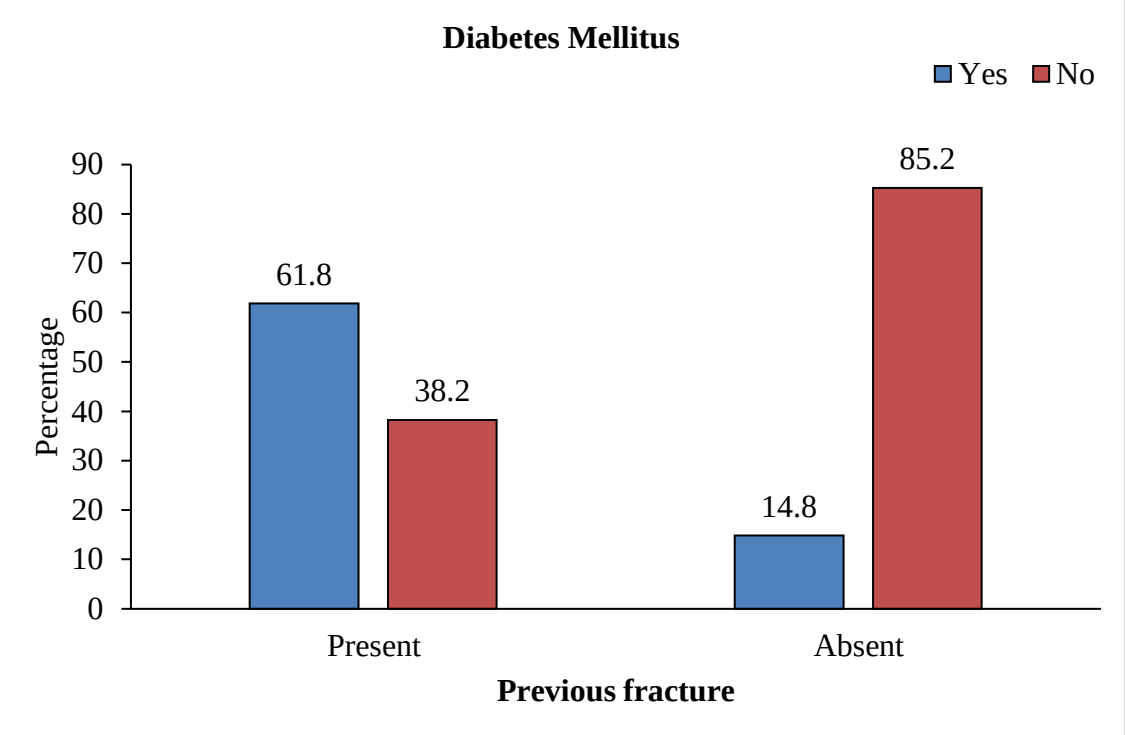


Figure 11. Association between previous fracture and Diabetes Mellitus (n = 82)

Table 12. Association between parent hip fracture and Diabetes Mellitus (n = 82)				
Parent hip fracture	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
Present	11(73.3)	4(26.7)	15(100.0)	0.020
Absent	27(40.3)	40(59.7)	67(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

A statistically significant association was observed between history of parent hip fracture and history of diabetes mellitus.

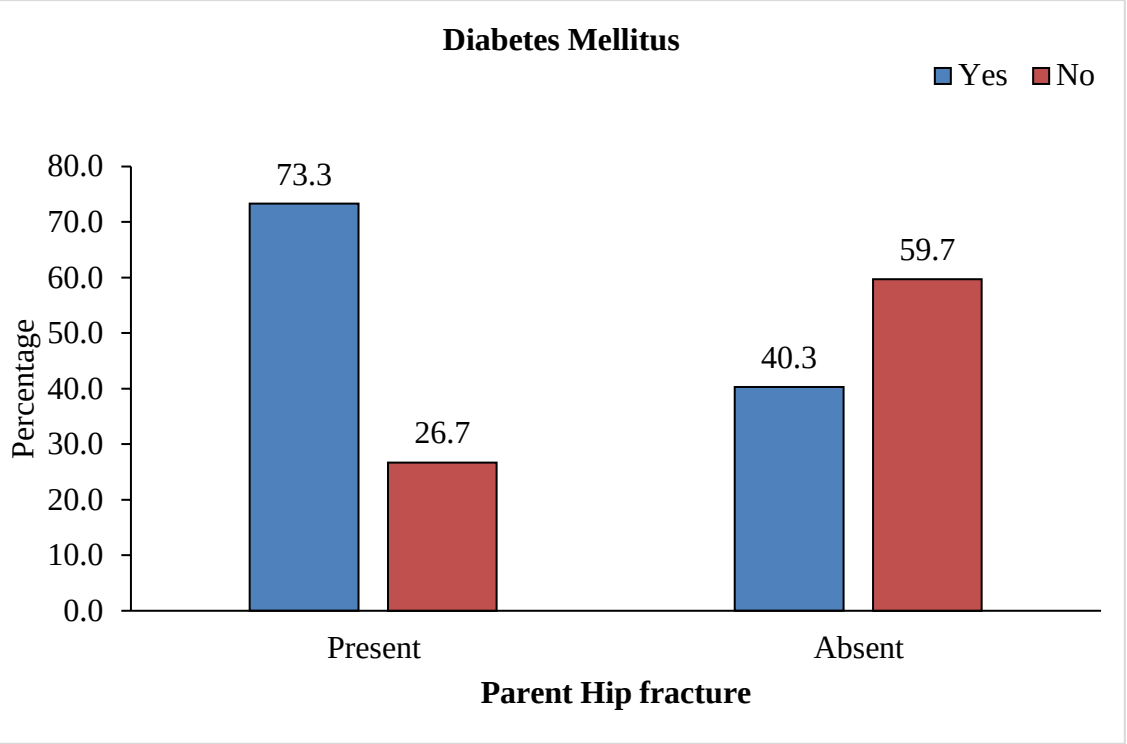


Figure 12. Association between parent hip fracture and Diabetes Mellitus (n = 82)

Table 13. Association between smoking and Diabetes Mellitus (n = 82)				
Smoking	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
No	35(45.5)	42(54.5)	77(100.0)	0.659
Yes	3(60.0)	2(40.0)	5(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Fischer's Exact test was applied to test statistical difference in proportions*

No significant association was observed between smoking habit and history of diabetes mellitus.

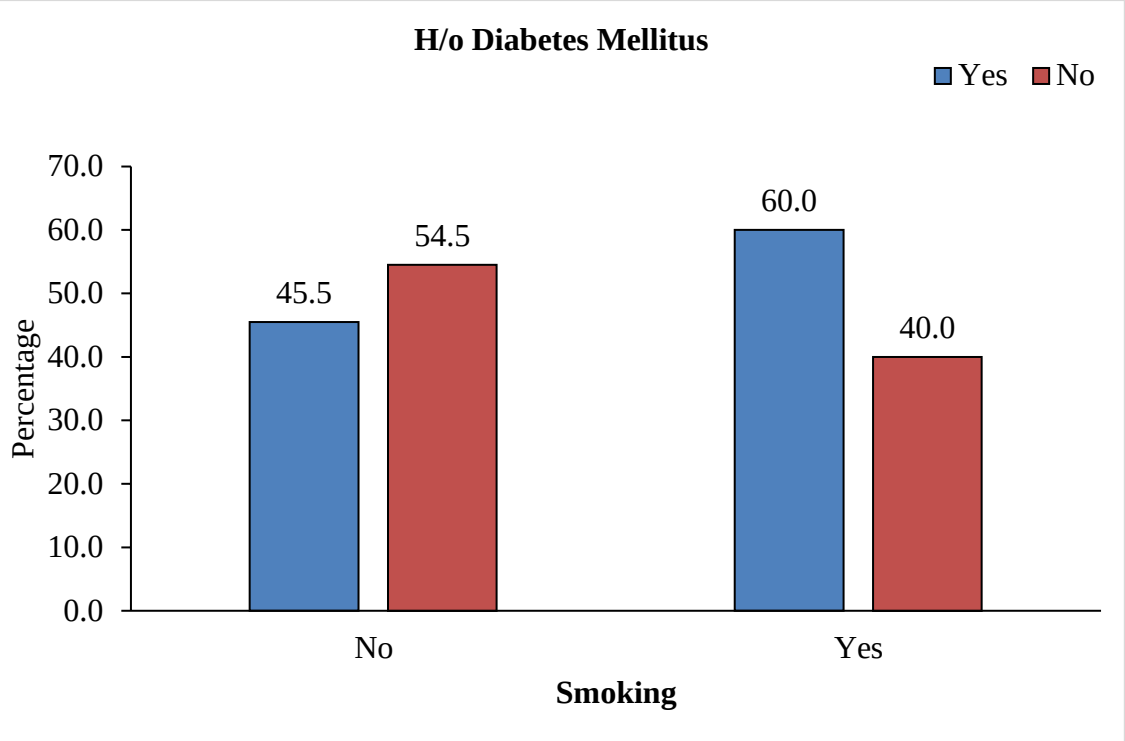


Figure 13. Association between Smoking and Diabetes Mellitus (n = 82)

Table 14. Association between alcoholic and Diabetes Mellitus (n = 82)				
Alcoholic	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
No	37(46.3)	43(53.8)	80(100.0)	1.0
Yes	1(50.0)	1(50.0)	2(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Fischer's Exact test was applied to test statistical difference in proportions*

No significant association was observed between alcoholism and history of diabetes mellitus.

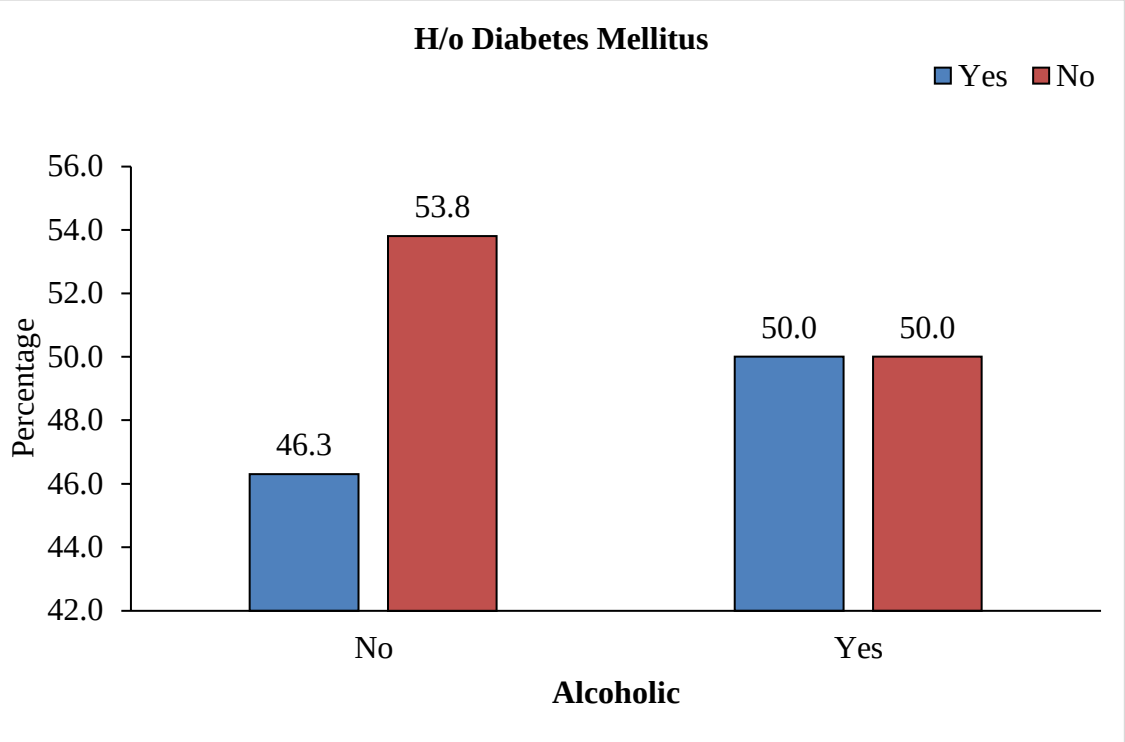


Figure 14. Association between alcoholic and Diabetes Mellitus (n = 82)

Table 15.	Association between secondary osteoporosis and Diabetes Mellitus (n = 82)			
Secondary osteoporosis	H/o Diabetes Mellitus		Total n (%)	p value*
	Yes n(%)	No n (%)		
No	35(44.3)	44(55.7)	79(100.0)	0.095
Yes	3(100.0)	0(0.0)	3(100.0)	
Total	38(46.3)	44(53.7)	82(100.0)	

** Fischer's Exact test was applied to test statistical difference in proportions*

All patients with secondary osteoporosis had history of diabetes mellitus. However, this association was not found to be statistically significant.

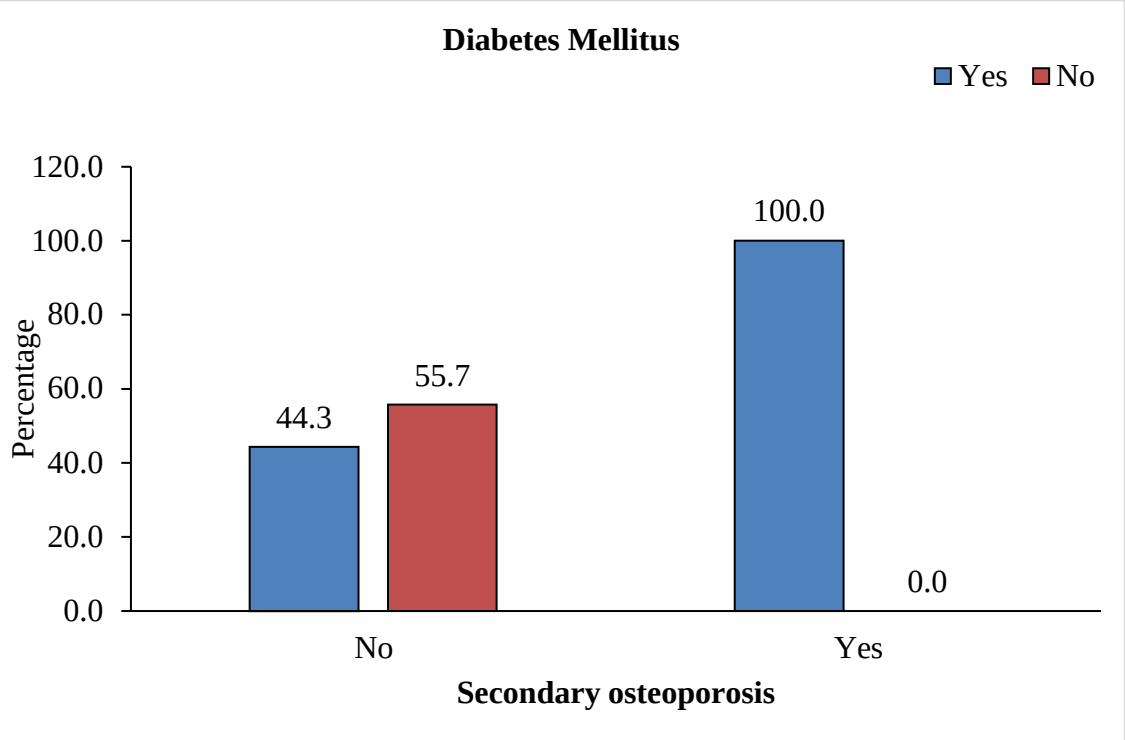


Figure 15. Association between secondary osteoporosis and Diabetes Mellitus (n = 82)

Table 16. Association between BMD and age (n = 82)					
Age (in years)	**BMD T Score Classification**			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
40-50	6(50.0)	4(33.3)	2(16.7)	12(100.0)	**0.026**
51-60	4(22.2)	12(66.7)	2(11.1)	18(100.0)	
61-70	4(12.9)	16(51.6)	11(35.5)	31(100.0)	
71-80	7(33.3)	5(23.8)	9(42.9)	21(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of patients in older age groups had osteoporosis, while higher proportions in the age group of 51-60 years had osteopenia. Also, this association was found to be statistically significant.

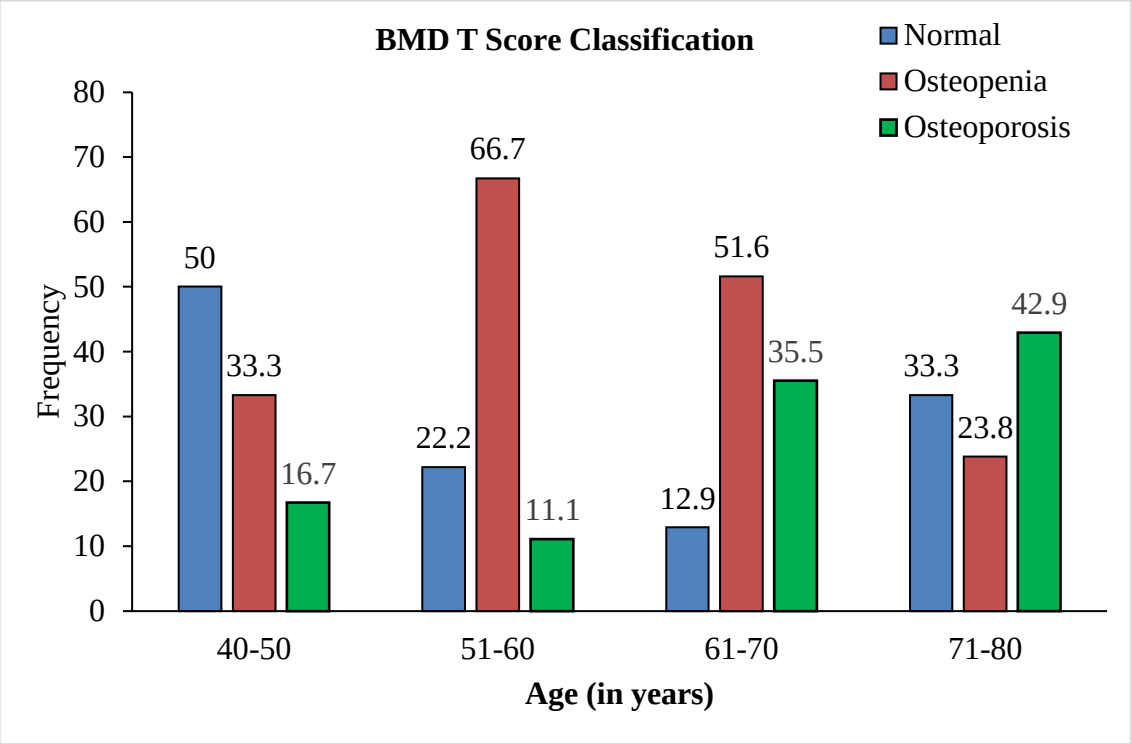


Figure 16. Association between BMD and age (n = 82)

Table 17. Association between BMD and gender (n = 82)

Gender	BMD T Score Classification			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Male	8(50.0)	5(31.3)	3(18.8)	16(100.0)	**0.045**
Female	13(19.7)	32(48.5)	21(31.8)	66(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of females had osteopenia and osteoporosis as compared to males.

Also, this association was found to be statistically significant.

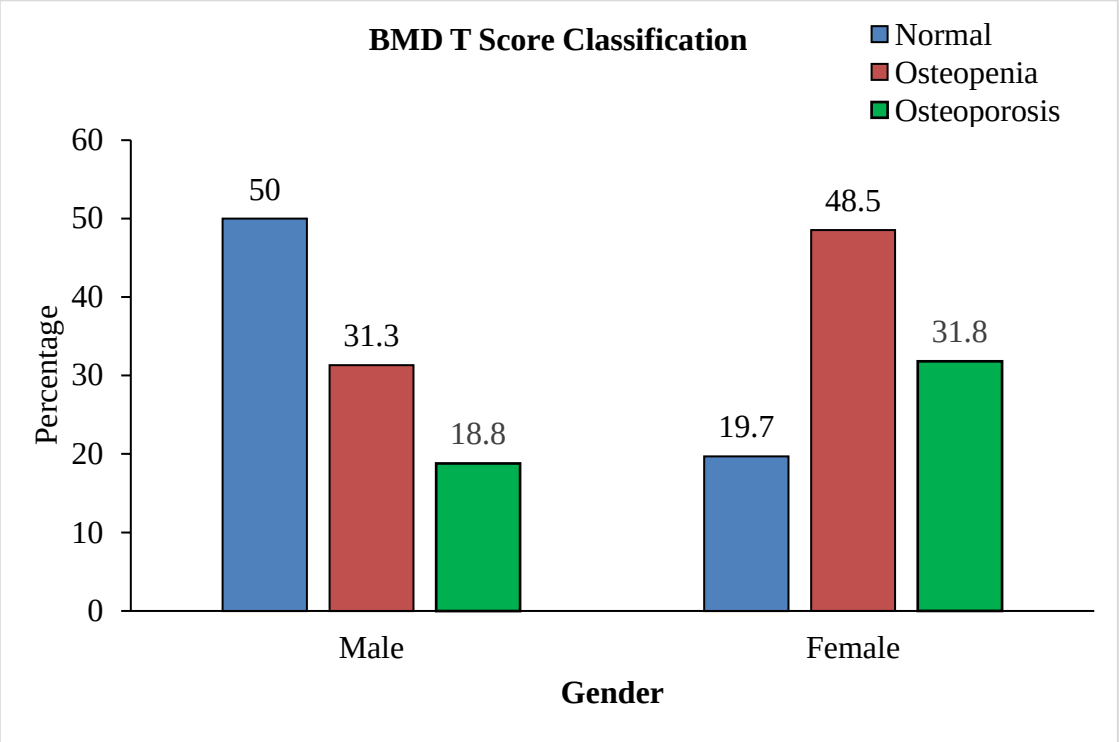


Figure 17. Association between BMD and gender (n = 82)

Table 18. Association between BMD and BMI Classification (n = 82)					
BMI Classification	**BMD T Score Classification**			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Normal (<23.5)	1(7.1)	7(50.0)	6(42.9)	14(100.0)	0.232
Overweight (23.5-24.99)	4(44.4)	2(22.2)	3(33.3)	9(100.0)	
Obese (25 and above)	16(27.1)	28(47.5)	15(25.4)	59(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of obese patient had osteopenia and who had normal BMI had osteoporosis. However, this association was not statistically significant.

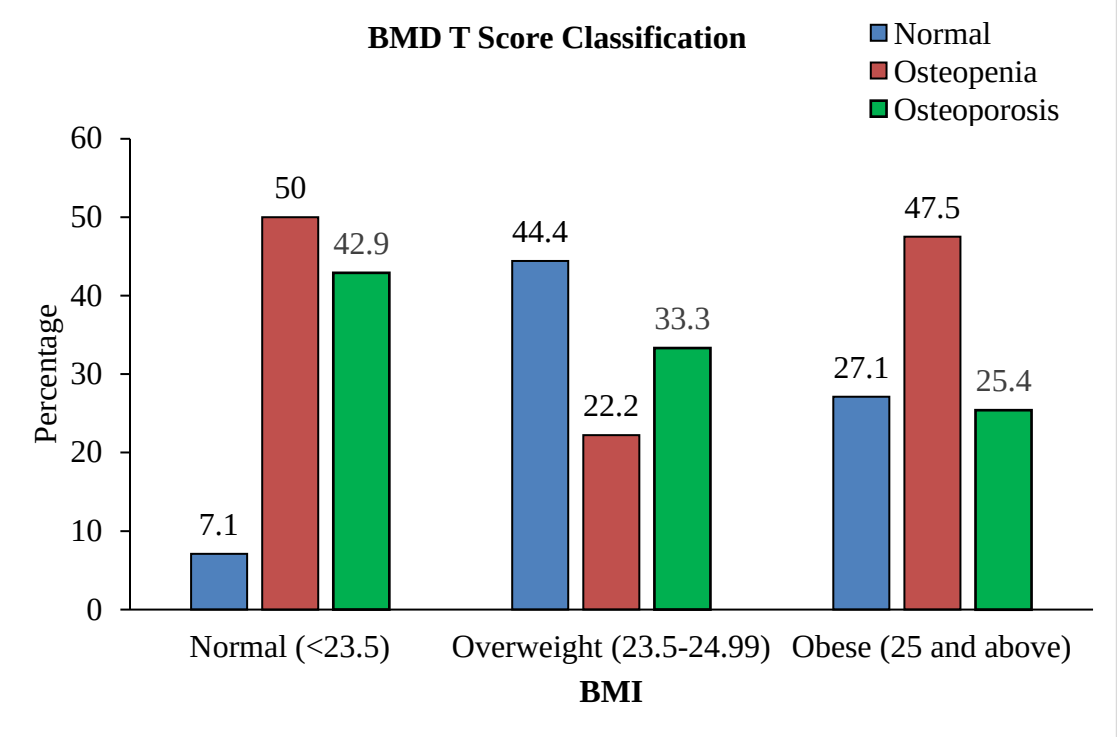


Figure 18. Association between BMD and BMI Classification (n = 82)

Table 19. Association between BMD and h/o Diabetes Mellitus (n = 82)

H/o Diabetes Mellitus	BMD T Score Classification			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Yes	0(0.0)	14(36.8)	24(63.2)	38(100.0)	<0.001
No	21(47.7)	23(52.3)	0(0.0)	44(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Significantly higher proportion of patients with history of diabetes mellitus had osteopenia and osteoporosis.

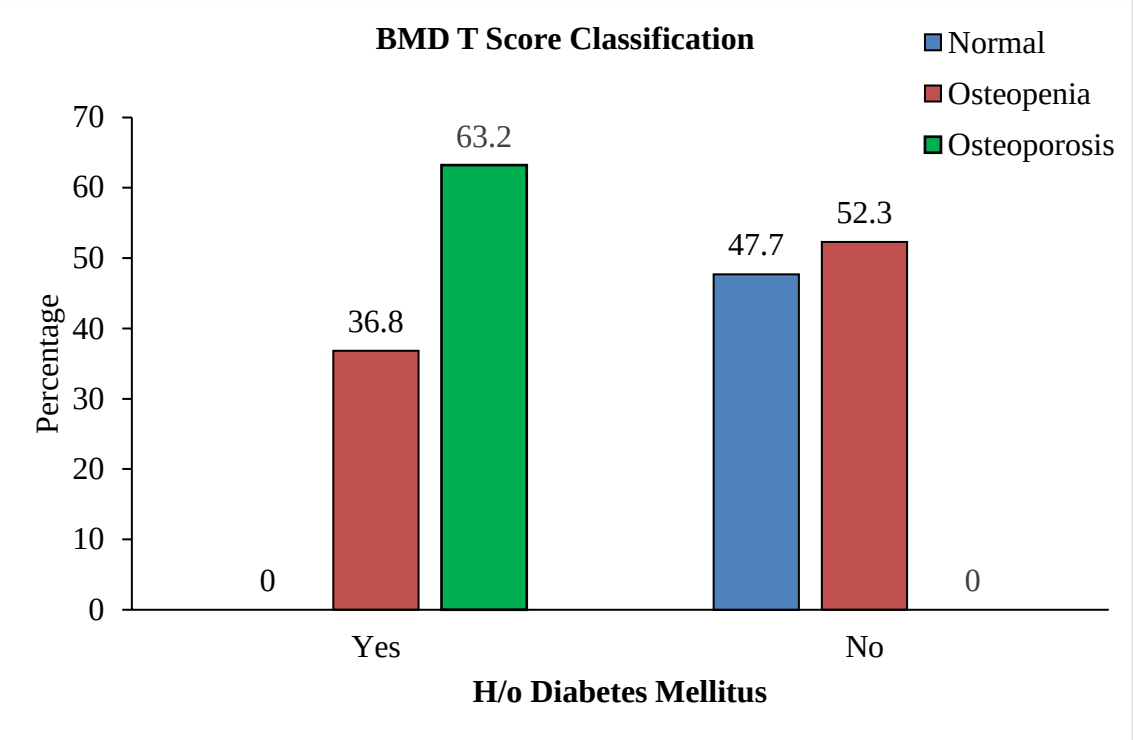


Figure 19. Association between BMD and h/o Diabetes Mellitus (n = 82)

Table 20. Association between BMD and h/o previous fracture(n = 82)

History of previous fracture	BMD T Score Classification			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Yes	7(12.7)	25(45.5)	23(41.8)	55(100.0)	<0.001
No	14(51.9)	12(44.4)	1(3.7)	27(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Significantly higher proportion of patients with history of previous fracture had osteopenia and osteoporosis.

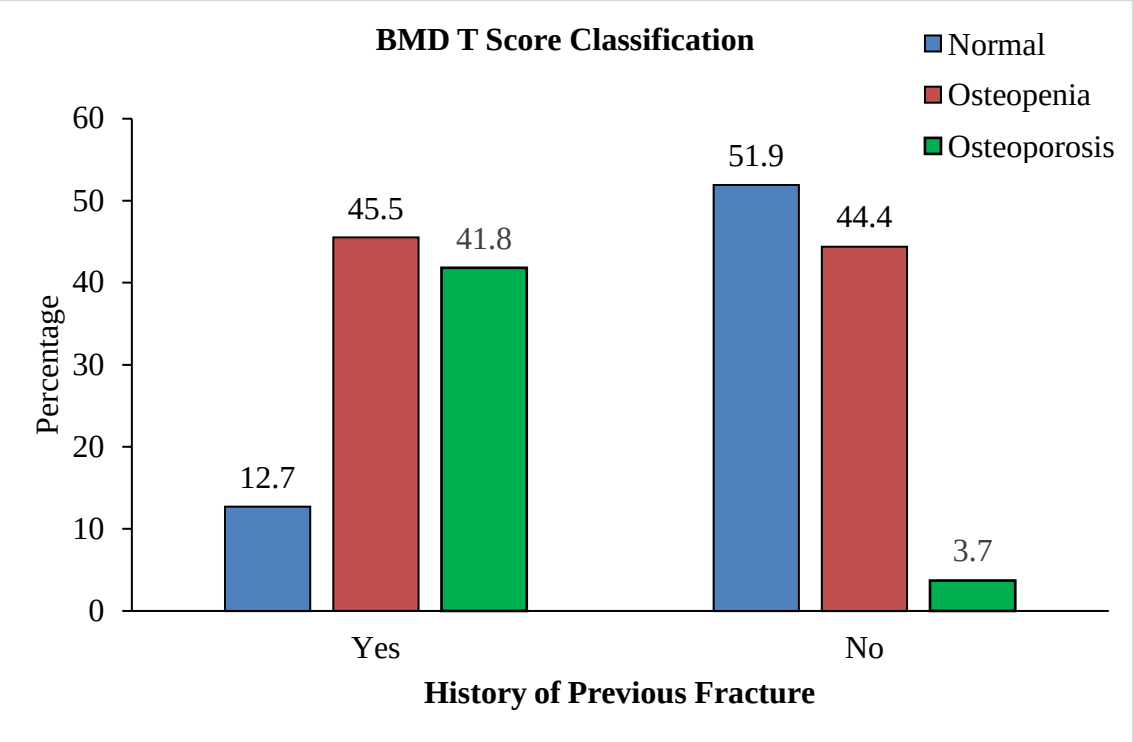


Figure 20. Association between BMD and h/o previous fracture (n = 82)

Table 21. Association between BMD and h/o parent hip fracture (n = 82)

H/o Parent Hip Fracture	BMD T Score Classification			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Yes	1(6.7)	6(40.0)	8(53.3)	15(100.0)	0.043
No	20(29.9)	31(46.3)	16(23.9)	67(100.0)	
Total	21(25.6)	37(45.1)	24(29.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Significantly higher proportion of patients with history of parent hip fracture had osteoporosis.

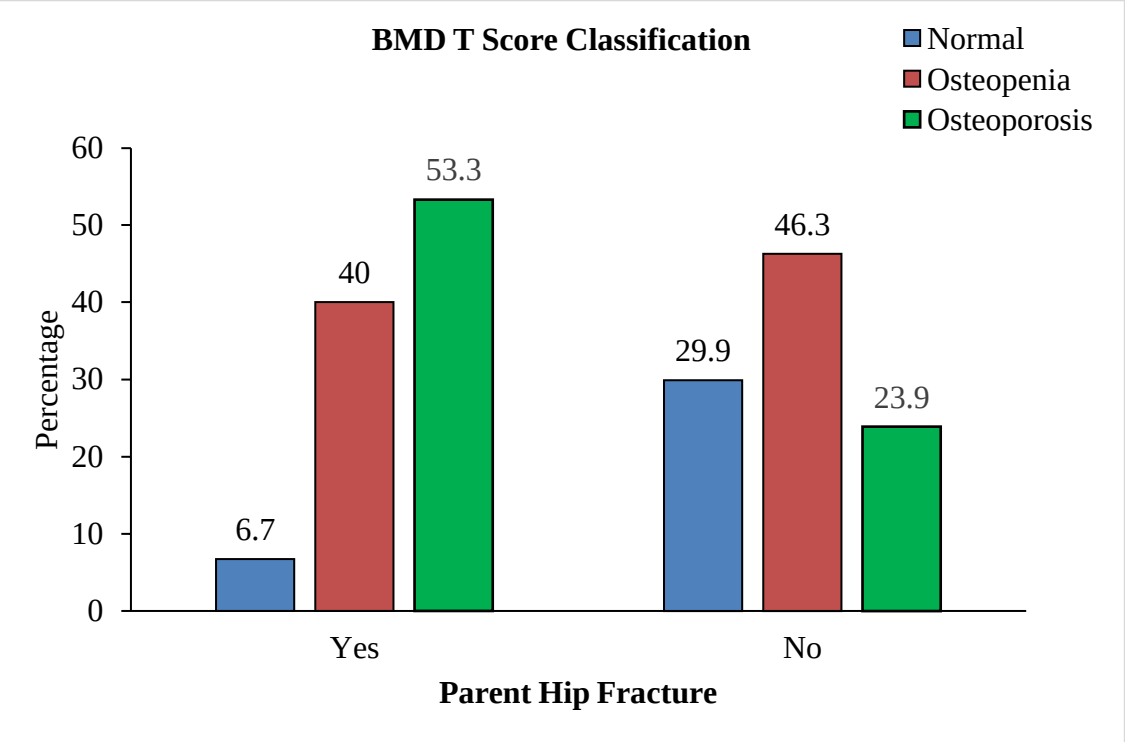


Figure 21. Association between BMD and h/o parent hip fracture (n = 82)

Table 22. Association between BMD and Ten year probability of Osteoporotic Fracture (n = 82)					
Ten year probability of Osteoporotic Fracture	**BMD T Score Classification**			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Low risk	20(95.2)	28(75.7)	2(8.3)	50(61.0)	<0.001
High risk	1(4.8)	8(21.6)	8(33.3)	17(20.7)	
Very high risk	0(0.0)	1(2.7)	14(58.3)	15(18.3)	
Total	21(100.0)	37(100.0)	24(100.0)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Significant association was observed between FRAX score for osteoporotic fracture and presence of osteoporosis as per BMD T score classification.

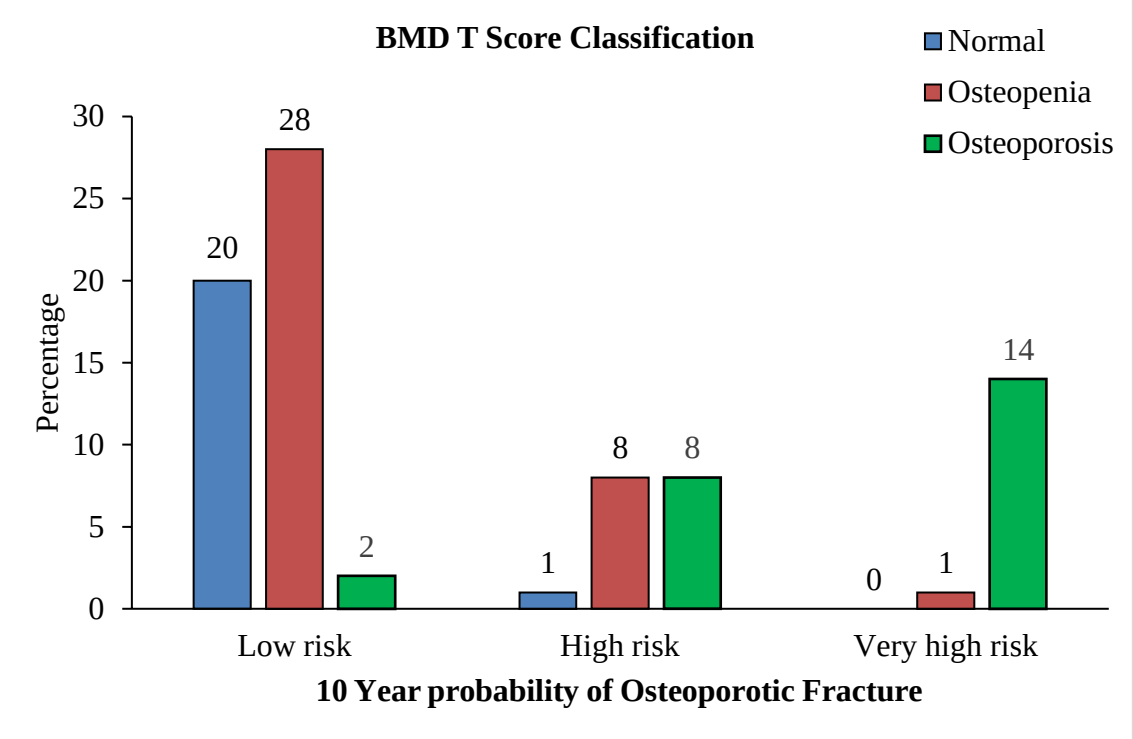


Figure 22. Association between BMD and Ten-year probability of Osteoporotic Fracture (n = 82)

Table 23. Association between BMD and Ten year probability of hip Fracture (n = 82)					
Ten year probability of hip Fracture	**BMD T Score Classification**			Total n (%)	p value*
	Normal n(%)	Osteopenia n (%)	Osteoporosis n (%)		
Low risk	21(100.0)	37(100.0)	10(41.7)	68(82.9)	<0.001
High risk	0(0.0)	0(0.0)	5(20.8)	5(6.1)	
Very high risk	0(0.0)	0(0.0)	9(37.5)	9(11.0)	
Total	21(100.0)	37(100.0)	24(100.0)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Significant association was observed between FRAX score for hip fracture and presence of osteoporosis as per BMD T score classification.

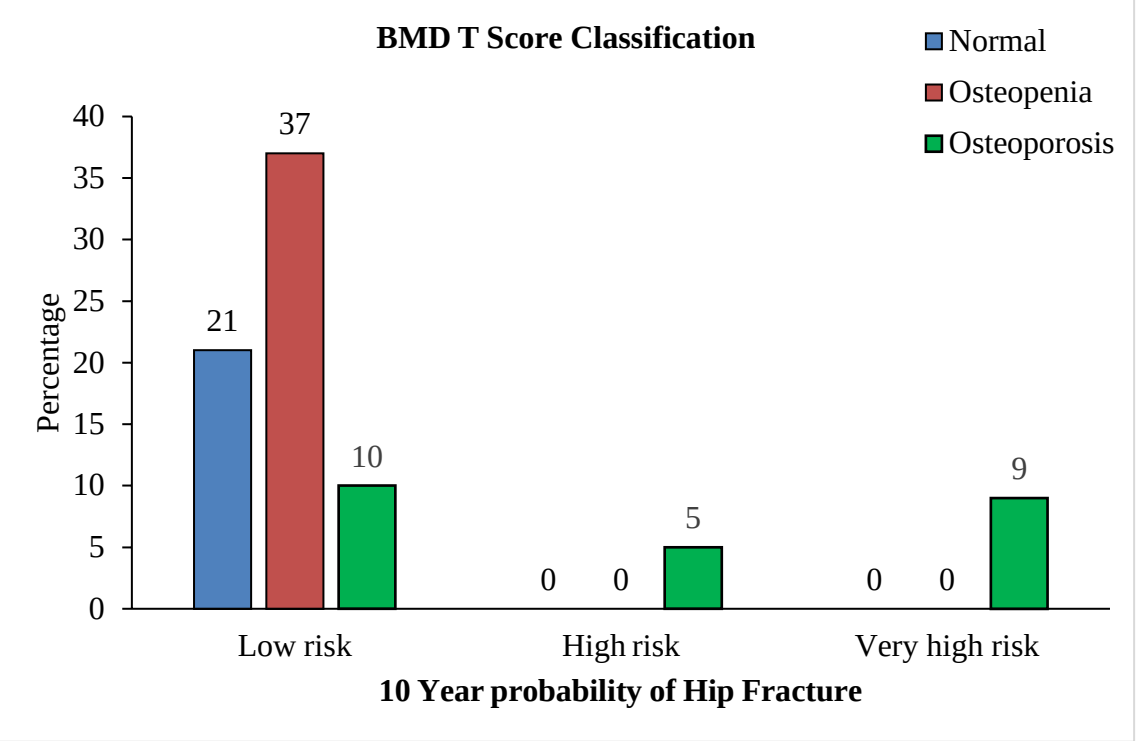


Figure 23. Association between BMD and Ten-year probability of Hip Fracture (n = 82)

Table 24. Association between FRAX score for osteoporotic fracture, diabetes and other parameters (n = 82)									
H/o Diabetes Mellitus	**FRAX score for osteoporotic fracture**								
	***Low Risk** (n=50)*		***p value***	***High Risk** (n=17)*		***p value***	***Very High Risk** (n=15)*		***p value***
	Yes *n(%)*	**No** *n(%)*		**Yes** *n(%)*	**No** *n(%)*		**Yes** *n(%)*	**No** *n(%)*	
Age (in years)									
40-50	2(18.2)	9(81.8)	0.731	1(100.0)	0(0.0)	0.141	1(100.0)	0(0.0)	NA
51-60	4(28.6)	10(71.4)		1(33.3)	2(66.7)		5(100.0)	0(0.0)	
61-70	3(20.0)	12(80.0)		10(90.9)	1(9.1)		9(100.0)	0(0.0)	
71-80	1(10.0)	9(90.0)		1(50.0)	1(50.0)		1(100.0)	0(0.0)	
Sex									
Male	2(15.4)	11(84.6)	0.629	3(100.0)	0(0.0)	0.541#	0(0.0)	0(0.0)	NA
Female	8(21.6)	29(78.4)		10(71.4)	4(28.6)		15(100.0)	0(0.0)	
BMI									
Normal (<23.5)	4(66.7)	2(33.3)	0.006	1(50.0)	1(50.0)	0.426#	6(100.0)	0(0.0)	NA
Overweight (23.5-24.99)	0(0.0)	6(100.0)		0(0.0)	0(0.0)		3(100.0)	0(0.0)	
Obese (25 and above)	6(15.8)	32(84.2)		12(80.0)	3(20.0)		6(100.0)	0(0.0)	
H/o Previous Fracture									
Yes	6(25.0)	18(75.0)	0.490#	13(81.3)	3(18.8)	0.235#	15(100.0)	0(0.0)	NA
No	4(15.4)	22(84.6)		0(0.0)	1(100.0)		0(0.0)	0(0.0)	
H/o Parent Hip Fracture									
Yes	0(0.0)	2(100.0)	1.0#	2(50.0)	2(50.0)	0.219#	9(100.0)	0(0.0)	NA
No	10(20.8)	38(79.2)		11(84.6)	2(15.4)		6(100.0)	0(0.0)	
Smoking									
Yes	1(50.0)	1(50.0)	0.363#	2(66.7)	1(33.3)	1.0	0(0.0)	0(0.0)	NA
No	9(18.8)	39(81.3)		11(78.6)	3(21.4)		15(100.0)	0(0.0)	
Alcoholic									
Yes	1(50.0)	1(50.0)	0.363#	0.0	0.0	NA	0(0.0)	0(0.0)	NA
No	9(18.8)	39(81.3)		13(76.5)	4(23.5)		15(100.0)	0(0.0)	
Secondary Osteoporosis									
Yes	0(0.0)	0(0.0)	NA	1(100.0)	0(0.0)	1.0	2(100.0)	0(0.0)	NA
No	10(20.0)	40(80.0)		12(75.0)	4(25.0)		13(100.0)	0(0.0)	

 # Fischer's Exact test was applied

Table 25. Association between FRAX score for hip fracture, diabetes and other parameters (n = 82)									
H/o Diabetes Mellitus	**FRAX score for hip fracture**								
	***Low Risk** (n=68)*		***p value***	***High Risk** (n=5)*		***p value***	***Very High Risk** (n=9)*		***p value***
	Yes *n(%)*	**No** *n(%)*		**Yes** *n(%)*	**No** *n(%)*		**Yes** *n(%)*	**No** *n(%)*	
Age (in years)									
40-50	2(18.2)	9(81.8)	0.124	1(100.0)	0(0.0)	NA	0(0.0)	0(0.0)	NA
51-60	5(29.4)	12(70.6)		0(0.0)	0(0.0)		1(100.0)	0(0.0)	
61-70	14(51.9)	13(48.1)		2(100.0)	0(0.0)		2(100.0)	0(0.0)	
71-80	3(23.1)	10(76.9)		2(100.0)	0(0.0)		6(100.0)	0(0.0)	
Sex									
Male	4(26.7)	11(73.3)	0.547	1(100.0)	0(0.0)	NA	0(0.0)	0(0.0)	NA
Female	20(37.7)	33(62.3)		4(100.0)	0(0.0)		9(100.0)	0(0.0)	
BMI									
Normal (<23.5)	6(66.7)	3(33.3)	0.027	1(100.0)	0(0.0)	NA	4(100.0)	0(0.0)	NA
Overweight (23.5-24.99)	0(0.0)	6(100.0)		2(100.0)	0(0.0)		1(100.0)	0(0.0)	
Obese (25 and above)	18(34.0)	35(66.0)		2(100.0)	0(0.0)		4(100.0)	0(0.0)	
H/o Previous Fracture									
Yes	20(48.8)	21(51.2)	0.004	5(100.0)	0(0.0)	NA	9(100.0)	0(0.0)	NA
No	4(14.8)	23(85.2)		0(0.0)	0(0.0)		0(0.0)	0(0.0)	
H/o Parent Hip Fracture									
Yes	4(50.0)	4(50.0)	0.354#	5(100.0)	0(0.0)	NA	7(100.0)	0(0.0)	NA
No	20(33.3)	40(66.7)		0(0.0)	0(0.0)		2(100.0)	0(0.0)	
Smoking									
Yes	2(50.0)	2(50.0)	0.610#	1(100.0)	0(0.0)	NA	0(0.0)	0(0.0)	NA
No	22(34.4)	42(65.6)		4(100.0)	0(0.0)		9(100.0)	0(0.0)	
Alcoholic									
Yes	1(50.0)	1(50.0)	1.0#	0(0.0)	0(0.0)	NA	0(0.0)	0(0.0)	NA
No	23(34.8)	43(65.2)		5(100.0)	0(0.0)		9(100.0)	0(0.0)	
Secondary Osteoporosis									
Yes	1(100.0)	0(0.0)	0.353#	0(0.0)	0(0.0)	NA	2(100.0)	0(0.0)	NA
No	23(34.3)	44(65.7)		5(100.0)	0(0.0)		7(100.0)	0(0.0)	

 # Fischer's Exact test was applied

Table 26. Association between Diabetes mellitus and Ten year probability of osteoporotic Fracture (n = 82)					
H/o Diabetes Mellitus	**Ten Year Probability of osteoporotic Fracture**			Total n (%)	p value*
	Low risk n(%)	High risk n (%)	Very high risk n (%)		
Yes	10(26.3)	13(34.2)	15(39.5)	38(100.0)	<0.001
No	40(90.9)	4(9.1)	0(0.0)	44(100.0)	
Total	50(61.0)	17(20.7)	15(18.3)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of patients with history of diabetes mellitus had a very high risk of osteoporotic fracture as per FRAX classification. Also, this association was found to be statistically significant.

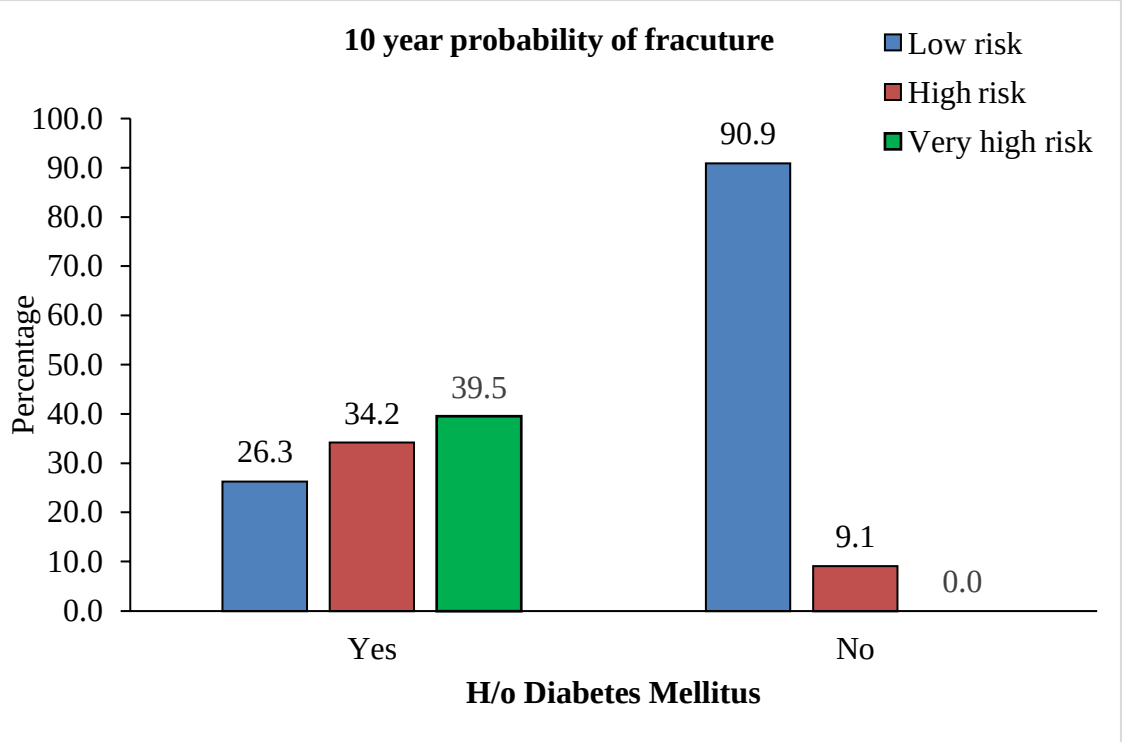


Figure 24. Association between Diabetes Mellitus and Ten-year probability of Fracture (n = 82)

Table 27. Association between Diabetes mellitus and Ten year probability of hip Fracture (n = 82)					
H/o Diabetes Mellitus	**Ten Year Probability of Hip Fracture**			Total n (%)	p value*
	Low risk n(%)	High risk n (%)	Very high risk n (%)		
Yes	24(63.2)	5(13.2)	9(23.7)	38(100.0)	<0.001
No	44(100.0)	0(0.0)	0(0.0)	44(100.0)	
Total	68(82.9)	5(6.1)	9(11.0)	82(100.0)	

** Chi Square test was applied to test statistical difference in proportions*

Higher proportion of patients with history of diabetes mellitus had a very high risk of hip fracture as per FRAX classification. Also, this association was found to be statistically significant.

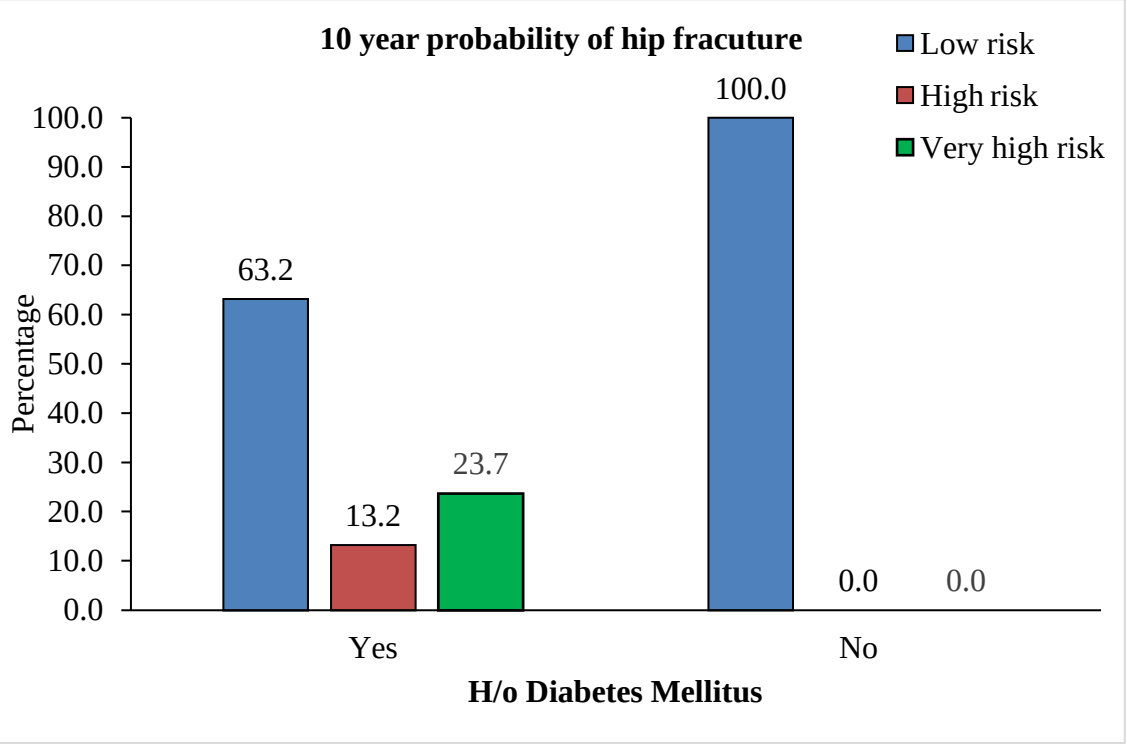


Figure 25. Association between Diabetes Mellitus and Ten-year probability of hip Fracture (n = 82)

DISCUSSION

The present study was carried out with an aim to assess the use of WHO FRAX score in diabetic patients and to compare the fracture risk between diabetic and healthy population using FRAX score. The study was undertaken as a hospital based cross sectional study of 82 patients in either sex aged 40 to 80 years.

Maximum of the study participants were in the age group of 61-70 years (37.8%) and females (80.5%). The mean age of the study participants was observed to be 62.3±10.3 years. Majority of the study participants were obese (72%), while 11% were overweight. Nearly 46.3% of the patients were known case of diabetes mellitus. A history of previous fracture was present in majority of the study participants (67.1%) and parent hip fracture (18.3%). Maximum of the study participants had osteopenia (45.1%) and nearly one third had osteoporosis (29.3%) as per BMD T score classification at femoral neck. A statistically significant association was observed between history of diabetes mellitus and history of previous fracture (p value <0.001), and history of parent hip fracture (p value -0.020). Higher proportion of patients in older age groups had osteoporosis, while higher proportions in the age group of 51-60 years had osteopenia (p value -0.026). Higher proportion of females had osteopenia and osteoporosis as compared to males (p value -0.045). Significantly higher proportion of patients with history of diabetes mellitus had osteopenia and osteoporosis (p value <0.001), history of previous fracture (p value <0.001), and history of parent hip fracture (p value -0.043). Significant association was observed between FRAX score for hip fracture & osteoporotic fracture and presence of osteoporosis as per BMD T score classification (p values <0.001). Higher proportion of patients with history of diabetes mellitus had a very high risk of osteoporotic fracture and hip fracture as per FRAX classification (p values <0.001).

Because the complicated underlying mechanisms also include diminished bone quality, decreased bone production, and cortical porosity, BMD testing is not the best method for predicting the risk of fracture in diabetes mellitus (DM). Diabetes participants certainly have a higher fracture risk, but there is still no risk categorization for these patients. In subjects with and without DM, the relationship between incident fractures and the traditional clinical risk factors for osteoporotic fractures (such as frequent fractures, chronic glucocorticoid use, alcohol or tobacco use, etc.) is similar.[161] However, there are additional considerations that are unique to the DM population. Regardless of diabetic treatment, having diabetes for a long time (more than 10 years) considerably raises the risk of all fractures.[162] Only after the disease has progressed for 10 years does the risk of hip fracture appear to be significantly increased. FRAX (fracture risk assessment), a popular fracture risk index, offers precise risk assessments in sizable populations of osteoporosis patients.

It is important to note that before comparison of the present study results with that of the other research works in India, different authors have evaluated different age group and population, which may not be totally comparable with that of the present research findings. Age is also determined as a risk factor for a decreased BMD.[163] Individuals with diabetes were slightly older, had higher mean BMI, and had a higher prevalence of prior fracture. Present study results were also in agreement with that of the above statement with respect to the association between increasing age and osteopenia/ osteoporosis.

Vaishya R et al[164] in their study observed that sex was significantly associated with T-score (P<0.001). Forty (8.99%) patients were osteoporotic, 265 (59.55%) were osteopenic and the remaining 140 (31.46%) were normal. Kadam NS et al[165] study noted that the prevalence of osteopenia was observed in men (50%–62%) and postmenopausal women (50%–59%) while for premenopausal women it was 32.6%. Bhabulkar S et al[166]

in their large scale retrospective study in India among adults above 18 years of age reported that the overall prevalence of osteopenia and osteoporosis was 49.9% and 18.3% respectively. A similar proportion of osteopenia and osteoporosis was noted in the present study as well.

Vaishya R et al[164] noted that a significant association of T-score was found with parent history of fracture ($P<0.05$), rheumatoid arthritis ($P<0.05$) and secondary osteoporosis ($P<0.05$). Previous history of fracture's association was not found to be significant. Smoking, alcohol intake and steroid intake were not found to be significantly associated with T-scores. A similar association was observed between the above discussed determinants and osteoporosis in the present study as well.

Diabetes has a diverse range of bone-related complications. Although the majority of research concur that diabetes increases the risk of fracture, bone mineral density (BMD), particularly in type 2 diabetes, may not accurately reflect bone fragility. There is ongoing discussion regarding the potential impact of the metabolic abnormalities of diabetes on bone metabolism, structure, quality, and mineral density. Kamalanathan S et al[151] study results indicated that bone mineral density was normal (Z score > -2) in 156 (80.5%) and low (Z score ≤ -2) in 38 (19.5%) patients in the diabetes study group. Bone mineral density in the diabetes group was significantly higher than the control group in both sexes at the hip and spine. Dutta MK et al[152] observed in their study that Bone mineral density was lower in diabetic patients as compared to controls (hip 0.962 ± 0.167 g/cm^2 vs 1.013 ± 0.184 g/cm^2, P = 0.05; spine 0.929 ± 0.214 g/cm^2 vs 1.113 ± 0.186 g/cm^2, P < 0.00001). Majima T et al[156] was found in their study that BMD and Z score at the distal radius were significantly lower in type 2 diabetic patients than those in control group. Arora H et al[167] study documented that out of 120 DM patients evaluated 48.33% cases had T score between -1 and -2.5(Osteopenia) and 28(23.33%) cases had T score ≤ -2.5(Osteoporosis).

A similar and comparable association was observed between BMD T score and presence of history of diabetes mellitus was noted in the present study as well. The hypothesized mechanisms include altered osteoblast-osteoclast function with elevated sclerostin, reduced insulin-like growth factor 1 (IGF1), reduced osteocalcin, and other molecular abnormalities, which results in a reduction in bone turnover and modified bone quality.

Finding fracture predictors is crucial since diabetes patients are becoming more prevalent, which raises the population-attributable risk of fracture. Diabetes patients still don't have adequate risk categorization, despite their higher fracture risk. The 10-year fracture probability can be calculated using the FRAX algorithm. One prospective study found that the FRAX algorithm underestimated fracture risk in patients with T2DM,[168] and a retrospective cohort study showed that FRAX underestimated the risk of hip fracture and major osteoporotic fracture in a group of combined T1DM and T2DM patients.[169]

Aishwarya TV et al[170] study subjects were assessed for future hip fracture risk within 10 years using WHO FRAX and reported that Type II DM patients taking hypoglycemic drugs were associated with increased risk of hip fracture (odds ratio [OR] =2.97). Incidence (19.2%) and prevalence (60%) of hip fractures was higher in patients taking hypoglycemic drugs than the incidence (14.8%) and prevalence (40%) of those who were not taking the drug. Valentini A et al[171] in their study among patients above 50 years of age noted that patients with T2DM had BMD and T-scores higher than those of non-diabetic subjects, while FRAX average values were higher in the non-diabetic group. Results of the above discussed studies were concordant with that of the findings observed in the present research work.

Leslie WD et al[172] depicted in their study that After adjusting for FRAX risk factors including BMD, diabetes was found to be a substantial independent predictor for major

osteoporotic fracture (MOF) (adjusted hazard ratio [aHR] 1.32 [95% confidence interval (CI) 1.20-1.46]). In investigations of MOF, no significant associations between diabetes and FRAX risk variables or prior fracture site were found. Age significantly changed the impact of diabetes in terms of predicting hip fractures (aHR age 60, 4.67 [95% CI 2.76-7.89], age 60-69, 2.68 [1.77-4.04], age 70-79, 1.57 [1.20-2.04], age >80, 1.42 [1. 10-1.99]; p interaction 0.001). This was also supported by the study carried out by Schwartz AV et al[173] where it was reported that for a given T-score and age or FRAX score, diabetic participants had a higher fracture risk than those without diabetes. For a similar hip fracture risk, diabetic participants had a higher T-score than nondiabetic participants. The subgroup analysis in the present study revealed comparable findings, however the sample size of the present study limited the extent of analysis.

In yet another research by Sumit R et al[174] duration of diabetes longer than 10 years was associated with a higher risk for MOF (hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.30 –1.66), and this was similar in the fully adjusted models (HR 1.34, 95% CI 1.17–1.54). However, duration of diabetes was not included as a variable of interest in the present study.

Because different studies have used very different sample sizes, looked at different geographic populations over different time periods, were limited to specific fracture types, or determined diabetes diagnoses and durations using different methods, the results from the prior literature are inconsistent and difficult to synthesize.

CONCLUSION

Osteopenia and osteoporosis were more prevalent among females and amongst those who belonged to older age group. Significant association was observed between FRAX score for hip fracture & osteoporotic fracture and presence of osteoporosis. Diabetes mellitus was found to be a risk factor for osteoporosis and impacted the FRAX score of the patients. The FRAX score indicates that people with type 2 diabetes are more likely to suffer from fractures. Diabetes patients had a higher 10-year observed risk of major osteoporotic fracture and hip fracture than healthy population. Diabetes is a risk factor that might be evaluated for inclusion as a clinical risk factor in the FRAX Score. Routine screening of people with diabetes is necessary to identify the fracture and avoid the related morbidity and death. Recent study demonstrating that fracture risk was higher among diabetics than nondiabetics for a given FRAX score or BMD T-score. We found that FN BMD T-score and FRAX are both associated with fracture risk in older adults with type 2 diabetes and appear to be useful for clinical evaluation of fracture risk, despite the paradox of higher BMD with increased fracture risk in this population. However, a given T-score or FRAX score is associated with a higher risk of fracture in older adults with compared to those without diabetes.

SUMMARY:

- The present study was carried out with an aim to assess the use of WHO FRAX score in diabetic patients and to compare the fracture risk between diabetic and healthy population using FRAX score. The study was undertaken as a hospital based cross sectional study of 82 patients in either sex aged 40 to 80 years.
- Maximum of the study participants were in the age group of 61-70 years (37.8%) and females (80.5%). The mean age of the study participants was observed to be 62.3±10.3 years.
- Majority of the study participants were obese (72%), while 11% were overweight. Nearly 46.3% of the patients were known case of diabetes mellitus.
- A history of previous fracture was present in majority of the study participants (67.1%) and parent hip fracture in (18.3%).
- Maximum of the study participants had osteopenia (45.1%) and nearly one third had osteoporosis (29.3%) as per BMD T score classification at femoral neck.
- A statistically significant association was observed between history of diabetes mellitus and history of previous fracture (p value <0.001), and history of parent hip fracture (p value - 0.020).
- Higher proportion of patients in older age groups had osteoporosis, while higher proportions in the age group of 51-60 years had osteopenia (p value -0.026).
- Higher proportion of females had osteopenia and osteoporosis as compared to males (p value - 0.045).
- Significantly higher proportion of patients with history of diabetes mellitus had osteopenia and osteoporosis (p value <0.001), history of previous fracture (p value <0.001), and history of parent hip fracture (p value -0.043).
- Significant association was observed between FRAX score for hip fracture & osteoporotic fracture and presence of osteoporosis as per BMD T score classification (p values <0.001).
- Higher proportion of patients with history of diabetes mellitus had a very high risk of osteoporotic fracture and hip fracture as per FRAX classification (p values <0.001).

STRENGTH AND LIMITATION:

Strength:

- Appropriate sample and use of healthy controls for comparison improved the validity of the study findings.

Limitation:

- Duration of diabetes mellitus, control of hyperglycemia and type of treatment being taken for diabetes could be potential confounders. However, these variables were not included in the study as the same was not under the scope of objectives and considering feasibility in obtaining accurate data.

BIBLIOGRAPHY

1. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL. Mechanisms of diabetes mellitus-induced bone fragility. Nature reviews Endocrinology 2016.
2. Yan W, Li X. Impact of diabetes and its treatments on skeletal diseases. Frontiers of medicine 2013;7(1):81-90.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International 2006;17(12):1726-33.
4. Riggs BL, Melton LJ. The worldwide problem of osteoporosis: Insights afforded by epidemiology. Bone 1995;17(5):S505-S11.
5. Adachi JD, Gehlbach S, Adami S, Boonen S, Chapurlat R, Compston J, et al. Impact of prevalent fractures on quality of life: global longitudinal study of osteoporosis in women. Bone 2010;47(S179-S80.
6. Poole KES, Compston JE. Osteoporosis and its management. BMJ (Clinical research ed) 2006;333(7581):1251-6.
7. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone Loss and Bone Size after Menopause. New England Journal of Medicine 2003;349(4):327-34.
8. Siris ES, Chen Y-T, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, et al. Bone Mineral Density Thresholds for Pharmacological Intervention to Prevent Fractures. Archives of internal medicine 2004;164(10):1108.
9. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, et al. Hip Fracture in Women without Osteoporosis. The Journal of Clinical Endocrinology & Metabolism 2005;90(5):2787-93.

10. Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B, Dawson A. Ten-year risk of osteoporotic fracture and the effect of risk factors on screening strategies. Bone 2002;30(1):251-8.
11. Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jönsson B. Intervention thresholds for osteoporosis in the UK. Bone 2005;36(1):22-32.
12. Ellis KJ. Human body composition: in vivo methods. Physiological reviews 2000;80(2):649-80.
13. Albanese CV, Diessel E, Genant HK. Clinical applications of body composition measurements using DXA. Journal of Clinical Densitometry 2003;6(2):75-85.
14. Goodsitt MM. Evaluation of a new set of calibration standards for the measurement of fat content via DPA and DXA. Medical physics 1992;19(1):35-44.
15. Haarbo J, Gotfredsen A, Hassager C, Christiansen C. Validation of body composition by dual energy X-ray absorptiometry (DEXA). Clinical Physiology 1991;11(4):331-41.
16. Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, et al. FRAX underestimates fracture risk in patients with diabetes. Journal of Bone and Mineral Research 2012;27(2):301-8.
17. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. Jama 2011;305(21):2184-92.
18. Leslie WD, Rubin MR, Schwartz AV, Kanis JA. Type 2 diabetes and bone. Journal of Bone and Mineral Research 2012;27(11):2231-7.
19. Bouillon R. Diabetic bone disease. Calcified Tissue International 1991;49(3):155-60.
20. Tuominen JT, Impivaara O, Puukka P, Rönnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. Diabetes Care 1999;22(7):1196-200.

21. Hygum K, Starup-Linde J, Harsløf T, Vestergaard P, Langdahl BL. MECHANISMS IN ENDOCRINOLOGY: Diabetes mellitus, a state of low bone turnover – a systematic review and meta-analysis. European Journal of Endocrinology 2017;176(3):R137-R57.
22. Pei Y, Hercz G, Greenwood C, Segre G, Manuel A, Saiphoo C, et al. Renal osteodystrophy in diabetic patients. Kidney International 1993;44(1):159-64.
23. Vincenti F. Decreased Secondary Hyperparathyroidism in Diabetic Patients Receiving Hemodialysis. JAMA: The Journal of the American Medical Association 1981;245(9):930.
24. Vincenti F, Arnaud SB, Recker R, Genant H, Amend WJC, Feduska NJ, et al. Parathyroid and bone response of the diabetic patient to uremia. Kidney International 1984;25(4):677-82.
25. Jara A, Bover J, Felsenfeld AJ. Development of secondary hyperparathyroidism and bone disease in diabetic rats with renal failure. Kidney International 1995;47(6):1746-51.
26. Andress DL, Kopp JB, Maloney NA, Coburn JW, Sherrard DJ. Early Deposition of Aluminum in Bone in Diabetic Patients on Hemodialysis. New England Journal of Medicine 1987;316(6):292-6.
27. Epstein S, LeRoith D. Diabetes and fragility fractures — A burgeoning epidemic? Bone 2008;43(1):3-6.
28. Farlay D, Armas LAG, Gineyts E, Akhter MP, Recker RR, Boivin G. Nonenzymatic Glycation and Degree of Mineralization Are Higher in Bone From Fractured Patients With Type 1 Diabetes Mellitus. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2016;31(1):190-5.

29. Krakauer JC, McKenna MJ, Buderer NF, Rao DS, Whitehouse FW, Parfitt AM. Bone loss and bone turnover in diabetes. Diabetes 1995;44(7):775-82.
30. Verhaeghe J, Suiker AMH, Einhorn TA, Geusens P, Visser WJ, van Herck E, et al. Brittle bones in spontaneously diabetic female rats cannot be predicted by bone mineral measurements: Studies in diabetic and ovariectomized rats. Journal of Bone and Mineral Research 2009;9(10):1657-67.
31. Raskin P, Stevenson MRM, Barilla DE, Pak CYC. THE HYPERCALCIURIA OF DIABETES MELLITUS: ITS AMELIORATION WITH INSULIN. Clinical Endocrinology 1978;9(4):329-35.
32. Thalassinos NC, Hadjiyanni P, Tzanela M, Alevizaki C, Philokiprou D. Calcium Metabolism in Diabetes Mellitus: Effect of Improved Blood Glucose Control. Diabetic Medicine 1993;10(4):341-4.
33. Hui SL, Epstein S, Johnston CC. A Prospective Study of Bone Mass in Patients with Type I Diabetes*. The Journal of Clinical Endocrinology & Metabolism 1985;60(1):74-80.
34. Parthasarathy LS, Khadilkar VV, Chiplonkar SA, Zulf Mughal M, Khadilkar AV. Bone status of Indian children and adolescents with type 1 diabetes mellitus. Bone 2016;82(16-20.
35. Weber G, Beccaria L, de'Angelis M, Mora S, Galli L, Cazzuffi MA, et al. Bone mass in young patients with type I diabetes. Bone and Mineral 1990;8(1):23-30.
36. Lettgen B, Hauffa B, ouml, hlmann C, Jeken C, Reiners C. Bone Mineral Density in Children and Adolescents with Juvenile Diabetes: Selective Measurement of Bone Mineral Density of Trabecular and Cortical Bone Using Peripheral Quantitative Computed Tomography. Hormone Research 1995;43(5):173-5.

37. Ponder SW, McCormick DP, Daniel Fawcett H, Tran AD, Ogelsby GW, Brouhard BH, et al. Bone mineral density of the lumbar vertebrae in children and adolescents with insulin-dependent diabetes mellitus. The Journal of pediatrics 1992;120(4):541-5.
38. Compston JE, Smith EM, Matthews C, Schofield P. Whole body composition and regional bone mass in women with insulin-dependent diabetes mellitus. Clinical Endocrinology 1994;41(3):289-93.
39. Forst T, Beyer J, Pfützner A, Kann P, Schehler B, Lobmann R, et al. Peripheral Osteopenia in Adult Patients with Insulin-dependent Diabetes Mellitus. Diabetic Medicine 1995;12(10):874-9.
40. Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quattrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. Diabetes care 2008;31(9):1729-35.
41. Kayath MJ, Dib SA, Vieira JH. Prevalence and magnitude of osteopenia associated with insulin-dependent diabetes mellitus. Journal of Diabetes and its Complications 1994;8(2):97-104.
42. Gallacher SJ, Fenner JAK, Fisher BM, Quin JD, Fraser WD, Logue FC, et al. An Evaluation of Bone Density and Turnover in Premenopausal Women with Type 1 Diabetes Mellitus. Diabetic Medicine 1993;10(2):129-33.
43. Barrett-Connor E. Sex Differences in Osteoporosis in Older Adults With Non—Insulin-Dependent Diabetes Mellitus. JAMA: The Journal of the American Medical Association 1992;268(23):3333.
44. Rishaug U, Birkeland KI, Falch JA, Vaaler S. Bone mass in non-insulin-dependent diabetes mellitus. Scandinavian Journal of Clinical and Laboratory Investigation 1995;55(3):257-62.

45. van Daele PLA. Bone Density in Non-Insulin-Dependent Diabetes Mellitus: The Rotterdam Study. Annals of internal medicine 1995;122(6):409.
46. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density measured by dual energy X-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. Bone 1993;14(1):29-33.
47. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, et al. Diabetes Is Associated Independently of Body Composition With BMD and Bone Volume in Older White and Black Men and Women: The Health, Aging, and Body Composition Study. Journal of Bone and Mineral Research 2004;19(7):1084-91.
48. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. The Journal of clinical endocrinology and metabolism 2010;95(11):5045-55.
49. Shanbhogue VV, Hansen S, Frost M, Jørgensen NR, Hermann AP, Henriksen JE, et al. Compromised cortical bone compartment in type 2 diabetes mellitus patients with microvascular disease. European Journal of Endocrinology 2016;174(2):115-24.
50. Dobnig H, Piswanger-Sölkner JC, Roth M, Obermayer-Pietsch B, Tiran A, Strele A, et al. Type 2 Diabetes Mellitus in Nursing Home Patients: Effects on Bone Turnover, Bone Mass, and Fracture Risk. The Journal of Clinical Endocrinology & Metabolism 2006;91(9):3355-63.
51. Heath H, Melton LJ, Chu C-P. Diabetes Mellitus and Risk of Skeletal Fracture. New England Journal of Medicine 1980;303(10):567-70.
52. Cundy TF, Edmonds ME, Watkins PJ. Osteopenia and Metatarsal Fractures in Diabetic Neuropathy. Diabetic Medicine 1985;2(6):461-4.

53. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR. Risk Factors for Fractures of the Distal Forearm and Proximal Humerus. American Journal of Epidemiology 1992;135(5):477-89.
54. Meyer HE, Tverdal A, Falch JA. Risk Factors for Hip Fracture in Middle-aged Norwegian Women and Men. American Journal of Epidemiology 1993;137(11):1203-11.
55. Paganini-Hill A. Menopausal Estrogen Therapy and Hip Fractures. Annals of internal medicine 1981;95(1):28.
56. Nicodemus KK, Folsom AR. Type 1 and Type 2 Diabetes and Incident Hip Fractures in Postmenopausal Women. Diabetes Care 2001;24(7):1192-7.
57. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, et al. Older Women with Diabetes Have an Increased Risk of Fracture: A Prospective Study. The Journal of Clinical Endocrinology & Metabolism 2001;86(1):32-8.
58. Wolf SK. Diabetes mellitus and predisposition to athletic pedal fracture. The Journal of Foot and Ankle Surgery 1998;37(1):16-22.
59. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, et al. Risk of Fracture in Women with Type 2 Diabetes: the Women's Health Initiative Observational Study. The Journal of Clinical Endocrinology & Metabolism 2006;91(9):3404-10.
60. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporosis International 2006;18(4):427-44.
61. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture. American Journal of Epidemiology 2007;166(5):495-505.

62. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and Risk of Fracture. Diabetes Care 2001;24(7):1198-203.

63. Melton LJ, 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2008;23(8):1334-42.

64. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older Women With Diabetes Have a Higher Risk of Falls. Diabetes Care 2002;25(10):1749-54.

65. Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: A population-based study. Bone 2007;40(6):1595-601.

66. Li C-I, Liu C-S, Lin W-Y, Meng N-H, Chen C-C, Yang S-Y, et al. Glycated Hemoglobin Level and Risk of Hip Fracture in Older People with Type 2 Diabetes: A Competing Risk Analysis of Taiwan Diabetes Cohort Study. Journal of Bone and Mineral Research 2015;30(7):1338-46.

67. Leslie WD, Tsang JF, Caetano PA, Lix LM. Effectiveness of Bone Density Measurement for Predicting Osteoporotic Fractures in Clinical Practice. The Journal of Clinical Endocrinology & Metabolism 2007;92(1):77-81.

68. Stone KL, Seeley DG, Lui L-Y, Cauley JA, Ensrud K, Browner WS, et al. BMD at Multiple Sites and Risk of Fracture of Multiple Types: Long-Term Results From the Study of Osteoporotic Fractures. Journal of Bone and Mineral Research 2003;18(11):1947-54.

69. Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W. Axial and appendicular bone density predict fractures in older women. Journal of Bone and Mineral Research 2009;7(6):633-8.

70. Schuit SCE, van der Klift M, Weel AEAM, de Laet CEDH, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 2004;34(1):195-202.
71. Kung AWC, Lee K-K, Ho AYY, Tang G, Luk KDK. Ten-Year Risk of Osteoporotic Fractures in Postmenopausal Chinese Women According to Clinical Risk Factors and BMD T-Scores: A Prospective Study. Journal of Bone and Mineral Research 2007;22(7):1080-7.
72. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(4):385-97.
73. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Does osteoporosis therapy invalidate FRAX for fracture prediction? Journal of Bone and Mineral Research 2012;27(6):1243-51.
74. Engelke K, Lang T, Khosla S, Qin L, Zysset P, Leslie WD, et al. Clinical Use of Quantitative Computed Tomography (QCT) of the Hip in the Management of Osteoporosis in Adults: the 2015 ISCD Official Positions—Part I. Journal of Clinical Densitometry 2015;18(3):338-58.
75. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporosis International 2004;16(6):581-9.
76. Leslie WD, Majumdar SR, Lix LM, Morin SN, Johansson H, Odén A, et al. Can Change in FRAX Score Be Used to “Treat to Target”? A Population-Based Cohort Study. Journal of Bone and Mineral Research 2014;29(5):1074-80.

77. Ensrud KE, Lui L-Y, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, et al. A comparison of prediction models for fractures in older women: is more better? Archives of internal medicine 2009;169(22):2087-94.

78. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ (Clinical research ed) 2009;339(b4229-b.

79. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The Burden of Osteoporotic Fractures: A Method for Setting Intervention Thresholds. Osteoporosis International 2001;12(5):417-27.

80. Borgström F, Johnell O, Kanis JA, Oden A, Sykes D, Jönsson B. Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden. PharmacoEconomics 2004;22(17):1153-65.

81. Tosteson ANA, Melton LJ, 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(4):437-47.

82. Dawson-Hughes B, Tosteson AN, Melton LJ, 3rd, Baim S, Favus MJ, Khosla S, et al. Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(4):449-58.

83. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis international : a journal established as result of

cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(4):399-428.

84. Sornay-Rendu E, Munoz F, Delmas PD, Chapurlat RD. The FRAX tool in French women: How well does it describe the real incidence of fracture in the OFELY cohort. Journal of Bone and Mineral Research 2010;25(10):2101-7.
85. Leib ES, Saag KG, Adachi JD, Geusens PP, Binkley N, McCloskey EV, et al. Official Positions for FRAX® Clinical Regarding Glucocorticoids: The Impact of the Use of Glucocorticoids on the Estimate by FRAX® of the 10 Year Risk of Fracture. Journal of Clinical Densitometry 2011;14(3):212-9.
86. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporosis International 2011;22(3):809-16.
87. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Spine–hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporosis International 2010;22(3):839-47.
88. Schacter GI, Leslie WD. DXA-Based Measurements in Diabetes: Can They Predict Fracture Risk? Calcified Tissue International 2016;100(2):150-64.
89. Miller PD, Barlas S, Brenneman SK, Abbott TA, Chen Y-T, Barrett-Connor E, et al. An Approach to Identifying Osteopenic Women at Increased Short-term Risk of Fracture. Archives of internal medicine 2004;164(10):1113.
90. Miller PD, Siris ES, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Prediction of Fracture Risk in Postmenopausal White Women With Peripheral Bone Densitometry: Evidence From the National Osteoporosis Risk Assessment. Journal of Bone and Mineral Research 2002;17(12):2222-30.

91. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. The Lancet 2002;359(9321):1929-36.

92. Liu H, Paige NM, Goldzweig CL, Wong E, Zhou A, Suttorp MJ, et al. Screening for Osteoporosis in Men: A Systematic Review for an American College of Physicians Guideline. Annals of internal medicine 2008;148(9):685.

93. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk Factors for Hip Fracture in White Women. New England Journal of Medicine 1995;332(12):767-73.

94. Sambrook PN, Flahive J, Hooven FH, Boonen S, Chapurlat R, Lindsay R, et al. Predicting fractures in an international cohort using risk factor algorithms without BMD. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2011;26(11):2770-7.

95. Kanis JA, Johnell O, Oden A, De Laet C, Dawson A, Jonsson B. Ten Year Probabilities of Osteoporotic Fractures According to BMD and Diagnostic Thresholds. Osteoporosis International 2001;12(12):989-95.

96. Cauley JA, Hochberg MC, Lui L-Y, Palermo L, Ensrud KE, Hillier TA, et al. Long-term Risk of Incident Vertebral Fractures. Jama 2007;298(23):2761.

97. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of Subsequent Fracture After Low-Trauma Fracture in Men and Women. Jama 2007;297(4):387.

98. Hodsman AB, Leslie WD, Tsang JF, Gamble GD. 10-Year Probability of Recurrent Fractures Following Wrist and Other Osteoporotic Fractures in a Large Clinical Cohort. Archives of internal medicine 2008;168(20):2261.

99. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, Berger M. Patients with Prior Fractures Have an Increased Risk of Future Fractures: A Summary of the Literature and Statistical Synthesis. Journal of Bone and Mineral Research 2010;15(4):721-39.

100. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35(2):375-82.
101. Mackey DC. High-Trauma Fractures and Low Bone Mineral Density in Older Women and Men. Jama 2007;298(20):2381.
102. Van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Use of Oral Corticosteroids and Risk of Fractures. Journal of Bone and Mineral Research 2000;15(6):993-1000.
103. Ensrud KE. Weight change and fractures in older women. Study of Osteoporotic Fractures Research Group. Archives of internal medicine 1997;157(8):857-63.
104. Ensrud KE, Lipschutz RC, Cauley JA, Nevitt MC, Cummings SR. Body composition and hip fracture risk in older women: A prospective study. Osteoporosis International 1996;6(S1):132-.
105. Green AD. Does This Woman Have Osteoporosis? Jama 2004;292(23):2890.
106. Langlois JA. Weight Change Between Age 50 Years and Old Age Is Associated With Risk of Hip Fracture in White Women Aged 67 Years and Older. Archives of internal medicine 1996;156(9):989.
107. Meyer HE, Falch JA, O'Neill T, Tverdal A, Varlow J. Height and body mass index in oslo, norway, compared to other regions of europe: do they explain differences in the incidence of hip fracture? Bone 1995;17(4):347-50.
108. Villareal DT. Bone Mineral Density Response to Caloric Restriction–Induced Weight Loss or Exercise-Induced Weight Loss. Archives of internal medicine 2006;166(22):2502.
109. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, et al. Smoking and fracture risk: a meta-analysis. Osteoporosis International 2004;16(2):155-62.

110. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcified Tissue International 2001;68(5):259-70.

111. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, et al. Alcohol intake as a risk factor for fracture. Osteoporosis International 2004;16(7):737-42.

112. Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA, Jr., et al. Association between alcohol consumption and both osteoporotic fracture and bone density. The American journal of medicine 2008;121(5):406-18.

113. Ensrud KE. Renal Function and Risk of Hip and Vertebral Fractures in Older Women. Archives of internal medicine 2007;167(2):133.

114. Jassal SK, von Muhlen D, Barrett-Connor E. Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2007;22(2):203-10.

115. Mezuk B, Eaton WW, Golden SH. Depression and osteoporosis: epidemiology and potential mediating pathways. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;19(1):1-12.

116. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM 2008;101(7):583-8.

117. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic Calcification and the Risk of Osteoporosis and Fractures. The Journal of Clinical Endocrinology & Metabolism 2004;89(9):4246-53.

118. Cauley JA, Danielson ME, Boudreau RM, Forrest KYZ, Zmuda JM, Pahor M, et al. Inflammatory Markers and Incident Fracture Risk in Older Men and Women: The

Health Aging and Body Composition Study. Journal of Bone and Mineral Research 2007;22(7):1088-95.

119. Schett G. High-Sensitivity C-Reactive Protein and Risk of Nontraumatic Fractures in the Bruneck Study. Archives of internal medicine 2006;166(22):2495.
120. Gregg EW. Physical Activity and Osteoporotic Fracture Risk in Older Women. Annals of internal medicine 1998;129(2):81.
121. Lloyd T, Rollings N, Eggli DF, Kieselhorst K, Chinchilli VM. Dietary caffeine intake and bone status of postmenopausal women. The American Journal of Clinical Nutrition 1997;65(6):1826-30.
122. Wu C-H, Yang Y-C, Yao W-J, Lu F-H, Wu J-S, Chang C-J. Epidemiological Evidence of Increased Bone Mineral Density in Habitual Tea Drinkers. Archives of internal medicine 2002;162(9):1001.
123. Barrett-Connor E. Coffee-Associated Osteoporosis Offset by Daily Milk Consumption. Jama 1994;271(4):280.
124. Dhonukshe-Rutten RAM, Pluijm SMF, de Groot LC, Lips P, Smit JH, van Staveren WA. Homocysteine and Vitamin B12 Status Relate to Bone Turnover Markers, Broadband Ultrasound Attenuation, and Fractures in Healthy Elderly People. Journal of Bone and Mineral Research 2005;20(6):921-9.
125. McLean RR, Jacques PF, Selhub J, Fredman L, Tucker KL, Samelson EJ, et al. Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. The Journal of clinical endocrinology and metabolism 2008;93(6):2206-12.
126. van Meurs JBJ, Dhonukshe-Rutten RAM, Pluijm SMF, van der Klift M, de Jonge R, Lindemans J, et al. Homocysteine Levels and the Risk of Osteoporotic Fracture. New England Journal of Medicine 2004;350(20):2033-41.

127. Kim SH, Morton DJ, Barrett-Connor EL. Carbonated beverage consumption and bone mineral density among older women: the Rancho Bernardo Study. American journal of public health 1997;87(2):276-9.

128. Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study. The American Journal of Clinical Nutrition 2006;84(4):936-42.

129. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al. Predictive Value of BMD for Hip and Other Fractures. Journal of Bone and Mineral Research 2005;20(7):1185-94.

130. Picard D, Brown JP, Rosenthall L, Couturier M, Lévesque J, Dumont M, et al. Ability of Peripheral DXA Measurement to Diagnose Osteoporosis As Assessed By Central DXA Measurement. Journal of Clinical Densitometry 2004;7(1):111-8.

131. Kanis JA, Glüer CC. An Update on the Diagnosis and Assessment of Osteoporosis with Densitometry. Osteoporosis International 2000;11(3):192-202.

132. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ (Clinical research ed) 1996;312(7041):1254-9.

133. Khosla S. High-Trauma Fractures and Bone Mineral Density. Jama 2007;298(20):2418.

134. Sanders KM, Pasco JA, Ugoni AM, Nicholson GC, Seeman E, Martin TJ, et al. The Exclusion of High Trauma Fractures May Underestimate the Prevalence of Bone Fragility Fractures in the Community: The Geelong Osteoporosis Study. Journal of Bone and Mineral Research 1998;13(8):1337-42.

135. Bauer DC, Glüer CC, Genant HK, Stone K. Quantitative ultrasound and vertebral fracture in postmenopausal women. Journal of Bone and Mineral Research 2009;10(3):353-8.

136. Khaw K-T, Reeve J, Luben R, Bingham S, Welch A, Wareham N, et al. Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. The Lancet 2004;363(9404):197-202.

137. Schott AM, Weill-Engerer S, Hans D, Duboeuf F, Delmas PD, Meunier PJ. Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray absorptiometry and independently of bone mineral density. Journal of Bone and Mineral Research 2009;10(2):243-9.

138. Bauer DC. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. Archives of internal medicine 1997;157(6):629-34.

139. Hodson J, Marsh J. Quantitative ultrasound and risk factor enquiry as predictors of postmenopausal osteoporosis: comparative study in primary care. BMJ (Clinical research ed) 2003;326(7401):1250-1.

140. Stewart A, Reid DM. Quantitative ultrasound or clinical risk factors--which best identifies women at risk of osteoporosis? The British journal of radiology 2000;73(866):165-71.

141. Pacifici R, Rupich R, Griffin M, Chines A, Susman N, Avioli LV. Dual Energy Radiography versus Quantitative Computer Tomography for the Diagnosis of Osteoporosis. The Journal of Clinical Endocrinology & Metabolism 1990;70(3):705-10.

142. Yamada M, Ito M, Hayashi K, Ohki M, Nakamura T. Dual energy X-ray absorptiometry of the calcaneus: comparison with other techniques to assess bone density and value in predicting risk of spine fracture. American Journal of Roentgenology 1994;163(6):1435-40.
143. Genant HK, Engelke K, Fuerst T, Glüer C-C, Grampp S, Harris ST, et al. Noninvasive assessment of bone mineral and structure: State of the art. Journal of Bone and Mineral Research 2009;11(6):707-30.
144. Mackey DC, Eby JG, Harris F, Taaffe DR, Cauley JA, Tylavsky FA, et al. Prediction of Clinical Non-Spine Fractures in Older Black and White Men and Women With Volumetric BMD of the Spine and Areal BMD of the Hip: The Health, Aging, and Body Composition Study. Journal of Bone and Mineral Research 2007;22(12):1862-8.
145. Link TM, Lang TF. Axial QCT: Clinical Applications and New Developments. Journal of Clinical Densitometry 2014;17(4):438-48.
146. Keegan THM, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL. Effect of Alendronate on Bone Mineral Density and Biochemical Markers of Bone Turnover in Type 2 Diabetic Women. Diabetes Care 2004;27(7):1547-53.
147. Inoue D, Muraoka R, Okazaki R, Nishizawa Y, Sugimoto T. Efficacy and Safety of Risedronate in Osteoporosis Subjects with Comorbid Diabetes, Hypertension, and/or Dyslipidemia: A Post Hoc Analysis of Phase III Trials Conducted in Japan. Calcified tissue international 2016;98(2):114-22.
148. Vestergaard P, Rejnmark L, Mosekilde L. Diabetes and Its Complications and Their Relationship with Risk of Fractures in Type 1 and 2 Diabetes. Calcified Tissue International 2008;84(1):45-55.
149. Lunt H. Women and Diabetes. Diabetic Medicine 1996;13(12):1009-16.

150. Räkel A, Sheehy O, Rahme E, LeLorier J. Osteoporosis among patients with type 1 and type 2 diabetes. Diabetes & Metabolism 2008;34(3):193-205.

151. Kamalanathan S, Nambiar V, Shivane V, Bandgar T, Menon P, Shah N. Bone mineral density and factors influencing it in Asian Indian population with type 2 diabetes mellitus. Indian J Endocrinol Metab 2014;18(6):831-7.

152. Dutta M, Pakhetra R, Garg M. Evaluation of bone mineral density in type 2 diabetes mellitus patients before and after treatment. Medical Journal Armed Forces India 2012;68(1):48-52.

153. Chakrabarty N, Sarkar P, Pal S, Banerjee R, Sarkar R, Debnath N. A study of bone mineral density in diabetes mellitus in eastern India. Journal of the Indian Medical Association 2004;102(8):418, 20, 22 passim-, 20, 22 passim.

154. Mathen PG, Thabah MM, Zachariah B, Das AK. Decreased Bone Mineral Density at the Femoral Neck and Lumbar Spine in South Indian Patients with Type 2 Diabetes. Journal of clinical and diagnostic research : JCDR 2015;9(9):Oc08-12.

155. Maisnam I, Dutta D, Mukhopadhyay S, Chowdhury S. Lean mass is the strongest predictor of bone mineral content in type-2 diabetes and normal individuals: an eastern India perspective. Journal of Diabetes & Metabolic Disorders 2014;13(1):1.

156. Majima T, Komatsu Y, Yamada T, Koike Y, Shigemoto M, Takagi C, et al. Decreased bone mineral density at the distal radius, but not at the lumbar spine or the femoral neck, in Japanese type 2 diabetic patients. Osteoporosis international 2005;16(8):907-13.

157. Haffner SM, Bauer RL. The association of obesity and glucose and insulin concentrations with bone density in premenopausal and postmenopausal women. Metabolism 1993;42(6):735-8.

158. Christensen J, Svendsen O. Bone mineral in pre-and postmenopausal women with insulin-dependent and non-insulin-dependent diabetes mellitus. Osteoporosis International 1999;10(4):307-11.
159. Sahin G, Bağis S, Cimen O, Ozişik S, Güler H, Erdoğan C. Lumbar and femoral bone mineral density in type 2 Turkish diabetic patients. Acta medica 2000;44(4):141-3.
160. Kaushal N, Vohora D, Jalali RK, Jha S. Prevalence of osteoporosis and osteopenia in an apparently healthy Indian population - a cross-sectional retrospective study. Osteoporosis and sarcopenia 2018;4(2):53-60.
161. Fraser L-A, Pritchard J, Ioannidis G, Giangegorio LM, Adachi JD, Papaioannou A, et al. Clinical risk factors for fracture in diabetes: a matched cohort analysis. Journal of Clinical Densitometry 2011;14(4):416-21.
162. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: the Blue Mountains Eye Study. Diabetes care 2001;24(7):1198-203.
163. Al-Homood IA, Sheshah I, Mohammed AGA, Gasim GI. The prevalence and risk factors of osteoporosis among a Saudi female diabetic population. Open access Macedonian journal of medical sciences 2017;5(2):177.
164. Vaishya R, Vijay V, Agarwal AK, Maheshwari P. Assessment of osteoporotic fracture risk in urban Indian population using quantitative ultrasonography & FRAX tool. The Indian journal of medical research 2017;146(Supplement):S51-s6.
165. Kadam NS, Chiplonkar SA, Khadilkar AV, Khadilkar VV. Prevalence of Osteoporosis in Apparently Healthy Adults above 40 Years of Age in Pune City, India. Indian journal of endocrinology and metabolism 2018;22(1):67-73.
166. Babhulkar S, Seth S. Prevalence of osteoporosis in India: an observation of 31238 adults. International Journal of Research in Orthopaedics 2021;7(2):362.

167. Himanshu Arora DTRK, Dr. Garima Goyal, Dr. Sandeep Parekh. A study of WHO FRAX score to predict Fracture risk in Indian type 2 diabetics. International Journal of Medicine Research 2018;3(3):58-65.
168. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. Jama 2011;305(21):2184-92.
169. Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, et al. FRAX underestimates fracture risk in patients with diabetes. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2012;27(2):301-8.
170. Aishwarya TV ASPB, Britto Duraisingh L, Mohanraj KP, Sivakumar T. A Case control study on incidence and prevalence of hip fracture in association with hypoglycaemic drugs among Type II Diabetes Mellitus patients in a major trauma care center. Indian Journal of Pharmacy Practice 2019;12(1):30-3.
171. Valentini A, Cianfarani MA, De Meo L, Morabito P, Romanello D, Tarantino U, et al. FRAX tool in type 2 diabetic subjects: the use of HbA1c in estimating fracture risk. Acta Diabetologica 2018;55(10):1043-50.
172. Leslie WD, Morin SN, Lix LM, Majumdar SR. Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2014;25(12):2817-24.
173. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. Jama 2011;305(21):2184-92.

174. Majumdar SR, Leslie WD, Lix LM, Morin SN, Johansson H, Oden A, et al. Longer duration of diabetes strongly impacts fracture risk assessment: the Manitoba BMD cohort. The Journal of Clinical Endocrinology & Metabolism 2016;101(11):4489-96.

ANNEXURE I

INFORMED CONSENT

Mrs/Ms_____

You are invited to participate in this study.

"ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY".

Principal Investigator: **Dr. Subash Bose S**

OBJECTIVES AND PURPOSE OF THE STUDY:

To assess the use of WHO FRAX score in diabetic patients and to compare the fracture risk between diabetic and healthy population using FRAX score**.**

You are invited to participate in this research as you are a patient suffering from diabetes. The study is being done to find out the prevalence rate and factors affecting osteoporosis as mentioned in the objectives.

PROCEDURE

If you consent to be in this study, the relevant data is collected as per the proforma provided to you. BMD (Bone mineral density) measurement would be done using Central DEXA Scan (Dual energy X ray absorptiometry) of make GE Wipro and 2008 Lunar model. You will undergo a DEXA Scan and after ruling out all the exclusion criteria. This test is painless and can be performed within 5 to 15 minutes. You will be asked to undergo this procedure only once.

BENEFITS

To the patient in the study.

1. It will act as a diagnostic tool for the patients in the study by providing information regarding the presence of the disease.

2. Will help to initiate therapy for osteoporosis once the diagnosis is confirmed.

3. As a prognostic tool it will help to determine future probability of osteoporosis.

To the community at large.

1. The data obtained from the study will help to provide information on the epidemiology of the thyroid disorders which will be then basis for initiation for various programs for osteoporosis prevention.

2. It will help create awareness regarding osteoporosis.

RISKS

There are no risks associated with this study.

ALTERNATIVES

If you decline to participate decision it will not change the present or future health care or other services that you will receive. The treatment given out to you will be the standard treatment for your condition.

WITHDRAWING / REMOVAL FROM THE STUDY:

You can withdraw from the study during anytime you want and you will not be penalized for the same. You can be removed from the study if you do not fulfil the inclusion criteria.

PRIVACY AND CONFIDENTIALITY:

All information about the subject during the course of the study will be kept confidential to the extent permitted by law. The code numbers will identify the subject in this research record. Information from this study may be published but the subject's identity will be confidential in any publication.

COSTS

Cost of each DEXA Scan will cost around Rs 1200/- and blood sugar test will be Rs 800/-. There will be no reimbursement for your expenses.

QUESTION

If any enquiries in the future or in case of study related problems you may contact

Principal Investigator:
Dr Subash Bose S
Post Graduate
Department of Orthopaedics,
J.N. Medical College,
K.L.E University, Belagavi-10
Ph No:8248365400

Guide
DR. KIRAN S PATILM.S.(ORTHO), D.ORTHO
Professor,
Department of Orthopaedics,
J.N. Medical College,
K.L.E. University, Belagavi-10
Ph No. 9844171844

STATEMENT OF CONSENT:

The details of the research study in which I am expected to participate, for which I have to undergo DEXA Scan and blood sugar test have been explained to me. I willingly, under no pressure from the researcher agree to take part in this study, and agree to participate in all investigations. I may withdraw at any time. I am not giving up any of my legal rights by signing this form.

My signature below indicates that I have read this entire consent form or it has been read to me, and had all my questions answered. I will be given a copy of this consent form.

Signature of the participant or legally authorized representative

Participants Name : Signature :

Name of the legally authorized representative : Signature :

Witness's name : Signature :

Investigators Name : Signature :

Date:

Place:

ANNEXURE II

STUDY TITLE: "ASSESSMENT OF FRACTURE RISK IN DIABETIC VERSUS APPARENTLY HEALTHY POPULATION WITHIN 40-80 YEARS OF AGE USING WHO FRAX SCORE – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

IP / OP / DEXA No:

PATIENT NO:

NAME:

AGE: SEX:

ADDRESS:

OCCUPATION:

CHIEF COMPLAINTS:

PRESENTING COMPLAINTS:

HISTORY:

Any prior surgery / Trauma :

Drug history:

-hormone replacement therapy:

-oral bisphosphonates:

-any other drugs

-others:

-c/o prolapsed intervertebral disc/spondylosis/spondylolisthesis:

PERSONAL HISTORY:

Diet	: Veg/ Mixed/ Nonveg
Appetite	: Increased or Decreased
Habits	: Smoking/ Alcohol /Tobacco chewer

INVESTIGATIONS:

RBS :

FBS:

PPBS:

BMD:

QUESTIONNAIRE

AGE

DATE OF BIRTH

SEX MALE FEMALE

WEIGHT(Kg)

HEIGHT(Cm)

PREVIOUS FRACTURE NO YES

PARENT FRACTURED HIP NO YES

CURRENT SMOKING NO YES

GLUCOCORTICOIDS NO YES

RHEUMATOID ARTHRITIS NO YES

SECONDARY OSTEOPOROSIS NO YES

ALCOHOL 3 ORMORE UNITS/DAY NO YES

FEMORAL NECK BMD (T-Score)

BMI

The ten year probability of fracture

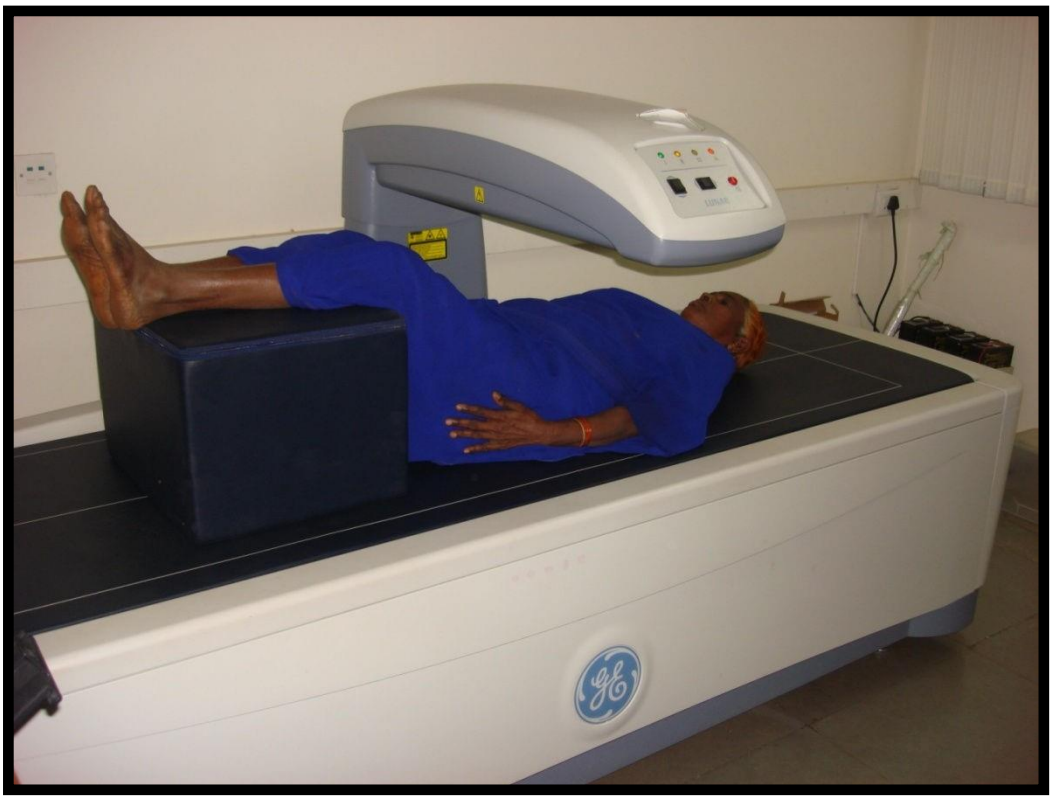
(With BMD)

OSTEOPOROTIC FRACTURE

HIP FRACTURE

ANNEXURE III

PHOTOGRAPH 1: DEXA EVALUATION APPARATUS



PHOTOGRAPH 2: DEXA SCAN OF LUMBAR SPINE

PHOTOGRAPH 3: DEXA SCAN OF DUAL HIP

ANNEXURE IV

MASTER CHART