Risk factors for ten-year risk of osteoporosis in type 2 DM patients attending Tikur Anbessa Specialized Hospital Diabetic center-cross-sectional study

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Lists of abbreviations

25 OHD-25 HYDROXY VITAMIN D

AOR-ADJUSTED ODDS RATIO

ARIC-ATHEROSCLEROSIS RISK IN COMMUNITY

BBSS-BERG BALANCE SCALE SCORE

BMD-BONE MINERAL DENSITY

CD-CRONS DISEASE

CHF- CONGESTIVE HEART FAILURE

CI-CONFIDENCE INTERVAL

CVD-CEREBROVASCULAR DISEASE

DISH-DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS

DM-DIABETES MELLITES

ETB-ETHIOPIAN BIRR

FBS- FASTING BLOOD SUGAR

FES-I-FALLS EFFICIENCY SCALE -INTERNATIONAL

FRAX-FRACTURE RISK ASSESSMENT TOOL

HDL-C-HIGH DENSITY LIPOPROTEIN CHOLESTEROL

HGA1C-HEMOGLOBIN A1C

HIV-HUMAN IMMUNODEFICIENCY VIRUS

HR-HAZARD RATIO

IBD-INFLAMMATORY BOWEL DISEASE

IHD-ISCHEMIC HEART DISEASE

IM- INTRAMUSCULAR

IQR- INTERQUARTILE RANGE

IRR-INCIDENCE RATE RATIO

IV- INTRAVENOUS

KG-KILOGRAM

LDL-C-LOW DENSITY LIPOPROTEIN-CHOLESTEROL

M-METER

MOF-MAJOR OSTEOPOROTIC FRACTURE

OC-OSTEOCALCITONIN

PAD-PERIPHERAL ARTERIAL DISEASE

RA-RHEUMATOID ARTHRITIS

SLE-SYSTEMIC LUPUS ERYTHEMATOSUS

SLS-SINGLE LEG STAND

T1DM-TYPE1 DM

T2DM-TYPE2 DM

TBS-TRABECULAR BONE SCAN

TC-TOTAL CHOLESTEROL

TUG -TIMED UP AND GO

UC-ULCERATIVE COLITIS

WHR-WAIST TO HIP RATIO

Abstract

Background.

Osteoporosis is characterized by decreased bone density and microarchitectural changes which lead to fragility fractures. Type 2 diabetes mellites is also exposed to fragility fractures by interfering with the metabolism of carbohydrates, fats, and proteins. It also dysregulates calcium, phosphorus, and magnesium metabolisms.

Objective

The purpose of this study was to assess the risk of high risk of fragility fractures and factors associated with increased risk of 10-year osteoporotic fracture in patients with type 2 diabetes mellites.

Methods

Data was collected from 175 patients aged >40(the fracture assessment tool includes individuals above 40 years).

ears) with type 2 diabetes mellites attending black lion specialized teaching hospital diabetes and endocrine clinics by a structured questionnaire. Diabetic complications, hemoglobin A1c, fasting blood sugar, and other medical diagnoses included in the questionnaire were collected from the electronic medical record system based on the medical record number. Fracture risk was calculated for all patients using the FRAX tool, Ethiopia; bone mineral density was not used. The data was coded and entered SPSS version 26, and factors associated with osteoporotic fractures were explored using a logistic regression model.

Results

Of the 175 patients who participated in the study, 88 (50.3%) were females, and the median (IQR) age was 60 (52-66) years. 134 (76.6%) were Orthodox Christians and 20 (11.4%) were Muslims. Most patients (74.3%) were married, and 78 (44.6%) had attended college and above. Most patients (85.1%) were from Addis Ababa, and almost all (97.1) lived in an urban setup. 68 (38.9%) were government employees, and the median monthly income of the participants was 5000 (3000-8000) ETB. The median (IQR) duration of diabetes was 11(6-20) years. The median (IQR) FRAX score for the 10-year probability of a hip fracture ≥ 3% and a 10-year probability of a major osteoporosis-related fracture ≥ 20% were 1.5 (0.5-3.3) and 7.8 (3.0-10.0), respectively. The overall prevalence of a 10-year risk of osteoporotic fracture in this study is 30.9%. The median (IQR) levels of HgA1c and FBS were 8.0 (7.0-9.4) and 150 (125-192), respectively. Macrovascular complications occurred in 137 (78.3%) patients, while neuropathy, retinopathy, and nephropathy were seen in 143 (81.7%), 140 (80.0%), and 126 (72.0%) patients, respectively. FBS (AOR, 1.01; 95% CI, 1.00-1.02; P= 0.011), higher HgA1c (AOR, 1.45; 95% CI, 1.11-1.88; P= 0.006), and presence of macrovascular complications (AOR, 2.73; 95% CI, 1.12-6.66; P= 0.027) are significantly associated with increased fragility fractures.

Conclusion: In our study, the combined (hip, MOF), the prevalence of ten-year risk of osteoporosis in type 2 DM was 30.9%, and higher HGA1C, FBS, and macrovascular complications were significantly associated with increased ten-year risk of osteoporosis and fragility fractures.

Introduction

Background of the study

Globally, an estimated 151 million people live with type 2 DM, and by 2030this number is expected to rise to 324 million—type 2 DM results in many harmful complications, cardiovascular and renal complications being the most common. Several factors increase the risk of falls in type 2 DM patients, which include diabetic foot ulcer, diabetic peripheral neuropathy, diabetic retinopathy, and autonomic disturbances like orthostatic hypotension (1).

A large-scale meta-analysis published in 2020 investigated the association between type 2 diabetes mellitus (T2DM) and fracture risk, encompassing over 17.5 million participants from cohort and case-control studies. The findings reinforce the link between T2DM and an increased risk of fractures, particularly hip fractures. The analysis revealed a significant increase in hip fracture risk for individuals with T2DM. Compared to controls, men with T2DM exhibited a 13% greater risk, while women with T2DM showed a 34% increase in hip fracture risk. The study also identified a 19% rise in the risk of nonvertebral fractures (e.g., spine or wrist) among individuals with T2DM compared to the non-diabetic group. Notably, the analysis suggests that the heightened fracture risk in T2DM patients might be influenced by specific T2DM-related risk factors, potentially explaining variations in risk across the entire T2DM population (2).

A well-established risk factor for fractures is low bone mineral density (BMD) (3). However, individuals with type 2 diabetes (T2DM) often have higher than expected BMD, potentially due to insulin resistance. Despite this higher BMD, T2DM patients experience fractures at a greater rate compared to those without diabetes. This suggests alternative mechanisms contributing to bone fragility in this population (4).

The FRAX tool, a commonly used method for fracture risk assessment, might underestimate the elevated risk of osteoporotic fracture in T2DM patients. This highlights the need to incorporate additional factors into this group's fracture risk prediction (5,6).

Elevated glycation of bone matrix proteins in type 2 diabetes mellitus patients might be a factor leading to their increased risk of fractures (6,7).

Studies have also shown an association between fracture risk and diabetes treatment, such as insulin and thiazolidinedione use (8, 9). However, due to the interactions among medication, glycemic control, and diabetes-associated comorbidities, the relative effects of each factor still need to be determined (10).

Diabetes-associated complications, including peripheral neuropathy and congestive heart failure, were found to play a significant role in fracture risk (11).

A U-shaped relationship exists between HbA1c and fracture risk; HbA1c levels between 6.5% and 6.9% are associated with the lowest risk of fragility fractures. Conversely, HbA1c levels equal to or exceeding 9% were linked to an increased risk of fragility fractures. Interestingly, this

could potentially indicate infrequent patient-provider interaction, as patients with uncontrolled diabetes might be less likely to receive regular healthcare (12).

Statement of the problem

Type 2 DM is considered a risk factor for osteoporosis and increased risk of fragility fracture. Longer duration of diabetes is associated with multiple metabolic changes in the bone matrix.

Chronic hyperglycemia in type DM disrupts the micro-architecture of the bone matrix via various mechanisms, which include higher levels of insulin, increased urinary calcium excretion, impaired kidney function, obesity, and Accumulation of advanced glycation end products (AGEs) in collagen. Insulin normally promotes the formation and maturation of osteoblasts. However, chronically high glucose levels directly impair osteoblast function and bone quality by altering gene expression.

Type 2 diabetes (T2DM) accounts for more than 90% of all individuals with diabetes, and more than 94 million people with diabetes are aged 65 to 79 years (13). In parallel, there is also an age-related epidemic ongoing as osteoporosis is estimated to affect 200 million women worldwide, and approximately 1.6 million hip fractures, the most severe of the osteoporotic fractures, occur annually (13).

Significance of the study

While infectious diseases, such as HIV and tuberculosis, pose a public threat in sub-Saharan Africa, non-communicable diseases, such as diabetes, are equally increasing in the region. The proportion of type 2 DM is 90-95% in sub-Saharan Africa (14).

Given the increasing burden of type 2 DM in Ethiopia, the prevalence of osteoporosis among this population is unknown; our study tries to narrow the knowledge gap and provide data about the prevalence of high-risk fragility fractures and possible associated factors.

In addition, this study is expected to provide evidence-based insights for policymakers to develop preventive measures, early diagnosis, and innervations, improving the quality of life of type 2 DM patients.

In conclusion, this study improves our understanding of high-risk fragility fractures and osteoporosis in type 2 DM patients, identifies related factors, and guides the development of intervention measures to tackle the problem.

It is also expected to be used as a reference for future large-scale studies.

Literature review

Multiple studies are showing the relation between type 2 DM and the risk of osteoporosis and fragility fractures.

A Nationwide Swedish Cohort Study (2007-2017) Examined Fracture Risk in T2DM: This study investigated the risk of fractures in individuals with type 2 diabetes mellitus (T2DM) using a national Swedish cohort. The analysis revealed a 13% prevalence of fragility fractures among T2DM patients, with an incidence rate of 22.2 fractures per 1,000 person-years.

Interestingly, the study found only a modest increase in overall fracture risk for T2DM patients compared to the general population. They also found a 1% increase in the risk of major osteoporotic fractures (MOF) and a 6% increase in hip fracture risk for T2DM patients. Importantly, the analysis identified that the slightly elevated fracture risk was statistically significant only in subgroups of T2DM patients with specific characteristics, including longer duration of diabetes, low body mass index (BMI), and low physical activity levels (1).

A large, population-based study in Taiwan followed individuals with and without diabetes for a median of 13.6 years. The incidence of osteoporosis was significantly higher in the diabetic group (34.2 per 1,000 person-years) compared to the non-diabetic group (20.55 per 1,000 person-years). This translates to a nearly 70% increased risk of osteoporosis in individuals with diabetes over this follow-up period. Subgroup analysis suggested a potential age interaction ($p=0.06$). While the association between diabetes and osteoporosis was present in all age groups, diabetes might have more of an effect on developing osteoporosis in older individuals. The study also showed a correlation between the level of glycemic control and osteoporosis risk. Individuals with HbA1c levels above 7% had a significantly higher risk of osteoporosis than those with HbA1c below 7% (adjusted HR: 1.49, 95% CI: 1.15-1.92; $p=0.002$). This suggests poor glycemic control plays a significant role in developing osteoporosis (15).

Rathman et al. examined fracture risk in 297,104 patients with type 2 diabetes (T2DM) in primary care centers in Germany. They found a significant increase in hip fractures (56%) and any fractures (36%). However, an important limitation is that the study excluded patients with a history of fractures, conditions linked to bone fragility, and other existing medical conditions (16). This exclusion means the results may not be generalizable to the entire T2DM population, particularly those at higher baseline risk of fractures due to pre-existing conditions. Consequently, the study might underestimate the true association between T2DM and fracture risk.

Ivers et al.in The Blue Mountains Eye Study found that diabetes duration ≥10 years, treatment with insulin, blood glucose >7 mmol/l, ≥25% of the lens involved by cortical cataract in the worst eye, or the presence of diabetic retinopathy in either eye was a risk factor for all fractures combined (17). Proximal humeral fracture was significantly associated with diabetes duration for more than ten years and treatment with insulin (17).

Li CI et al. observed an increasing trend between the HbA1c level and hip fracture incidence in patients with type 2 diabetes aged 65 years and over. The risk of hip fracture was 24%–31%

higher among patients with HbA1c levels ≥ 9% than among patients with HbA1c levels of 6%–7% after we adjusted for numerous risk factors for fracture (18).

In the Rotterdam Study, Oei et al. examined the effect of inadequate glycemic control (HbA1c ≥ 7.5%) on fracture risk. They found that participants with insufficient glycemic control had 62% higher fracture risk than diabetic patients with adequate glycemic control (19).

In the Atherosclerosis Risk in Communities (ARIC) Study, Schneider et al. reported that there was a significantly increased risk of fracture-related hospitalization among persons with diagnosed diabetes with HbA1c ≥8% compared with those with HbA1c <8% (20).

A Chinese retrospective cohort study investigated the prevalence of osteoporosis and related factors in patients with type 2 diabetes mellitus (T2DM) in Nanchang and found a high prevalence of osteoporosis (35.77%) and osteopenia (44.67%) among type 2DM patients. A statistically significant differences were observed in factors like age, gender, body mass index (BMI), waist-to-hip ratio (WHR), educational background, and duration of T2DM ($p < 0.05$). Interestingly, HbA1c, total cholesterol, triglycerides, and LDL-C did not differ significantly between bone density groups ($p > 0.05$). The study identified gender, age, BMI, T2DM duration, HDL-C levels, diabetic retinopathy, and diabetic peripheral neuropathy as significant contributors to osteoporosis in type2 DM patients (21)

A Chinese meta-analysis and systematic review examined the prevalence of osteoporosis in patients with type 2 diabetes mellitus. A Pooled analysis of 21 studies encompassing 11,603 T2DM patients revealed a significant prevalence of osteoporosis at 27.67% (95% confidence interval [CI] 21.37-33.98%). The meta-analysis did not identify a statistically significant correlation between the age of participants when tested for OP and the prevalence of the condition in diabetic patients ($P = 0.354$). A noteworthy finding was the higher prevalence of OP observed in studies with a greater proportion of female participants (32.96%, 95% CI: 25.90-40.02%) compared to those with a lower proportion of females (23.01%, 95% CI: 16.09-29.92%) (22). The finding regarding age is particularly interesting, potentially suggesting that factors besides age at diagnosis may play a more prominent role in osteoporosis development for diabetic patients. Additionally, the higher OP prevalence in studies with a larger female population aligns with existing knowledge about the increased vulnerability of women to osteoporosis.

In a meta-analysis investigating low energy fracture in type 2 diabetes patients, 938,742 participants were enrolled. There were 12 studies: two from Asia, four from Europe, five from the USA, and one from Canada. Pooled IRR and adjusted pooled IRR revealed a significantly increased risk of low-energy fracture in type 2 DM patients compared to healthy controls. Low energy hip fracture risk was also higher in type 2 DM patients (1.08,95% CI1.02-1.15); p=0.007). The subgroup analysis showed that the risk of low-energy fracture was significant no matter the follow-up duration (p value<0.005 for all) (23).

A US retrospective study examined the association between diabetes and fracture risk in male veterans aged 65-99 receiving primary care in the Veterans Health Administration from 2000 to 2010 found that, after adjusting for confounding factors, individuals with diabetes exhibited a

1.22(95% CI,1.21-1.23) increased risk of any clinical fracture and a 1.21(95% CI,1.19-1.23)increased risk of hip fracture compared to those without diabetes.

Notably, the study identified diabetes-related complications as significant mediating factors for fracture risk. Peripheral neuropathy explained the largest portion of the increased fracture risk (21.1% for all fractures, 20% for hip fractures). Congestive heart failure and cardiovascular disease also contributed, explaining 16.6% and 6.9% of all fracture risk, respectively. 41% of hip fracture risk associated with diabetes was explained by peripheral diabetic neuropathy, CHF, and other cardiovascular diseases (11).

This study highlights the link between diabetes and increased fracture risk in older male veterans. It goes beyond simply demonstrating the association by pinpointing specific diabetes complications – particularly peripheral neuropathy – as crucial mediating factors. These findings suggest that managing diabetes complications might be a valuable strategy for reducing fracture risk in this population.

Chinese study at Hebei investigated the influence of glycated hemoglobin (HbA1c) levels on bone metabolism markers in patients with type 2 diabetes mellitus (T2DM) and identified significant differences in patient characteristics across HbA1c groups (<7%, 7-9%, and ≥9%). These differences included age, duration of T2DM, and various blood markers such as TC, LDL-C, apolipoprotein B, albumin, and BUN. The groups' serum levels of 25-hydroxyvitamin D (25OHD) and osteocalcin (OC) among bone metabolism biomarkers displayed significant variations. Correlation analysis revealed statistically significant negative correlations between HbA1c and 25OHD ($r = -0.200$) and OC ($r = -0.183$). This suggests that higher HbA1c levels are associated with lower levels of these bone health markers. Importantly, even after adjusting for potential confounding factors like age, sex, and T2DM duration, the HbA1c ≥9% group still exhibited significantly lower 25OHD and OC concentrations than the HbA1c <7% group (24). The observed reductions in 25OHD and OC, crucial markers of bone metabolism, suggest a potential link between glycemic control and bone health in T2DM patients.

A Danish registry-based study by Kvist AVet et al. (1997-2017) investigated site-specific fracture rates in individuals with type 1 diabetes (T1D), type 2 diabetes (T2D), and non-diabetic controls, revealed a significant increase in fracture incidence rates (IRRs) across various skeletal sites for both T1D and T2D patients compared to the non-diabetic group. Notably, foot fractures were the only exception where no significant difference was observed. After adjusting for age, the increased IRRs remained statistically significant for T1D patients compared to controls. However, the IRRs for T2D patients appeared to converge with those of the non-diabetic group, suggesting a potential attenuation of the fracture risk association with increasing age (25).

A Danish nationwide cohort study by Rasmussen NH et al. investigated the risk of falls and fall-related injuries in individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D) compared to a non-diabetic control group. The study reported a higher cumulative incidence of falls requiring hospitalization in both diabetic groups compared to controls. The rates were 13.3% for T1D and 11.9% for T2DM. Individuals with diabetes exhibited a heightened risk of experiencing a first fall and sustaining fall-related injuries, including fractures. Compared to controls, T2D patients

had significantly higher incidence rate ratios (IRRs) for specific fall-related fractures, including Hip: IRR 1.02 (95% CI: 1.01-1.04) Radius IRR 1.39 (95% CI: 1.18-1.61) Humerus (IRR 1.24 (95% CI: 1.12-1.37) and Skull/facial, IRR 1.15 (95% CI: 1.07-1.24). Notably, T1D patients specifically showed an increased IRR for hip fractures compared to controls (IRR: 1.11, 95% CI: 1.02-1.23) (26).

A study by Timar et al. explored the influence of diabetic neuropathy (DN) on balance and fall risk in patients with type 2 diabetes mellitus (T2DM). It revealed that the presence of diabetic neuropathy was significantly associated with poorer balance performance in T2DM patients. This was evidenced by Lower scores on the Berg Balance Scale (BBS) - a measure of static balance (40.5 vs. 43.7 points for DN vs. no DN; $p < 0.001$). Decreased time spent standing on one leg (Single Leg Stand, SLS) - a measure of dynamic balance (9.3 vs. 10.3 seconds for DN vs. no DN; $p = 0.003$). Increased Timed Up and Go (TUG) test scores, indicating slower gait and potential mobility limitations (8.9 vs. 7.6 seconds for DN vs. no DN; $p = 0.002$). Higher scores on the Falls Efficacy Scale-International (FES-I), signified a greater fear of falling (38 vs. 33 points for DN vs. no DN; $p = 0.034$) (27).

This study highlights diabetic neuropathy as a crucial factor contributing to impaired balance and increased fall risk in T2DM patients. The findings suggest that assessing DN and implementing interventions to improve balance and gait might be valuable strategies for fall prevention in this population.

A study by Bonaccorsi G. et al. investigated bone health in post-menopausal women with type 2 diabetes mellitus (T2DM). Utilizing dual-energy X-ray absorptiometry (DXA) trabecular bone score (TBS) and other measurements, the study revealed a high prevalence of compromised bone mineral density. Specifically, a significant proportion of women with T2DM exhibited Low bone mineral density (BMD), a marker of bone strength, in 63.2% of cases. Deteriorated trabecular bone score (TBS), an indicator of bone microarchitecture, in 72.6% of cases (28).

This study emphasizes the vulnerability of post-menopausal women with T2DM to compromised bone health. The high prevalence of both low BMD and poor TBS scores suggests a potential increased risk of fractures in this population.

In a study done in South Africa, there is evidence of low bone mass (osteopenia) in general for this population, and it has been observed that type 2 diabetes mellitus negatively affects bone strength, regardless of bone mineral density. Furthermore, diabetes mellitus is a risk factor for osteoporosis, and fractures account for 13%, and fractures can occur at higher bone mineral density levels in patients with diabetes mellitus (29).

A study by Conway et al. examined the association between glycemic control (HbA1c) and fracture risk in elderly diabetic patients and identified a non-linear relationship between HbA1c and fracture risk, characterized as a cubic association ($p < 0.05$). This suggests that both very low and very high HbA1c levels might be associated with increased fracture risk. After adjusting for factors like age, sex, race, and frequency of mass index (BMI) measurements (considered a marker of patient-provider interaction), the analysis revealed the following hazard ratios (HR) with an HbA1c of 7.0-7.9% as the reference group: HbA1c < 6.5% (very good glycemic

control): HR = 0.97 (95% CI: 0.82-1.14) - No significant difference in fracture risk compared to the reference group. HbA1c 6.5-6.9% (moderately good glycemic control): HR = 0.80 (95% CI: 0.66-0.97) - Significantly lower fracture risk than the reference group. HbA1c 8.0-8.9% (moderately poor glycemic control): HR = 1.13 (95% CI: 0.92-1.40) - No significant difference in fracture risk compared to the reference group, but a trend towards increased risk. HbA1c ≥ 9% (poor glycemic control): HR = 1.19 (95% CI: 0.93-1.54) - No significant difference in fracture risk compared to the reference group, but again, a trend towards increased risk (12).

Lee RH et al. found that men over age 65 years with diabetes and with HbA1c <6.5% had a statistically significant increased risk of both hip and other site fractures. The use of insulin modified this effect, such that those with HbA1c <6.5% treated with insulin had a 22% increased risk of clinical fracture, suggesting that hypoglycemia significantly contributes to the increased fracture risk observed among older adults with diabetes. The result also observed an approximately 10% increase in hip fracture risk among those with HbA1c >9.5%. This result suggests a detrimental impact of hyperglycemia on bone quality (10).

Objective of the study

General objectives

To assess the risk of high-risk fractures and factors associated with increased risk of fracture in patients with type 2DM.

Specific objectives

To identify common risk factors of osteoporosis in patients with type 2DM

To quantify osteoporosis risk via FRAX score in patients with type 2DM

To describe factors associated with increased risk of high-risk fracture in patients with type 2DM.

Methods

Study setting and participants.

This cross-sectional study aimed to assess the risk of high-risk fractures and associated factors in type 2 DM patients who had follow-at black lion specialized hospital diabetic center. Type 2 DM patients aged above 40 years and who provided informed consent were included in the study.

With random sampling, every sixth patient was included in the study. Patients who declined consent were excluded from the study.

Study period.

February 2023-February 2024

Study design.

Institution-based cross-sectional study

Source population.

The source population was all type 2 DM patients visiting the TASH diabetic center.

Source population.

All eligible patients who gave consent

Sample size.

The sample size was determined based on the assumption of a confidence interval of 95% and a margin of error <0.05%

n= (z^2 p(1-p))/d^2 where z=standard score of 95% confidence interval which is 1.96, d=margin of error which is 5%

p- prevalence of fracture among type 2 DM patients 13%

n=173

since the source population is <10,000

sample size=n/(1+n/N) =173/ (1+173/2000) =159

adding 10% to the non-respondent rate

sample size=175

sampling procedure

The first patient who visited the clinic on the first day of the study period was recruited. Then, a systematic random sampling method was used, assuming 1000-1200 patients visited the clinic per year.

k= 1100/175=6

study variables.

Dependent variable

The effect of type DM on the risk of OP and fragility fractures

Independent variables

Age

Sex

Economic status (income)

Duration of diabetes

Level of glycemic control (HGA1C, FBS)

Smoking

Alcohol abuse

History of fractures

Microvascular complications (diabetic retinopathy, diabetic nephropathy, diabetic peripheral neuropathy)

Macrovascular complications (PAD, IHD, CVD)

Parental history of hip fracture

awareness about osteoporosis

usage of vitamin supplements and calcium supplements, a diet rich in vitamin D and calcium

frequency of fall-down accidents in the past year

bone pain

use of glucocorticoids

presence of rheumatoid arthritis, malabsorption syndromes

difficulty of vision

poor lighting condition

inclusion and exclusion criteria

All type 2 DM patients above 40 who gave consent were included.

Exclusion criteria

Active malignancy

Type1 DM

Patients on anticoagulation

ESRD other than diabetic nephropathy

Age <40 years

Data collection

A structured questionnaire was used to collect socio-demographic data, smoking, alcohol use, Parental history of hip fracture, awareness about osteoporosis, usage of vitamin supplements and calcium supplements, a diet rich in vitamin D and calcium, frequency of fall-down accidents in the past year, bone pain use of glucocorticoids and other risk factors for osteoporosis.

Laboratory data and macrovascular and microvascular complications were obtained from the electronic record system.

Trained health professionals collected the data, and the principal investigator conducted continuous follow-up and supervision throughout the study.

Ethical clearance

The study was approved by the research and ethics committee of the Internal Medicine Department, School of Medicine, College of Health Sciences, Addis Ababa University, black lion Specialized Hospital. Written and verbal informed consent was obtained from all the participants. Participants were de-identified, and anonymity was respected throughout the study process.

Data processing and statistical analysis

Collected data was checked for completeness and internal consistency by cross-checking, and then it was entered and managed using the Kobo toolbox, then extracted and analyzed by SPSS version 26. Statistical significance was considered at $P < 0.05$. Factors associated with osteoporosis were determined by binary regression; those with a p-value <0.25 were taken to multiple logistic regression.

Results

Sociodemographic characteristics

The study included a total of 175 patients. Out of this, 88 (50.3%) were females, and the median (IQR) age was 60 (52-66) years. 134 (76.6%) were Orthodox Christians and 20 (11.4%) were Muslims. Most patients (74.3%) were married, and 78 (44.6%) had attended college and above. Most patients (85.1%) were from Addis Ababa, and almost all (97.1) lived in an urban setup. 68 (38.9%) were government employees, and the median monthly income of the participants was 5000 (3000-8000) ETB. (Table 1, Figure 1&2).

Table 1: Sociodemographic characteristics of patients

		N	%	Median (IQR)
Sex	Male	87	49.7	
	Female	88	50.3	
Age (years)				60 (52-66)
Educational level	Unable to read and write	4	2.3	
	Able to read and write	10	5.7	
	Primary education	30	17.1	
	High school	53	30.3	
	College and above	78	44.6	
Residence	Rural	5	2.9	
	Urban	170	97.1	
Address	Addis Ababa	149	85.1	
	SNNPR	2	1.1	
	Amhara	1	0.6	
	Harare	1	0.6	
	Oromia	22	12.6	
Occupation	Daily laborer	2	1.1	
	Farmer	2	1.1	
	Government employee	68	38.9	
	Housewife	50	28.6	
	Merchant	8	4.6	
	Self-employed	45	25.7	
Monthly income (ETB)				5000 (3000-8000)

Figure 1: Religion of participants

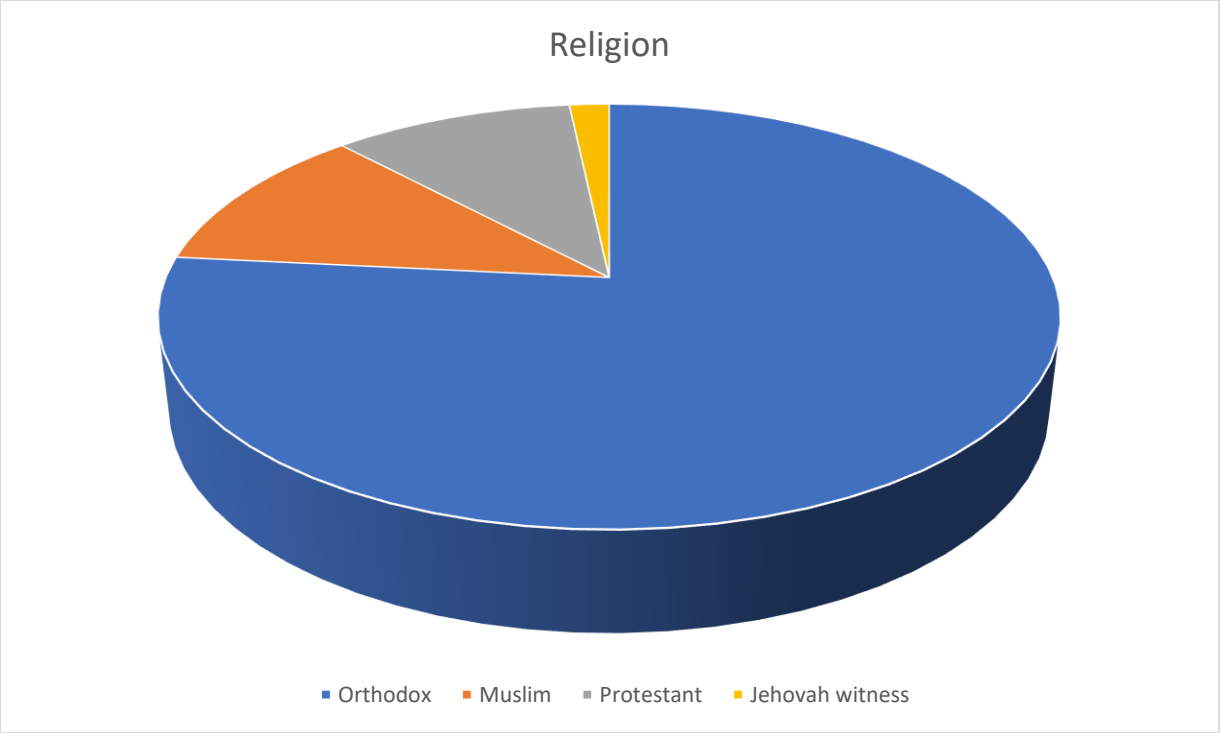
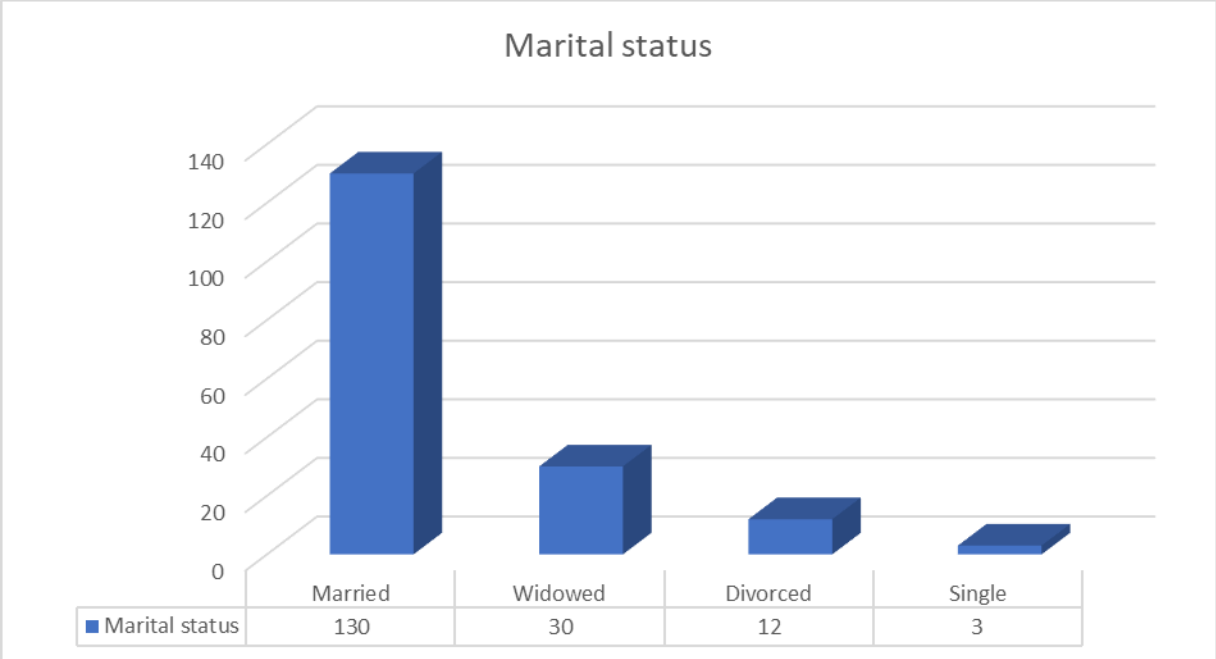


Figure 2: Marital status of participants



Diabetes profile of patients

The median (IQR) duration of diabetes among participants was 11(6-20) years. The median (IQR) levels of HgA1c and FBS were 8.0 (7.0-9.4) and 150 (125-192), respectively. Macrovascular complications occurred in 137 (78.3%) patients, while neuropathy, retinopathy, and nephropathy were seen in 143 (81.7%), 140 (80.0%), and 126 (72.0%) patients, respectively.

Table 2: Diabetes profile of patients

		Median (IQR)	N	%
Duration of DM (years) - median (IQR)		11(6-20)		
Degree of control HgA1c		8.0 (7.0-9.4)		
Degree of glycemic control /FBS		150 (125-192)		
Macrovascular complications	No		137	78.3
	Yes		38	21.7
Neuropathy	No		143	81.7
	Yes		32	18.3
Nephropathy	No		126	72.0
	Yes		49	28.0
Retinopathy	No		140	80.0
	Yes		35	20.0

Risk factors for ten years risk of osteoporosis.

The most common risk factors identified were drinking alcohol, personal history of fracture, family history of hip fracture, and cigarette smoking seen in 115 (65.7%), 113 (64.6%), 110 (62.9%) and 17 (9.7%) patients, respectively. 151 (86.3%) patients took milk, cheese, or yogurt, while 42 (24.0%) used vitamin supplements. The median (IQR) weight and height were 71 (63-80) kilograms and 1.65 (1.58-.70) meters, respectively.

Risk factors for fracture.

124 (70.9%) patients had a history of fall accidents in the past year, whereas 74 (42.3%) complained of difficulty keeping their balance. 71 (40.6%) had trouble with their vision, and 18

(10.3%) thought the lighting condition in their living and bathrooms was poor. History of bone pain and arrhythmia was elicited in 57 (32.6%) and 5 (2.9%) patients, respectively.

Table 3: Risk factors for osteoporosis

Variables		N	%	Median (IQR)
Alcohol intake≥3 units/day	No	60	34.3	
	Yes	115	65.7	
Active Cigarette smoking	No	158	90.3	
	Yes	17	9.7	
Vitamin supplement intake	No	133	76.0	
	Yes	42	24.0	
Calcium supplement intake	No	155	88.6	
	Yes	20	11.4	
Hormonal supplement intake	No	175	100.0	
	Yes	0	0.0	
Milk, cheese, or yogurt intake	No	24	13.7	
	Yes	151	86.3	
Family history of hip fracture (father or mother)	No	65	37.1	
	Yes	110	62.9	
Epilepsy	No	171	97.7	
	Yes	4	2.3	
Stroke	No	167	95.4	
	Yes	8	4.6	
RA	No	173	98.9	
	Yes	2	1.1	
SLE	No	175	100.0	
	Yes	0	0.0	
Spinal cord injury	No	175	100.0	
	Yes	0	0.0	

Malabsorption	No	174	99.4	
	Yes	1	0.6	
IBD	No	174	99.4	
	Yes	1	0.6	
Cirrhosis	No	173	98.9	
	Yes	2	1.1	
Glucocorticoid intake	No	172	98.3	
	Yes	3	1.7	
Previous history of fracture	No	62	35.4	
	Yes	113	64.6	
Weight (Kg)				71 (63-80)
Height (M)				1.65 (1.58-.70)

Table 4: Risk factors for fall and fracture

Variables		N	%
Fall accident in the past year.	No	51	29.1
	Yes	124	70.9
Difficulty of keeping balance	No	101	57.7
	Yes	74	42.3
Difficult in vision	No	104	59.4
	Yes	71	40.6
Condition of lighting in living and bathrooms	Poor	18	10.3
	Good	157	89.7
History of arrhythmia	No	170	97.1
	Yes	5	2.9
History of bone pain	No	118	67.4
	Yes	57	32.6
Multiple myeloma	No	175	100.0
	Yes	0	0.0

Knowledge about osteoporosis(bone thinning)

61 (34.9%) patients knew about bone thinning, and 40 (22.9%) patients knew that T2DM is related to bone thinning. Only 22 (12.6%) patients were screened for osteoporosis, out of which 12 (54.5%) received treatment. 77 (44%) patients knew the importance of osteoporosis screening.

Table 5: Knowledge about osteoporosis

Variables		N	%
Know about osteoporosis(bone thinning)	No	114	65.1
	Yes	61	34.9
Screened for osteoporosis(bone thinning)	No	153	87.4
	Yes	22	12.6
Know the importance of osteoporosis (bone thinning) screening	No	98	56.0
	Yes	77	44.0
Know that T2DM is related to osteoporosis(bone thinning)	No	135	77.1
	Yes	40	22.9

Prevalence of 10-year risk of osteoporosis

The median (IQR) FRAX score for the 10-year probability of a hip fracture ≥ 3% and a 10-year probability of a major osteoporosis-related fracture ≥ 20% were 1.5 (0.5-3.3) and 7.8 (3.0-10.0), respectively. Using the FRAX score for the 10-year probability of a hip fracture, 54 (30.9%) patients were classified as having a 10-year risk of osteoporosis. However, only 8 (4.8%) had an increased risk of 10-year risk of osteoporosis using the FRAX score for the 10-year probability of a major osteoporosis-related fracture, and all had a 10-year probability of a hip fracture of ≥3%. Accordingly, the overall prevalence of a 10-year risk of osteoporosis in this study is 30.9%.

Factors associated with ten-year risk of osteoporosis.

Upon binary regression, monthly income ≤5000 ETB, longer duration of DM, higher FBS, higher HgA1c, and the presence of macrovascular complications, diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy were associated with using a P-value of 0.25 as a cutoff. These variables were then taken to multivariate logistic regression, after which only three variables were found to have a statistically significant association with increased risk of 10-year osteoporosis. These variables were higher FBS (AOR, 1.01; 95% CI, 1.00-1.02; P= 0.011), higher HgA1c (AOR, 1.45; 95% CI, 1.11-1.88; P= 0.006), and presence of macrovascular complications (AOR, 2.73; 95% CI, 1.12-6.66; P= 0.027).

Variables	Osteoporosis	COR	P value	AOR	P value

		No	Yes	(5% CI)		(5% CI)	
Monthly income (ETB)	≤5K	69	36	1.00	0.230	1.00	
	>5K	52	18	0.66 (0.34-1.30)		0.54 (0.24-1.21)	0.134
Duration of DM (years) – median (IQR)		10 (5-18)	15 (9-21)	1.05 (1.01-1.09)	0.010	1.02 (0.98-1.07)	0.397
FBS (mg/dL) – median (IQR)		138 (118-160)	189 (155-240)	1.02 (1.01-1.03)	<0.001	1.01 (1.00-1.02)	0.011*
HgA1c (%) – median (IQR)		7.6 (6.9-8.8)	9.3 (8.5-10.3)	1.78 (1.42-2.23)	<0.001	1.45 (1.11-1.88)	0.006*
Nephropathy	No	91	35	1.00	0.159	1.00	
	Yes	30	19	1.65 (0.82-3.30)		0.86 (0.36-2.05)	0.730
Neuropathy	No	102	41	1.00	0.189	1.00	
	Yes	19	13	1.70 (0.77-3.76)		1.11 (0.42-2.91)	0.835
Retinopathy	No	101	39	1.00	0.089	1.00	
	Yes	20	15	1.94 (0.90-4.17)		1.55 (0.61-3.92)	0.353
Macrovascular complications	No	102	35	1.00	0.005	1.00	
	Yes	19	19	2.91 (1.39-6.13)		2.73 (1.12-6.66)	0.027*

* Variables that showed significant association with osteoporosis upon multivariate logistic regression.

Discussion

The prevalence of non-communicable diseases such as diabetes Mellitus is equally rampant as that of non-communicable diseases in Sub-Saharan Africa. Ethiopia is one of the countries with a high prevalence of type 2 DM. Different studies show the association of type 2 DM with an increased risk of fragility fractures.

Despite this, there is no data on the prevalence of fragility fracture and osteoporosis and associated factors. In this study, we found that the prevalence of osteoporosis is 30.9% using the 10-year probability of FRAX-score-Ethiopia.

The diagnosis of osteoporosis is based on BMD measurements or clinically by the presence of a fragility fracture; multiple studies showed an association between type 2 DM and the risk of osteoporotic fractures but showed mixed outcomes (15, 30-32). Some studies have shown a surprisingly lower prevalence of osteoporosis, as measured by bone mineral density (BMD), in patients with type 2 diabetes compared to healthy controls (33-35). One potential explanation for this unexpected finding could be the presence of degenerative changes and diffuse idiopathic skeletal hyperostosis (DISH), which are frequently observed in patients with type 2 diabetes (36). In contrast, a systematic review conducted in China found a greater prevalence of osteoporosis among individuals with type 2 diabetes mellitus (T2DM) (37)

Our study participants' median age (IQR) was 60 (52-66) years, consistent with different metanalysis. Our result showed no association between fragility fracture with age and sex, suggesting that type DM might play a vital role in both sexes and across different age groups; this finding is also seen in other meta-analyses (15).

Our study showed a strong association between the degree of glycemic control (HGA1C and fasting blood sugar) and increased risk of fragility fractures, FBS (AOR, 1.01; 95% CI, 1.00-1.02; P= 0.011), HgA1c (AOR, 1.45; 95% CI, 1.11-1.88; P= 0.006). This finding is consistent with different studies; Conway et al. revealed a complex relationship between HbA1c levels and the risk of osteoporosis-related fractures. This relationship was described as cubic, meaning that both very low and very high HbA1c levels were associated with increased fracture risk, as opposed to a simple linear relationship where only high HbA1c would be a risk factor (12).

A meta-analysis by Lin et al. found a strong link between HbA1c and osteoporosis risk. Individuals with HbA1c levels equal to or above 7 had a significantly increased risk of osteoporosis compared to those with HbA1c below 7. This translates to an adjusted hazard ratio (HR) of 1.49, with a 95% confidence interval (CI) ranging from 1.15 to 1.92 (p = 0.002) (15). Krakauer JC et al. also found that poor glycemic control metabolic effects led to increased bone resorption and bone loss in young adults (38).

Li CI et al. found an increasing trend between the HbA1c level and hip fracture incidence in individuals with type 2 DM above 65 years. The risk of hip fracture was 24%–31% higher

among patients with HbA1c levels ≥ 9% than among patients with HbA1c levels of 6%–7% after adjusting for numerous risk factors for fracture (18).

A study investigated bone mineral density (BMD) in 78 poorly controlled type 2 diabetes patients (T2DM) aged 28-73 with initial HbA1c exceeding 8%. The patients underwent BMD measurements before and after three weeks of improved glycemic control. The study found that better blood sugar control decreased bone mineral loss within this short period. This suggests that managing blood sugar levels in T2DM patients might play a role in protecting against bone loss (39).

Macrovascular complications such as ischemic heart disease, peripheral arterial diseases, and cerebrovascular diseases were found to be significantly associated with increased fragility fractures and osteoporosis in our study.

Macrovascular complications occurred in 137 (78.3%) patients, while neuropathy, retinopathy, and nephropathy were seen in 143 (81.7%), 140 (80.0%), and 126 (72.0%) patients, respectively. A statistically significant association between macrovascular complications and risk of osteoporosis was seen (AOR, 2.73; 95% CI, 1.12-6.66; P= 0.027).

These findings agreed with findings from different studies. A retrospective study by Lee et al. examined the link between diabetes and fracture risk. After accounting for various factors like age, ethnicity, and medical conditions, the study found that Individuals with diabetes had an approximately 22% increased risk of any clinical fracture compared to those without diabetes (adjusted risk ratio: 1.22, 95% CI: 1.21-1.23). Similarly, the risk of hip fracture was also about 21% higher in diabetic patients (adjusted risk ratio: 1.21, 95% CI: 1.19-1.23). Crucially, the study identified specific health conditions that might explain a significant portion of this increased fracture risk in diabetic patients. These mediating factors were Peripheral neuropathy, cardiovascular disease, and Congestive heart failure. These three conditions together accounted for 45.5% of the fracture risk associated with diabetes (11).

Although other studies indicated a correlation between microvascular complications and increased risk of osteoporosis (11), we did not find a significant association between microvascular complications and the risk of fragility fracture and osteoporosis in this study. Diabetic retinopathy (AOR,1.00;1.55 (0.61-3.92, p=0.353), diabetic nephropathy (AOR,1.00;0.86 (0.36-2.05; p=0.730) and diabetic peripheral neuropathy (AOR,1.00;1.11 (0.42-2.91; p=0.835). This discrepancy might be explained by the effects of treatments to control microvascular complications, although further investigation is needed.

To our knowledge, this is the first study in our country focusing on the prevalence of osteoporosis in type 2 DM patients and associated risk factors. Despite the lack of materials to do BMD in our setup, the study tried to estimate the risk of fragility fracture.

Limitations of the study

Since the study was done in a single center and most participants were urban dwellers, it is challenging to generalize the result for the general population.

The unavailability of the DEXA scan in our center for BMD measurements limited our ability to exclude potential confounding factors. FRAX score without BMD risk calculation may underestimate the risk of osteoporosis and fragility fractures.

Recall bias also might be a factor.

Conclusion- The prevalence of a 10-year risk of osteoporosis was 30.9% in this study. Levels of HGA1C, FBS, and macrovascular complications were significantly associated with the risk of fragility fractures and osteoporosis.

Recommendation – early osteoporosis screening and intervention are essential in type 2 DM patients to prevent major fragility fractures and hip fractures. A large-scale multicenter study is needed to see the reproducibility of the result.

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Annex

Consent form.

Title of the study - Risk factors for osteoporosis in patients with type 2 diabetes mellites attending Black lion specialized hospital diabetic center a cross-sectional study.

Name of researchers: _____
Position of researchers: _____ _____

Contact address of researchers: _____ _____

I, the undersigned here _____, have agreed to participate in the study voluntarily without any pressure. The investigator explained to me the purpose of the study, which is to identify the risk of osteoporosis in type 2 DM and other associated factors. The investigator also explained to me the benefit of the study, which I understand is to identify type 2 DM patients at risk of high-risk fractures and do early interventions on the risks to reduce major osteoporosis-associated fractures. I am told that I can withdraw from the study at any time, and the information I provide, including my name or identifier, is kept confidential. I am informed that the survey takes about 3-4 months, and in the end, no harm will occur from my participation. I am told I can ask any question about the study at any time; therefore, I am signing the consent to confirm my participation.

Name of Researcher_____

Date _____

Signature _____

Questionnaires

Sociodemographic characteristics

MRN

Sex

Male

Female

Age

Weight

Religion

Orthodox

Muslim

Protestant

Other, specify.

Marital status

Married

Single

Widowed

Divorced

Level of Education

Unable to read and write.

Able to read and write.

Primary education

Highschool

College and above

Residence

Urban

Rural

Address

Addis Ababa

Afar

Amhara

Oromia

Gambelia

Benishangul gumuz

SNNPR

Sidamo

Southwest Region

Tigray

Dire Dawa

Harare

Occupation

Housewife

Farmer

Government employee

Self-employee

Merchant

Daily laborer

Average monthly income

Diabetic profile of patients

Duration of DM in years

Level of glycemic control

HGA1C

FBS

Diabetes-related microvascular complications.

Diabetic retinopathy

Yes

No

Diabetic kidney disease

Yes

No

Diabetic Peripheral neuropathy

Yes

No

Macrovascular complications.

PAD

Yes

No

IHD

Yes

No

CVD

Yes

No

Risk factors for osteoporosis.

Do you use alcohol?

Yes

No

Do you smoke cigarettes?

Yes

No

Have you had a fall accident in the past year?

Yes

No

If yes, how many times

Are you taking any vitamin D supplements?

Yes

No

If yes, how many times?

Are you taking any calcium supplements?

Yes

No

If yes, how many times?

Do you take milk, cheese, yogurt, or soya beans?

Yes

No

If yes, how many times per week?

Do you have a parental history of hip fractures?

Yes

No

Rheumatoid arthritis

Yes

No

SLE

Yes

No

Spinal cord injury

Yes

No

Multiple myeloma

Yes

No

Do you use glucocorticoids (oral, IV, IM)?

Yes

No

Malabsorption syndromes (celiac disease, tropical sprue, chronic diarrhea)

Yes

No

IBD (UC, CD)

Yes

No

Cirrhosis

Yes

No

Risk factors for falls.

Do you have a history of epilepsy?

Yes

No

Do you have a history of stroke?

Yes

No

Do you have difficulty keeping your balance?

Yes

No

History of arrhythmia?

Yes

No

Knowledge about osteoporosis

Do you know about osteoporosis?

Yes

No

Do you have any bone pain?

Yes

No

Have you ever been screened for osteoporosis?

Yes

No

Do you know that osteoporosis screening is important?

Yes

No

Do you know that type 2 DM is related to osteoporosis?

Yes

No

Do you have a previous history of low-energy trauma associated with 1fracture (such as a fall from a standing height)

Yes

No

FRAX score; major osteoporosis fracture

FRAX score, hip
