CHAPTER 32

BONE AND JOINT COMPLICATIONS IN DIABETES

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SUMMARY

Fractures and osteoarthritis (OA) are common conditions among older adults, account for considerable morbidity in the United States, and occur more frequently with diabetes. At age 50 years, the lifetime risk of a hip fracture, an event associated with substantial risk of increased disability, is 17% for women and 6% for men in the United States. Type 1 diabetes is characterized by lower bone mineral density and an estimated sevenfold increase in the risk of hip fracture. In type 2 diabetes, in spite of average or higher bone density, the risk of hip fractures is increased by about 70% and risk of non-spine fractures by about 20%.

An important clinical implication is that current methods of assessing fracture risk in older adults, which rely primarily on bone density, tend to underestimate risk in those with type 2 diabetes. More frequent falls are observed in older adults with type 2 diabetes, and this is likely a contributing factor to increased fracture risk. In addition, there is evidence from clinical and animal studies that diabetic bone is more fragile for a given bone density, although the reasons for this increased fragility remain unclear.

Diabetes therapies may also influence skeletal health. In particular, thiazolidinediones are associated with increased fracture risk in women. The effects of maintaining good glycemic control on fracture risk are not clearly established. Successful prevention of fractures among those with diabetes may include interventions to reduce the risk of falls and to promote bone strength through physical activity and proper nutrition, with use of pharmacological treatments in those at very high risk of fracture.

Over 20% of adults age 60–74 years have knee OA, a leading cause of disability in older adults, and the prevalence rises to >40% in those with diabetes. OA and diabetes are both associated with overweight and obesity, and this may account at least in part for the higher prevalence of OA among those with diabetes. In addition, both conditions are characterized by higher levels of inflammation. Rheumatoid arthritis is also more common in those with diabetes, affecting about 8% of older adults without diabetes and 13% of those with diabetes. Other joint problems, including Charcot joint (neuropathic arthropathy) and frozen shoulder, are less common but are also seen more frequently in those with diabetes. Measures to prevent OA include weight reduction and physical activity. As with fractures, the effects of maintaining glycemic control on OA are not clearly understood.

BONE COMPLICATIONS IN DIABETES

INTRODUCTION

Health Burden and Economic Costs of Fractures

Fractures are an important source of mortality, morbidity, and health care costs in older adults in the United States. Among U.S. women at age 60 years, the median estimated 10-year risk of a major osteoporotic fracture (hip, vertebral, wrist, or humerus) is 22% (1). The lifetime risk of a hip fracture at age 50 years has been estimated as 17% in women and 6% in men (2).

Hip fractures are the most devastating fracture in older adults. Mortality is higher in the year after a hip fracture in men (37%) and women (26%) (3). Some of this excess mortality is due to comorbidities in those who experience hip fracture. About 25% of the excess mortality is estimated to be causally related to the hip fracture itself (4). Morbidity following hip fracture is a serious concern. Most older adults do not return to their functional status before the hip fracture (5). Walking ability in particular is decreased, with 50% of hip fracture patients experiencing the need for additional aid in walking a year after the fracture (6). Patients with diabetes are more likely to have a poor outcome after a hip fracture. A study in the United States found longer length of stay in the hospital or rehabilitation facility, slower recovery of functional status, and lower likelihood of being discharged home in diabetic patients with renal or neuropathy complications compared with nondiabetic patients (7).

Vertebral fractures are also associated with higher post-fracture mortality, largely due to their association with physical frailty and weight loss (8). Health-related quality of life is reduced on average even several years after a vertebral fracture (9). Other fractures are associated

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with significant short-term morbidity, measured as days of bed rest and reduced activity, but do not appear to have substantial long-term effects on functional status (9,10).

The health care costs associated with treatment of fractures in the United States are substantial. Annual costs for an estimated 2 million incident fractures in those age ≥50 years were approximately $17 billion in 2005 (11). Hip fractures represented 14% of the total fractures but accounted for 72% of total costs. Costs are predicted to rise nearly 50% by 2025, driven in particular by increases in the population age 65–74 years. Separate assessments of the costs of fractures among those with diabetes are not available. However, with the high prevalence of diabetes in older adults, the increased risk of incident fracture in those with diabetes, and the greater likelihood of poor recovery after a fracture, it is clear that fractures in patients with diabetes result in significant health care costs.

Frequent Falls and Bone Fragility Increase Fracture Risk

Fractures result when the strength of a bone is not sufficient to sustain a particular trauma. In older adults, bone strength declines, and moderate trauma, often due to a fall from standing height or less, may be enough to cause a fracture. Ninety percent of hip fractures are the result of a moderate trauma fall (12). The majority of wrist, pelvis, humerus, rib, leg, hand, patella, ankle, elbow, and face fractures are also due to a fall (13). On the other hand, falls are common among older adults, with one-third reporting at least one fall per year, and most falls do not result in injury. About 3%–5% of falls in older adults result in a fracture; about 1% result in hip fracture (14). Even with this small proportion of falls that result in a fracture, increased falling is a risk factor for non-spine fractures (15).

Bone fragility contributes to fracture risk, and bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DXA), is an established method of assessing bone strength and predicting fracture risk. BMD at the hip or spine is often expressed as a BMD T-score, the number of standard deviations below the average BMD in healthy 20–29-year-old non-Hispanic white women (16,17). A negative T-score indicates BMD lower than this young adult average. Using BMD, osteoporosis was originally operationally defined by the World Health Organization as a femoral neck BMD T-score of -2.5 or lower. This has since been expanded to include total hip and lumbar spine BMD T-scores of -2.5 or less. Osteoporosis can also be identified based on a history of low trauma fracture, particularly of the spine or hip. In addition, Dr. Kanis and colleagues have developed a fracture prediction algorithm (FRAX) that predicts the 10-year fracture risk of an individual based on bone density and other risk factors for fracture, including age, sex, race/ethnicity, and body size (18). A specific FRAX algorithm has been developed for the United States.

Sources of Fracture Data

Limited sources of data are available in the United States that identify both diabetes and fracture. The National Health and Nutrition Examination Surveys (NHANES) administered during 1999–2010 asked participants about a history of fractures and also collected data on diabetes status. Ascertainment of prevalent fractures in the NHANES was based solely on self-report without any adjudication, which likely results in both over- and underreporting of fractures (19). A more important limitation of this approach is the inability to distinguish fractures that occurred before or after the onset of diabetes. For the population in nursing homes, the National Nursing Home Survey (NNHS) conducted in 2004 included questions regarding the occurrence of a hip or any other fracture in the previous 180 days. Questions were answered by the nursing home staff familiar with a participating resident. The staff members were asked to consult medical records when providing answers to the NNHS questions.

Identification of diabetes in the NHANES is discussed in more detail in Chapter 3 *Prevalence and Incidence of Type 2 Diabetes and Prediabetes*. Briefly, the NHANES includes a fasting plasma glucose (FPG) test and glycosylated hemoglobin (A1c) assay, as well as self-reported diabetes diagnosis, and therefore identifies those who were unaware of their diabetes status. In certain years, the NHANES also included a 2-hour oral glucose tolerance test (OGTT) to identify undiagnosed diabetes; however, this test was not used for identifying diabetes in this chapter. In the NHANES, it is difficult to distinguish those with type 1 and type 2 diabetes. Participants who reported a diagnosis of diabetes were not queried regarding the type of diabetes. Since fractures are primarily a concern in older individuals, the analyses in this chapter are limited to participants age ≥50 years. In this age group, the great majority (~99%) of participants reporting diabetes have type 2 rather than type 1 diabetes.

For incident fracture, data on diabetes status from the NHANES III (1988–1994) and NHANES 1999–2004 were combined with Medicare claims records to compare fracture rates in participants age ≥65 years (20). For analyses comparing fracture rates in those with and without diabetes, diabetes status was based on self-report of a physician's diagnosis of diabetes. For analyses comparing those with diabetes, prediabetes, and normal glucose levels, diabetes status was based on self-report and A1c levels. Participants were excluded from analyses if they reported a previous hip, wrist, or spine fracture (13%). The prevalence of diagnosed diabetes was 15% in people age ≥65 years. Only about 3% of those with diagnosed diabetes appeared to have type 1 diabetes, identified based on age at diagnosis and exclusive use of insulin.

Additional sources of data for incident fracture are longitudinal cohort studies in populations of older adults. Data for this chapter are provided from five cohorts in the United States. Four are fixed cohorts established for longitudinal studies of older adults: the Women's Health Initiative Observational Study (WHI-OS); the Study of Osteoporotic Fractures (SOF) in older women; the Osteoporotic Fractures in Men (MrOS) study; and the Health, Aging, and

Body Composition (Health ABC) study in older men and women. The fifth cohort is a dynamic population—the residents of Rochester, Minnesota. Each cohort is described in more detail in the following sections. In the Rochester population, fractures were identified by medical record review. In the fixed cohorts, fractures were first identified by self-report and then adjudicated using medical records. All fractures were adjudicated in SOF, MrOS, and Health ABC; only hip fracture was adjudicated in WHI-OS. Thus, specificity for fracture is high in these studies, but some fractures were likely not identified.

In the four fixed cohorts, diabetes was ascertained by self-report of a diabetes diagnosis and/or reported use of diabetes medications. In MrOS, an elevated fasting serum glucose level (≥126 mg/dL [≥6.99 mmol/L]), measured in baseline serum specimens, was also used to identify diabetes. In Health ABC, elevated fasting serum glucose (≥126 mg/dL) and elevated OGTT (≥200 mg/dL [≥11.10 mmol/L]) levels were used. In the Rochester, Minnesota, population, diabetes was determined by medical record review, based on a record of diabetes diagnosis after age 30 years combined with evidence of diabetes medication use or elevated FPG (≥140 mg/dL [≥7.77 mmol/L]) or elevated OGTT (≥200 mg/dL). Those studies using only self-report of a diagnosis or of diabetes medication use, WHI-OS and SOF, probably misclassified some participants with diabetes, who were unaware of their status, as not having diabetes.

TYPE 1 DIABETES AND BONE COMPLICATIONS

Too few NHANES participants with probable type 1 diabetes (diagnosis at age <30 years, current use of insulin, and started insulin use within 1 year of diabetes diagnosis) were available in whom to assess prevalence of fractures or of low bone density.

A few longitudinal cohort studies in the United States have reported relative hip fracture rates among those with type 1 diabetes. The Iowa Women's Health Study of postmenopausal women defined type 1 diabetes as age at onset ≤30 years and current use of insulin (21). The study found that those with type 1 diabetes had a 12 times higher rate of hip fracture compared to those without diabetes in models adjusted for age, body mass index (BMI), and other factors (adjusted hazard ratio [HR] 12.2, 95% confidence interval [CI] 5.0–29.7). The Nurses' Health Study followed women who were age 34–59 years in 1980 for up to 22 years for the occurrence of hip fracture (22). Type 1 diabetes was defined based on age at onset (≤30 years), current use of insulin, or being prone to ketosis. The incidence of hip fracture in women with type 1 diabetes was 383 per 100,000 person-years compared to an incidence in nondiabetic women of 59 per 100,000 person-years. The multivariable adjusted hazard ratio for hip fracture, comparing women with type 1 diabetes and those without diabetes, was 6.4 (95% CI 3.9–10.3). In a meta-analysis of type 1 diabetes and hip fracture based on these two studies from the United States and four additional studies in Europe, the combined relative risk for hip fracture associated with type 1 diabetes was 6.3 (95% CI 2.6–15.1) (23). Evidence regarding the association between type 1 diabetes and incident fracture at other skeletal sites is very limited. No studies are available for U.S. populations. Studies in European populations have generally reported an increased risk of non-spine or all clinical fractures in type 1 diabetes, but the magnitude has ranged from 1.3 (24) to 3.1 (25).

Smaller studies in the United States have reported that type 1 diabetes is associated with lower bone density in adult women. Among middle-aged (average age 43 years) premenopausal women in the ProHealth Study, recruited in Pittsburgh, Pennsylvania, BMD was lower at the total hip and femoral neck, but not at the spine, in women with type 1 diabetes compared with healthy controls (26). Similarly, among younger premenopausal women (average age 28 years) recruited in western New York, total hip and femoral neck, but not spine, BMD were lower in those with type 1 diabetes (27). Studies in the United States are not available for men, but reports from other regions indicate that BMD is lower in men with type 1 diabetes as well (28). Consistent with these findings, a meta-analysis of studies from North America, Europe, and Australia found a modest reduction in bone density among those with type 1 diabetes (29). Average BMD Z-score was -0.22 at the spine and -0.37 at the total hip in those with type 1 diabetes. More frequent falls contribute to fracture risk along with low bone density, but studies of fall frequency in type 1 diabetes are not available.

The reasons for reduced BMD and increased fracture risk with type 1 diabetes are not clearly understood. Insulin is anabolic for bone, and lack of insulin may contribute to bone fragility (30). Hyperglycemia may have negative effects on bone-forming cells (osteoblasts) (31). Another potential source of bone fragility is higher levels of advanced glycation endproducts (AGEs) in bone collagen. AGEs are the end result of reactions between protein and sugar. They accumulate in collagen throughout the body, including bone collagen. Higher AGE levels are found with older age and with diabetes. Their presence in bone collagen appears to change the material properties of bone, potentially increasing the risk of fracture (32,33,34).

TYPE 2 DIABETES AND BONE COMPLICATIONS

Occurrence of Fractures

Prevalence of Fractures. Data were analyzed for *Diabetes in America, 3rd edition,* based on the NHANES 1999–2010, in which participants were asked "Has a doctor ever told you that you had broken or fractured your hip, wrist, or spine?" Starting in 2005, participants were also asked a separate question about the occurrence of any other fractures after age 20 years. Fracture reports were not adjudicated but relied solely on self-report. Studies that have compared self-report of fractures with medical records have found that fractures may be over- and underreported (19). In a cohort of older women, about 11% of self-reported fractures were not confirmed

when radiographs were examined (35). A common pattern of overreporting is an injury event with radiographs showing no fracture, while the participant reports that a fracture occurred. Studies have also documented a failure to report fractures. About 7% of fractures found through review of medical records were not reported by participants (36,37). For the NHANES analyses, all fractures were included regardless of the degree of trauma involved. Fractures resulting from higher trauma events, such as a car accident or fall from a ladder, are also associated with lower bone density (38).

These data available from the NHANES provide the prevalence, not the incidence, of fracture. Among participants who also reported diabetes, a prevalent fracture may have occurred before the onset of diabetes. Similarly, prevalent fractures in participants with prediabetes may have occurred before the development of prediabetes.

In these analyses of NHANES data, the definition of diabetes is based on self-report of diabetes, an elevated FPG (≥126 mg/dL), or an elevated A1c (≥6.5% [≥48 mmol/mol]) test. Additional participants may have been identified with diabetes if the 2-hour OGTT had also been considered in defining diabetes. However, FPG and A1c are the tests commonly used to identify diabetes in clinical practice. Both type 1 and type 2 diabetes are included in the NHANES data. In the age range considered (≥50 years), the overwhelming majority of participants had type 2 diabetes. In the NHANES 1999–2010, 0.7% of those with diagnosed diabetes matched the definition of probable type 1 diabetes.

Based on NHANES data, older adults with diabetes were more likely to report a history of hip fracture, but the differences were not statistically significant (Table 32.1). Among adults age ≥50 years in the United States, 2.2% of those with diabetes, 2.0% with prediabetes (defined by FPG 100–125 mg/dL [5.55–6.94 mmol/L] or A1c 5.7%–6.4% [39–46 mmol/mol]), and 1.4% with normal glucose levels have experienced a hip fracture (not significantly different). Numbers were too small to estimate hip fracture rates by race/ethnicity for all groups.

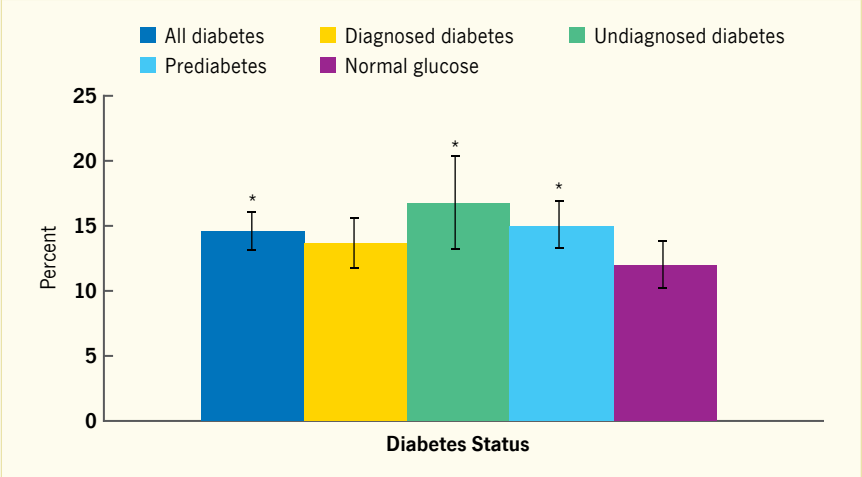
TABLE 32.1. Percent With a History of Hip Fractures Among Adults Age ≥50 Years, by Diabetes Status, Age, and Sex, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	All Diabetes	Prediabetes	Normal Glucose
Overall	2.2 (0.32)	2.0 (0.33)	1.4 (0.31)
Age (years)			
50–64	1.6 (0.42)	1.0 (0.32)[1]	0.6 (0.27)[2]
65–74	1.9 (0.61)[1]	2.2 (0.66)[1]	1.5 (0.63)[2]
≥75	4.0 (0.82)	4.6 (1.22)	4.9 (1.35)
Sex			
Men	2.5 (0.50)	2.2 (0.44)	1.2 (0.42)[1]
Women	1.9 (0.36)	1.8 (0.42)	1.5 (0.40)

Hip fractures are self-reported. Diabetes is based on self-report, A1c ≥6.5%, or FPG ≥126 mg/dL. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.
All p>0.05 (not significant) compared to participants with normal glucose levels
[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

FIGURE 32.1. Percent With a History of Hip, Wrist, or Spine Fractures Among Adults Age ≥50 Years, by Diabetes Status, U.S., 1999–2010



Fractures and diagnosed diabetes are self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

The prevalence of any hip, spine, or wrist fracture, the most common fractures among older adults, was also higher among those with diabetes (14.6%, p<0.05) and prediabetes (14.9%, p<0.05) compared to those with normal glucose levels (12.0%) (Figure 32.1, Table 32.2).

The prevalence of any fracture was not higher in those with diabetes (39.3%) or prediabetes (40.4%) compared with normal glucose levels (40.7%), considering all participants together (Table 32.3). When results were considered separately by sex, women had a higher prevalence of any fracture with diabetes (39.2%) compared with normal glucose levels (35.6%), but this difference was not statistically significant. In men, prevalence of any fracture was lower with diabetes

TABLE 32.2. Percent With a History of Hip, Wrist, or Spine Fractures Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	14.6 (0.85)*	13.7 (0.86)	16.7 (1.96)*	14.9 (0.96)*	12.0 (0.90)
Age (years)					
50–64	12.6 (1.11)	12.0 (1.15)	14.1 (3.08)	12.6 (1.33)	10.9 (1.06)
65–74	16.9 (1.85)*	15.1 (1.74)*	21.6 (4.05)*	15.5 (1.62)*	10.3 (1.64)
≥75	15.6 (1.12)	15.4 (1.37)	16.1 (2.81)	20.8 (1.70)	19.4 (2.23)
Sex					
Men	15.5 (1.12)	14.6 (1.18)	17.1 (2.65)	14.5 (1.06)	14.1 (1.74)
Women	13.6 (1.16)	12.8 (1.26)	16.2 (2.84)	15.3 (1.39)*	10.8 (0.99)
Race/ethnicity					
Non-Hispanic white	17.1 (1.09)*	16.2 (1.13)*	19.0 (2.52)*	15.9 (1.11)*	12.4 (1.05)
Non-Hispanic black	6.5 (0.95)	5.8 (0.98)	8.8 (2.57)	6.8 (1.49)	6.1 (1.43)
All Hispanic	10.0 (1.33)	10.5 (1.43)	8.4 (2.33)	12.4 (1.85)	12.1 (2.69)
Mexican American	11.1 (1.53)	11.0 (1.58)	11.5 (2.96)	11.0 (1.57)	11.9 (2.43)

Fractures and diagnosed diabetes are self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.05 compared to participants with normal glucose levels

All relative standard errors <30%

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

TABLE 32.3. Percent With a History of Any Fractures Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 2005–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	39.3 (1.45)	37.4 (1.79)	43.8 (3.22)	40.4 (1.94)	40.7 (2.65)
Age (years)					
50–64	36.4 (1.89)	35.1 (2.75)	39.6 (4.21)	38.9 (2.60)	40.9 (3.14)
65–74	42.5 (2.63)	39.7 (2.90)	49.9 (7.36)	39.1 (3.14)	35.6 (3.78)
≥75	41.2 (2.10)	39.4 (2.67)	44.9 (4.45)	46.8 (2.90)	45.9 (3.84)
Sex					
Men	39.3 (2.21)*	37.2 (2.54)*	43.5 (4.34)	41.7 (2.10)	48.8 (3.68)
Women	39.2 (1.92)	37.6 (2.19)	44.1 (5.24)	39.2 (2.93)	35.6 (3.23)
Race/ethnicity					
Non-Hispanic white	46.3 (1.87)	44.5 (2.08)	50.2 (4.53)	43.8 (2.13)	43.7 (2.95)
Non-Hispanic black	24.7 (2.11)	24.6 (2.32)	25.1 (5.50)	24.8 (2.84)	19.0 (3.98)
All Hispanic	26.9 (3.09)	29.3 (3.48)	19.8 (3.45)	24.7 (2.97)	28.8 (4.62)
Mexican American	26.7 (2.80)	29.0 (2.85)	21.0 (4.64)	26.1 (3.81)	31.0 (5.48)

Fractures and diagnosed diabetes are self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.05 compared to participants with normal glucose levels

All relative standard errors <30%

SOURCE: National Health and Nutrition Examination Surveys 2005–2010

(39.3%, p<0.05) compared with normal glucose levels (48.8%).

Nursing home residents are at high risk of hip and other fractures. NNHS 2004 data were analyzed for *Diabetes in America*. About 2% of residents had a hip fracture in the previous 180 days, and about 4% had any fracture in the same time period (Table 32.4). The prevalence was not higher in those with diabetes.

TABLE 32.4. Age-Standardized Percent of Nursing Home Residents With Fractures in the Past 180 Days, by Diabetes Status and Sex, U.S., 2004

	PERCENT (STANDARD ERROR)			
	Men		Women	
	Diabetes	No Diabetes	Diabetes	No Diabetes
Hip fracture in past 180 days	1.9 (0.73)[1]	1.8 (0.30)	1.4 (0.28)	2.0 (0.19)
Any fracture in past 180 days	3.5 (0.89)	3.7 (0.45)	3.9 (0.49)	4.2 (0.29)

History of fractures and diabetes status are based on medical records. Diabetes status is based on International Classification of Diseases, Ninth Revision (ICD-9), codes 250, 357.2, 362.0, 366.41, 648.0, or 775.1. Data are age-standardized to the National Nursing Home Survey 2004 whole population using age categories <64, 65–74, 75–84, and ≥85 years.

[1] Relative standard error >30%–40%

SOURCE: National Nursing Home Survey 2004

Incidence of Fractures. NHANES data, combined with Medicare claim records, have also been used to assess the relationship between diabetes and incident fracture (20). Fractures of the skull were excluded; other fractures were included regardless of trauma level. Models were adjusted for age, sex, survey (NHANES III [1988–1994] or NHANES 1999–2004), BMI, physical activity, hospital visits in the past year, and smoking. In these analyses, the relationship between diagnosed diabetes and incident fracture differed by race/ethnicity (p for interaction<0.05), but not by age or sex. Increased fracture risk with diabetes was found in non-Hispanic blacks and Mexican Americans. There was a modest increase in fracture risk among non-Hispanic whites, but it was not statistically significant. The hazard ratios, comparing those with and without diabetes, were 1.22 (95% CI 0.93–1.61) for non-Hispanic whites, 1.87 (95% CI 1.02–3.40) for non-Hispanic blacks, and 2.37 (95% CI 1.49–3.75) for Mexican Americans (Table 32.5) (20). Because of small numbers, hip fracture risk was only assessed in non-Hispanic whites (HR 1.35, 95% CI 0.82–2.22).

TABLE 32.5. Diabetes, Prediabetes, and Relative Risk of Incident Fracture Among Adults Age ≥65 Years, by Race/Ethnicity, U.S., 1988–1994 and 1999–2004

RACE/ETHNICITY	RELATIVE RISK ADJUSTED FOR AGE, SEX, AND SURVEY (95% CI)	RELATIVE RISK MULTIVARIABLE ADJUSTED* (95% CI)
Diagnosed diabetes†		
Non-Hispanic white	1.17 (0.89–1.52)	1.22 (0.93–1.61)
Non-Hispanic black	1.86 (1.05–3.30)	1.87 (1.02–3.40)
Mexican American	2.29 (1.41–3.73)	2.37 (1.49–3.75)
Diabetes status‡		
Non-Hispanic white		
Diabetes	1.12 (0.89–1.42)	1.20 (0.94–1.53)
Prediabetes	1.17 (0.93–1.47)	1.20 (0.96–1.51)
Normal glucose (ref)	1.00	1.00
Mexican American		
Diabetes	2.22 (1.35–3.64)	2.70 (1.70–4.31)
Prediabetes	1.14 (0.55–2.36)	1.42 (0.72–2.81)
Normal glucose (ref)	1.00	1.00

Incident fractures, defined as any clinical fracture except skull, were identified in Medicare claim records. Data include participants of the NHANES III (1988–1994) and NHANES 1999–2004; participants were excluded from analyses if they reported a previous hip, wrist, or spine fracture. A1c, glycosylated hemoglobin; CI, confidence interval.

* Adjusted for age, sex, survey, body mass index, physical activity, hospital visits in past year, and smoking.

† Self-reported physician diagnosis of diabetes. Reference groups are participants without diagnosed diabetes.

‡ Diabetes is based on self-report or A1c ≥6.5%. Prediabetes is based on A1c 5.7%–6.4%. Normal glucose is defined as A1c <5.7%. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.*

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In additional analyses, diabetes status was determined by A1c level in addition to self-report. Incident fracture rates were compared for three groups—diabetes, prediabetes and normal glucose—in non-Hispanic whites and Mexican Americans (Table 32.5) (20). Numbers were too small to consider these categories among non-Hispanic blacks. The results comparing those with diabetes (based on self-report or A1c) and normal glucose were similar to results for diagnosed diabetes (self-report alone). Fracture incidence was not statistically different in those with prediabetes and normal glucose in either race/ethnic group. The hazard ratios comparing those with prediabetes and normal glucose were 1.20 (95% CI 0.96–1.51) for non-Hispanic whites and 1.42 (95% CI 0.72–2.81) for Mexican Americans.

Comparisons of the incidence of fracture in those with and without diabetes have also been assessed from longitudinal studies that identified fracture events during follow-up of cohorts of older women and men. The WHI-OS, a cohort of women age 50–79 years at baseline, provides the largest study of diabetes and fracture incidence in the United States (39). The cohort included 93,405 older women, including 5,285 women with diabetes, who were followed for incident fractures for an average of 7 years. Fractures were first identified by self-report at annual clinic visits. Hip fracture reports, but not those for other fracture sites, were adjudicated by review of medical records. Fractures were included regardless of degree of trauma since lower BMD is associated with fracture risk in high as well as low trauma fracture cases (38). Diabetes was ascertained based on participant report of a diabetes diagnosis or use of diabetes medication. In models adjusted for age, women with diabetes had a 30% increased rate of any fracture (age-adjusted relative risk [RR] 1.3, 95% CI 1.2–1.4) (Table 32.6). Diabetes was associated with an increased fracture rate in non-Hispanic black women and in non-Hispanic white women. The rate of hip fracture was elevated in women with diabetes (age-adjusted RR 1.4, 95% CI 1.2–1.7) (Table 32.7). Fractures at other specific sites considered, including ankle, foot, shoulder, and clinical spine, were also elevated, with the exception of wrist/forearm fractures. The unadjusted incidence rates for hip and non-spine fracture among WHI-OS women with diabetes, including follow-up from baseline (1993–1998) to 2010, are provided in Tables 32.8 and 32.9 (A. Schwartz, unpublished data).

The association between diabetes and fracture has also been studied in men in the United States, although these studies have been smaller than the WHI-OS. The largest study to date followed men in Rochester, Minnesota, with diabetes (N=992) for up to 30 years for incident fractures (40). Fractures were identified from medical records of inpatient and outpatient visits. Those due to excessive trauma were excluded. Diabetes was ascertained from medical record review, based on a record of diabetes diagnosis after age 30 years combined with evidence of elevated FPG (≥140 mg/dL) or OGTT (≥200 mg/dL) or evidence of diabetes medication use. Their fracture rate was compared with the rate for the broader population of men in Rochester adjusted for age (40). Men with diabetes had an increased rate of any fracture (RR 1.4, 95% CI 1.3–1.6) and of hip fracture (RR 1.4, 95% CI 1.0–1.9) compared to

TABLE 32.6. Diabetes and Relative Risk of Incident Fracture in Older Adults in Five U.S. Cohorts

COHORT, YEARS	AGE AT BASELINE (YEARS)	NUMBER OF PARTICIPANTS WITH DIABETES	RELATIVE RISK ADJUSTED FOR AGE (95% CI)	RELATIVE RISK ADJUSTED FOR AGE AND BMD (95% CI)
Men				
Rochester*, 1970–2007	30–97	992	1.4 (1.3–1.6)	NA
MrOS†, 2000–2009	≥65	881	1.1 (0.9–1.3)	1.3 (1.1–1.5)
Women				
WHI-OS*, 1993–2004	≥65	5,285	1.3 (1.2–1.4)	1.2 (1.0–1.6)‡
Rochester*, 1970–2007	30–97	972	1.3 (1.2–1.4)	NA
SOF†, 1998–2008	≥65			
Not using insulin		551	1.2 (1.0–1.4)	1.3 (1.1–1.5)
Using insulin		106	1.6 (1.1–2.2)	1.7 (1.2–2.4)
Men and women				
Health ABC*, 1997–2007	70–79	566	1.2 (0.8–1.9)§	1.7 (1.1–2.6)§

BMD, bone mineral density; CI, confidence interval; Health ABC, Health, Aging, and Body Composition Study; MrOS, Study of Osteoporosis in Men; NA, not available; Rochester, residents of Rochester, Minnesota; SOF, Study of Osteoporotic Fractures; WHI-OS, Women's Health Initiative Observational Study.
* Any clinical fracture
† Non-vertebral fracture
‡ Subgroup of women (N=6,394) with BMD measurements, including 472 women with diabetes
§ Also adjusted for sex

SOURCE: References 39, 40, 41, 56, and 64

TABLE 32.7. Diabetes and Relative Risk of Hip Fracture in Older Adults in Three U.S. Cohorts

COHORT, YEARS	AGE AT BASELINE (YEARS)	NUMBER OF PARTICIPANTS WITH DIABETES	RELATIVE RISK, ADJUSTED FOR AGE (95% CI)	RELATIVE RISK, ADJUSTED FOR AGE AND BMD (95% CI)
Men				
Rochester, 1970–2007	30–97	992	1.4 (1.0–1.9)	NA
Women				
WHI-OS, 1993–2004	≥65	5,285	1.4 (1.2–1.7)	1.8 (0.9–3.6)*
Rochester, 1970–2007	30–97	972	1.0 (0.8–1.2)	NA
SOF, 1998–2008	≥65			
Not using insulin		551	1.5 (1.1–2.0)	1.8 (1.3–2.5)
Using insulin		106	1.3 (0.6–2.8)	1.7 (0.8–3.8)

BMD, bone mineral density; CI, confidence interval; NA, not available; Rochester, residents of Rochester, Minnesota; SOF, Study of Osteoporotic Fractures; WHI-OS, Women's Health Initiative Observational Study.
* Subgroup of women (N=6,394) with BMD measurements, including 472 women with diabetes

SOURCE: References 39, 40, and 41

TABLE 32.8. Hip Fracture Rates in Older Women, by Diabetes Status, Age, and Race, in Four U.S. Cohorts

			DIABETES		NO DIABETES	
COHORT, YEARS	RACE	AGE (YEARS)	Number With Hip Fracture	Incidence Rate* (95% CI)	Number With Hip Fracture	Incidence Rate* (95% CI)
WHI-OS, 1993–2010	White	65–79	91	3.9 (3.2–4.9)	1,035	2.0 (1.9–2.1)
		≥80	52	13.5 (10.3–17.7)	770	8.6 (8.0–9.2)
	Black	≥65	10	1.7 (0.9–3.1)	32	0.8 (0.6–1.2)
SOF, 1998–2008	White	65–79	33	7.0 (5.0–9.9)	333	4.7 (4.2–5.2)
		≥80	62	20.4 (15.9–26.2)	1,008	17.6 (16.5–18.7)
	Black	≥65	4	4.3 (1.6–11.5)	13	2.6 (1.5–4.4)
Health ABC, 1997–2007	White	≥70	9	12.7 (6.6–24.4)	71	9.1 (7.2–11.5)
	Black	≥70	13	8.4 (4.9–14.5)	18	3.4 (2.1–5.3)
Rochester, 1970–1994	White	30–64	5	1.1 (0.4–2.6)	†	
		65–79	18	4.2 (2.5–6.7)	†	
		≥80	42	19.6 (14.1–26.4)	†	

CI, confidence interval; Health ABC, Health, Aging, and Body Composition Study; Rochester, residents of Rochester, Minnesota; SOF, Study of Osteoporotic Fractures; WHI-OS, Women's Health Initiative Observational Study.
* Incidence of first hip fracture during follow-up, per 1,000 person-years
† No participants without diabetes were included in the study.

SOURCE: A. Schwartz, unpublished analyses of data from the WHI-OS, SOF, and Health ABC studies. E. Atkinson, unpublished analyses of data from the Rochester study.

TABLE 32.9. Non-Spine Fracture Rates in Women, by Diabetes Status, Age, and Race, in Four U.S. Cohorts

			DIABETES		NO DIABETES	
COHORT, YEARS	RACE	AGE (YEARS)	Number With Fracture	Incidence Rate* (95% CI)	Number With Fracture	Incidence Rate* (95% CI)
WHI-OS, 1993–2010	White	50–64	203	28.6 (25.0–32.9)	4,669	19.4 (18.9–20.0)
		65–79	735	38.6 (35.9–41.5)	12,673	29.0 (28.5–29.5)
		≥80	155	55.9 (47.8–65.4)	3,239	52.0 (50.2–53.8)
	Black	50–64	52	15.6 (11.9–20.5)	293	11.4 (10.2–12.8)
		65–79	89	18.5 (15.0–22.8)	438	14.3 (13.0–15.7)
		≥80	20	38.7 (25.0–60.0)	84	24.6 (19.9–30.5)
SOF, 1998–2008	White	65–79	167	44.3 (38.1–51.6)	2,030	36.0 (34.5–37.6)
		≥80	130	67.5 (56.8–80.1)	1,911	51.8 (49.6–54.2)
	Black	≥65	16	18.3 (11.2–29.9)	77	17.0 (13.6–21.2)
Health ABC, 1997–2007	White	≥70	30	50.1 (35.0–71.6)	212	30.6 (26.7–35.0)
	Black	≥70	30	20.9 (14.6–29.9)	64	12.6 (9.9–16.1)
Rochester, 1970–1994	White	30–64	94	23.7 (19.2–29.0)	†	
		65–79	109	30.9 (25.4–37.3)	†	
		≥80	108	65.6 (53.8–79.2)	†	

CI, confidence interval; Health ABC, Health, Aging, and Body Composition Study; Rochester, residents of Rochester, Minnesota; SOF, Study of Osteoporotic Fractures; WHI-OS, Women's Health Initiative Observational Study.
* Incidence of first non-spine fracture during follow-up, per 1,000 person-years
† No participants without diabetes were included in the study.

SOURCE: A. Schwartz, unpublished analyses of data from the WHI-OS, SOF, and Health ABC studies. E. Atkinson, unpublished analyses of data from the Rochester study.

men in the broader population (Tables 32.6 and 32.7). The unadjusted incidence rates for hip and non-spine fracture among male Rochester residents with diabetes are provided in Tables 32.10 and 32.11 (E. Atkinson, unpublished data).

Several smaller cohorts have also examined the association between diabetes and incident fracture in the United States, using models that accounted for BMD. They include the SOF, a cohort of women age ≥65 years at baseline; MrOS, men age ≥65 years at baseline; and the Health ABC study that followed well-functioning adults age 70–79 years at baseline (39,41). In these three cohorts, participants were queried at regular intervals (every 4 months in SOF and MrOS by postcard; every year in Health ABC during a clinic or phone visit) regarding the occurrence of fractures. Reported fractures were then adjudicated using medical records. Fractures were included regardless of degree of trauma (38). In all three cohorts, diabetes was ascertained based on self-report of a diagnosis or use of diabetes medication. In MrOS, an elevated fasting serum glucose (≥126 mg/dL) was also used to identify participants with diabetes. In Health ABC, an elevated fasting serum glucose (≥126 mg/dL) or OGTT (≥200 mg/dL) was also used. The unadjusted incidence rates for hip fracture in these cohorts, stratified by diabetes status and sex, are provided in Tables 32.8 and 32.10 (A. Schwartz, unpublished data). The unadjusted incidence rates for all non-spine fractures are provided in Tables 32.9 and 32.11 (A. Schwartz, unpublished data). When the incidence of fractures in those with and without diabetes was compared in age-adjusted models, the relative rate of non-spine fracture was only statistically elevated among diabetic participants in the SOF, not in MrOS or Health ABC. However, with adjustment for BMD, the relative rates of fracture were generally increased compared with the age-adjusted models and all were statistically significant, with adjusted relative rates ranging from 1.2 to 1.7 (Table 32.6). In other words, for a given level of BMD, those with diabetes had a higher fracture rate than those without diabetes. As discussed in the next section, BMD tends to be higher in those with diabetes,

TABLE 32.10. Hip Fracture Rates in Older Men, by Diabetes Status, Age, and Race, in Three U.S. Cohorts

			DIABETES		NO DIABETES	
COHORT, YEARS	RACE	AGE (YEARS)	Number With Hip Fracture	Incidence Rate* (95% CI)	Number With Hip Fracture	Incidence Rate* (95% CI)
MrOS, 2000–2009	White	≥65	28	4.6 (3.1–6.6)	155	3.7 (3.1–4.3)
Health ABC, 1997–2007	White	≥70	12	7.5 (4.3–13.2)	39	5.4 (3.9–7.3)
	Black	≥70	4	3.3 (1.3–8.9)	11	3.2 (1.8–5.8)
Rochester, 1970–1994	White	30–64	2	0.4 (0.05–1.4)	†	
		65–79	24	5.0 (3.2–7.4)	†	
		≥80	14	12.0 (6.5–20.1)	†	

CI, confidence interval; Health ABC, Health, Aging, and Body Composition Study; MrOS, Study of Osteoporosis in Men; Rochester, residents of Rochester, Minnesota.
* Incidence of first hip fracture during follow-up, per 1,000 person-years
† No participants without diabetes were included in the study.

SOURCE: A. Schwartz, unpublished analyses of data from the MrOS and Health ABC studies. E. Atkinson, unpublished analyses of data from the Rochester study.

TABLE 32.11. Non-Spine Fracture Rates in Older Men, by Diabetes Status, Age, and Race, in Three U.S. Cohorts

			DIABETES		NO DIABETES	
COHORT, YEARS	RACE	AGE (YEARS)	Number With Fracture	Incidence Rate* (95% CI)	Number With Fracture	Incidence Rate* (95% CI)
MrOS, 2000–2009	White	65–79	52	14.7 (11.2–19.3)	320	13.1 (11.8–14.6)
		≥80	56	25.0 (19.2–32.4)	387	25.2 (22.8–27.9)
Health ABC, 1997–2007	White	≥70	25	16.3 (11.0–24.1)	103	14.7 (12.8–17.9)
	Black	≥70	11	9.4 (5.2–17.0)	21	6.2 (4.1–9.6)
Rochester, 1970–1994	White	30–64	78	16.8 (13.3–21.0)	†	
		65–79	105	25.3 (20.7–30.6)	†	
		≥80	40	39.3 (28.1–53.5)	†	

CI, confidence interval; Health ABC, Health, Aging, and Body Composition Study; MrOS, Study of Osteoporosis in Men; Rochester, residents of Rochester, Minnesota.
* Incidence of first non-spine fracture during follow-up, per 1,000 person-years
† No participants without diabetes were included in the study.

SOURCE: A. Schwartz, unpublished analyses of data from the MrOS and Health ABC studies. E. Atkinson, unpublished analyses of data from the Rochester study.

but this higher BMD does not provide the same protection from fracture risk as it does in those without diabetes.

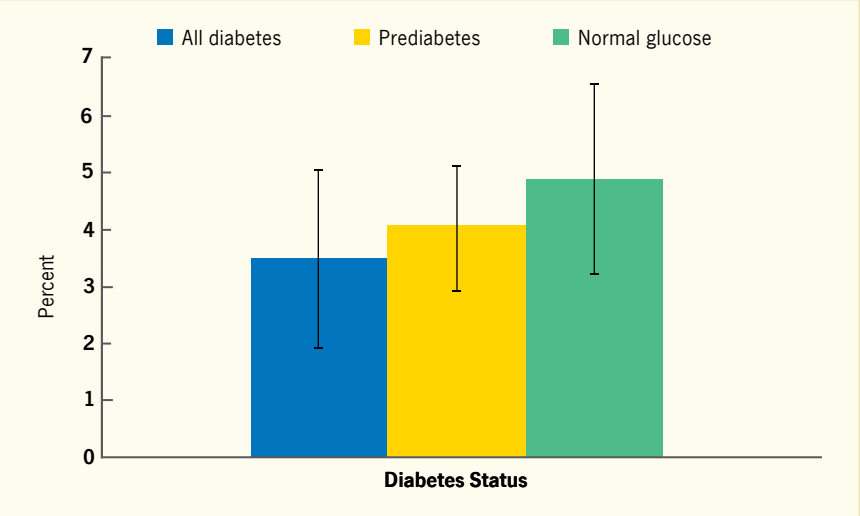
A meta-analysis of the association between diabetes and hip fracture incidence, based on 12 studies from Europe, the United States, and Australia, reported a combined relative risk of hip fracture of 1.7 (95% CI 1.3–2.2) comparing those with and without type 2 diabetes (23). Type 2 diabetes was also associated with a modest increase in the risk of all non-spine fractures (RR 1.2, 95% CI 1.01–1.5), based on a meta-analysis of eight studies (23).

Bone Mineral Density

BMD is usually measured in the clinic using DXA, an x-ray imaging tool, and is the basis for identifying increased fracture risk in older adults. Femoral neck BMD T-score is an index that compares measured BMD to the average BMD in healthy 20–29-year-old non-Hispanic white women. A negative T-score indicates BMD lower than this young adult average. Osteoporosis is defined as a femoral neck BMD T-score of -2.5 or lower, or history of a low trauma hip or spine fracture. A T-score higher than -2.5 but lower than -1.0 is considered "low bone density."

BMD of the femoral neck was measured using DXA in the NHANES 2005–2008 (42) and analyzed for *Diabetes in America*. Osteoporosis, defined as femoral neck BMD T-score less than -2.5, was present in 3.5% of adults with diabetes and 4.9% of those with normal glucose levels (Figure 32.2, Table 32.12). A lower prevalence of osteoporosis in those with diabetes

FIGURE 32.2. Percent With Osteoporosis Among Adults Age ≥50 Years, by Diabetes Status, U.S., 2005–2008



Osteoporosis is based on femoral neck BMD T-score -2.5 or less. Diabetes is based on self-report, A1c ≥6.5%, or FPG ≥126 mg/dL. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; BMD, bone mineral density; FPG, fasting plasma glucose.

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

TABLE 32.12. Percent With Osteoporosis Among Adults Age ≥50 Years, by Diabetes Status, Age, and Sex, U.S., 2005–2008

	PERCENT (STANDARD ERROR)		
CHARACTERISTICS	All Diabetes	Prediabetes	Normal Glucose
Overall	3.5 (0.77)	4.1 (0.53)	4.9 (0.84)
Age (years)			
50–64	0.9 (0.42)[2]	[3]	1.4 (0.70)[2]
65–74	3.4 (1.25)[1]	2.6 (1.11)[2]	6.9 (3.15)[2]
≥75	10.0 (2.58)*	19.4 (2.56)	24.9 (4.83)
Sex			
Men	1.1 (0.35)[1]	1.8 (0.46)	1.0 (0.45)[2]
Women	6.4 (1.42)	6.7 (0.97)	7.6 (1.41)

Osteoporosis is based on femoral neck BMD T-score -2.5 or less. Diabetes is based on self-report, A1c ≥6.5%, or FPG ≥126 mg/dL. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin A1c; BMD, bone mineral density; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels
[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

compared with normal glucose levels was evident in those age ≥75 years (10.0% vs. 24.9%, p<0.05). A similar trend was seen in those age 65–74 years, but the difference was not statistically significant.

The proportion of adults age ≥50 years with low bone density, defined as a femoral neck BMD T-score between -2.5 and -1.0, was lower in those with diabetes compared with normal glucose levels among women (36.2% vs. 54.7%, p<0.05), but did not differ in men (28.5% vs. 27.2%, p>0.05) (Figure 32.3, Table 32.13). The proportion with low bone density was consistently lower in those with diabetes across age groups.

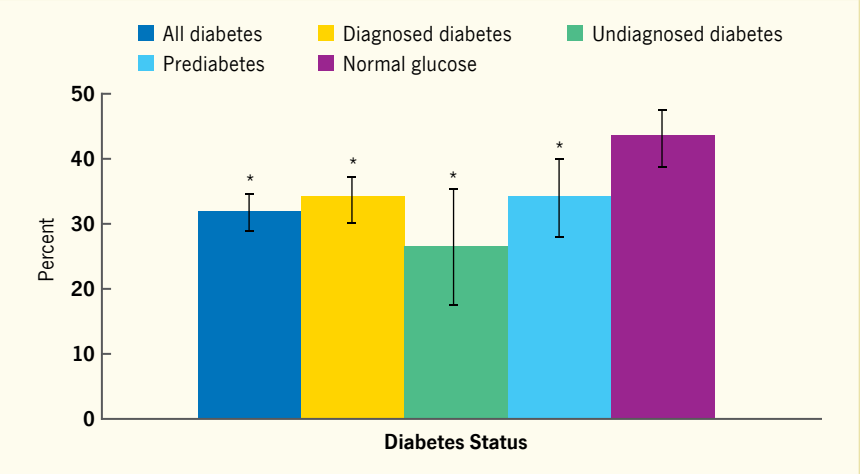
Two published meta-analyses of studies that included the United States and other regions of the world reported that type 2 diabetes is associated with higher bone density at the spine and hip (29,43). Larger body size is associated with higher BMD, which accounts for some of the reduced prevalence of osteoporosis and low bone density in those with diabetes. However, several studies have reported higher BMD with diabetes even after adjustment for BMI (44,45,46,47). Insulin is mildly anabolic for bone, and hyperinsulinemia may contribute to higher BMD (48).

Fall Frequency

Falls are a risk factor for fracture. Although most falls in older adults do not result in a serious injury, most fractures are caused by a fall (13). In studies of older adults, those with diabetes appear to fall more often. Most of these studies have defined a fall as ''an unexpected event in which the participants come to rest on the ground, floor, or lower level'' (49). However, these studies generally rely on self-report to assess falls, and individual interpretations of this definition may differ.

In the NHANES 1999–2004, participants were asked "During the past 12 months have you had any difficulty with falling?" This question probably did not capture all of those who fell in the previous year, since some participants might not view a

FIGURE 32.3. Percent With Low Bone Density Among Adults Age ≥50 Years, by Diabetes Status, U.S., 2005–2008



Low bone density (osteopenia) is based on femoral neck BMD T-score -2.5 to -1. Diagnosed diabetes is self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; BMD, bone mineral density; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

TABLE 32.13. Percent With Low Bone Density Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 2005–2008

	PERCENT (STANDARD ERROR)				
CHARACTERISTICS	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	32.0 (1.40)*	34.2 (2.06)*	26.6 (4.09)*	34.3 (2.54)*	43.6 (2.24)
Age (years)					
50–64	23.8 (2.37)*	25.5 (3.18)*	19.2 (5.43)*	26.3 (3.33)*	39.0 (3.27)
65–74	37.2 (3.29)	41.5 (4.26)	26.8 (5.68)*	44.4 (4.72)	52.9 (7.64)
≥75	44.9 (3.90)*	45.2 (3.57)*	44.0 (9.73)	47.2 (3.74)*	60.6 (5.58)
Sex					
Men	28.5 (2.14)	31.3 (2.82)	22.9 (5.58)	25.0 (2.82)	27.2 (2.65)
Women	36.2 (2.21)*	37.2 (2.60)*	33.0 (5.86)*	44.5 (3.33)*	54.7 (3.57)
Race/ethnicity					
Non-Hispanic white	33.8 (1.67)*	35.7 (2.81)*	29.6 (5.10)*	35.0 (3.30)*	44.1 (2.61)
Non-Hispanic black	23.1 (2.22)	26.9 (3.23)	11.1 (4.29)*[1]	18.8 (3.55)	33.3 (8.70)
All Hispanic	35.4 (3.73)	37.4 (4.05)	28.5 (4.31)	33.7 (4.62)	42.8 (7.19)
Mexican American	31.3 (3.93)	32.5 (4.07)	27.7 (5.80)	37.1 (6.60)	32.6 (6.41)

Low bone density (osteopenia) is based on femoral neck BMD T-score -2.5 to -1. Diagnosed diabetes is self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; BMD, bone mineral density; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels
[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

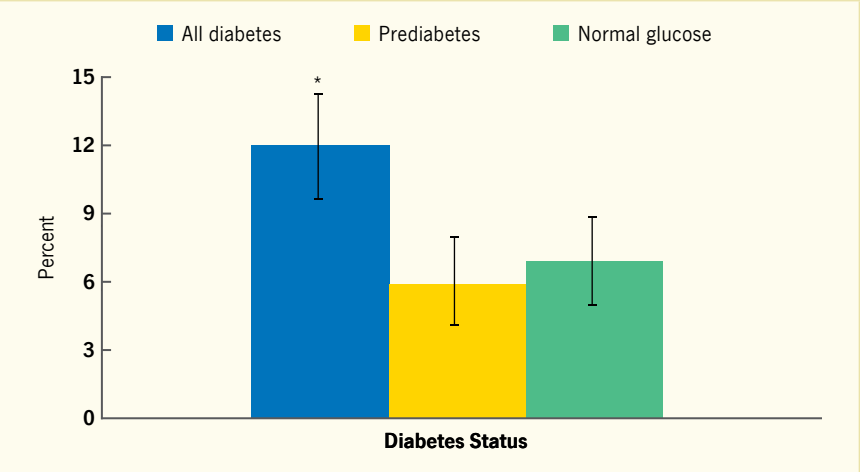
fall as evidence of "difficulty with falling." The proportion reporting any difficulty with falling was 6.9% in adults with normal glucose levels (age ≥50 years). In response to a question about "any falls," approximately one-third of older adults reported having at least one fall in the previous year (14).

In analyses of the NHANES 1999–2004 for *Diabetes in America*, older adults with diabetes were more likely to report difficulty with falling in the previous year (Figure 32.4, Table 32.14). Of those with diabetes, 12.0% reported difficulty with falling compared with 5.9% of those with prediabetes and 6.9% with normal glucose levels. However, when results were stratified by age, the higher prevalence of difficulty with falling associated with diabetes was only seen in the 65–74-year-old age group and not in those age ≥75 years. Diabetes was associated with increased prevalence of difficulty with falling among both men and women and among non-Hispanic whites and non-Hispanic blacks, but not Hispanics.

The frequency of falls is very high in nursing home populations. Based on a new analysis of the NNHS 2004, approximately one-third of nursing home residents had one or more falls in the previous 6 months (Table 32.15). In contrast, among community-dwelling older adults, only 12%–16% of those age ≥75 years reported difficulty with falling in the previous year (Table 32.14). The proportion of fallers did not differ by diabetes status in nursing home residents.

In longitudinal studies that have collected data on falls, older adults with diabetes have a modest increase in the proportion reporting any fall and are more likely to have multiple falls than those without diabetes (50,51). In the Health ABC study, diabetes was associated with increased risk of a fall resulting in hospitalization (52). An increased risk of falls associated with diabetes has also been reported in the nursing home population (53).

FIGURE 32.4. Percent With a History of Falling Among Adults Age ≥50 Years, by Diabetes Status, U.S., 1999–2004



History of falling is based on self-reported "difficulty with falling" in the previous year. Diabetes is based on self-report, A1c ≥6.5%, or FPG ≥126 mg/dL. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 32.14. Percent With a History of Falling Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	All Diabetes	Prediabetes	Normal Glucose
Overall	12.0 (1.19)*	5.9 (0.94)	6.9 (0.94)
Age (years)			
50–64	10.8 (1.95)*	3.9 (1.00)	5.0 (1.10)
65–74	11.9 (1.96)	5.7 (1.40)	6.2 (1.93)[1]
≥75	15.0 (1.93)	11.8 (2.07)	16.1 (2.50)
Sex			
Men	9.1 (1.18)*	4.1 (0.93)	5.1 (1.22)
Women	15.0 (1.72)*	8.0 (1.45)	8.0 (1.19)
Race/ethnicity			
Non-Hispanic white	11.9 (1.48)*	5.5 (0.99)	6.7 (0.99)
Non-Hispanic black	12.8 (2.17)*	4.0 (1.85)[2]	5.4 (1.78)[1]
All Hispanic	13.8 (2.95)	10.8 (2.78)	15.0 (5.06)[1]

History of falling is based on self-reported "difficulty with falling" in the previous year. Diabetes is based on self-report, A1c ≥6.5%, or FPG ≥126 mg/dL. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.
* p<0.05 compared to participants with normal glucose levels
[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

TABLE 32.15. Age-Standardized Percent of Nursing Home Residents With a Previous History of Falling, by Diabetes Status and Sex, U.S., 2004

	PERCENT (STANDARD ERROR)			
	Men		Women	
	Diabetes	No Diabetes	Diabetes	No Diabetes
Fell in past 30 days	16.7 (1.58)	18.0 (0.96)	12.8 (0.80)	13.7 (0.50)
Fell in past 180 days	35.2 (2.10)	38.1 (1.18)	32.4 (1.25)	33.5 (0.72)

History of falls and diabetes status are based on medical records. Diabetes status is based on International Classification of Diseases, Ninth Revision (ICD-9), codes 250, 357.2, 362.0, 366.41, 648.0, or 775.1. Data are age-standardized to the National Nursing Home Survey 2004 whole population using age categories <64, 65–74, 75–84, and ≥85 years.

SOURCE: National Nursing Home Survey 2004

Prediction of Fracture Risk in Older Adults With Type 2 Diabetes

Because BMD is central to fracture prediction, the paradox of increased fracture risk without reduced BMD in those with type 2 diabetes has led to concerns that standard tools for predicting fracture may not apply in diabetic patients. BMD T-score is used to assess fracture risk and the need for pharmacological therapy. A femoral neck or total hip BMD T-score of -2.5 is recommended as the threshold to consider pharmacological therapy in older adults (54). In a study comparing fracture incidence in older adults with and without diabetes in three cohorts based in the United States, a lower femoral neck BMD T-score predicted fracture risk in diabetic patients but tended to underestimate risk relative to nondiabetic patients (Figure 32.5) (41). For example, a diabetic woman with a T-score of -2.0 had a fracture risk similar to a nondiabetic woman with a T-score of -2.6. The paradox of higher fracture risk with higher BMD in older adults with type 2 diabetes requires using a different T-score threshold to identify diabetic patients at the highest risk of fracture.

The FRAX algorithm is another established method for predicting fracture risk that relies on BMD and other factors, such as age, sex, and body size (18). Two separate investigations, in the United States and Canada, found that the FRAX algorithm tends to underestimate fracture risk in diabetic patients (Figure 32.6) (41,55). This result is not surprising since the FRAX algorithm relies heavily on BMD. In the future, the FRAX algorithm may be adjusted to include type 2 diabetes. Until that time, clinicians need to be aware that underestimation of fracture risk occurs with the use of BMD T-score or FRAX to assess risk in patients with diabetes.

Reasons for Increased Fracture Risk With Type 2 Diabetes

Although older adults with type 2 diabetes tend to have higher BMD, they also paradoxically have increased fracture risk. This observation is likely due in part to a higher rate of falls in those with diabetes, but falls do not fully account for the increased fracture risk (39,46,56). In addition, diabetic bone appears to be more fragile for a given BMD. Understanding the reasons for this reduced bone strength in diabetes is a focus of research. In a small study of postmenopausal women using high resolution peripheral computed tomography, increased porosity of cortical bone at the tibia and radius was found in diabetic women with a history of fracture compared with controls (57). These deficits in cortical bone microarchitecture could weaken bone but would not be identified in a DXA measurement of BMD. As discussed for type 1 diabetes, higher levels of AGEs in bone collagen may make the bone brittle and increase fracture risk (32,33,34).

RISK FACTORS FOR FRACTURE OF PARTICULAR CONCERN IN PATIENTS WITH DIABETES

Other traditional risk factors for fracture, in addition to low BMD and more frequent falls, appear to be associated with fracture risk in those with diabetes. In the study of diabetes and fracture in Rochester, Minnesota, residents, predictors of incident fracture included older age, female gender, prior fracture, lower BMI, reduced physical activity, and use of corticosteroids (40). The following sections review risk factors related to complications or treatment of diabetes.

Diabetes Complications

In broader populations, poor vision, reduced kidney function, and reduced peripheral nerve function have been identified as risk factors for fracture. Stroke is strongly associated with increased fracture risk, and some studies have found that myocardial infarction is associated with fracture. These findings suggest microvascular and macrovascular complications are probably risk factors for fracture in diabetic patients. However, there is limited direct evidence regarding the association between diabetes-related complications and fracture in diabetic populations. The Health ABC study found that increased risk of fracture among diabetic participants was associated with neuropathy and history of stroke/transient ischemic attack (56). In Rochester, Minnesota, residents with type 2 diabetes, neuropathy was a risk factor for fracture (HR 1.3, 95% CI 1.1–1.6) in multivariable models, and renal failure was a risk factor (HR 1.6, 95% CI 1.2–2.2) in age-adjusted models, but clinically diagnosed nephropathy and retinopathy were not (40). Outside the United States, a large study conducted using the Danish National Hospital Discharge Register did not find increased fracture risk associated with macrovascular complications, diabetic eye disease, or neuropathy considered separately (58). However, there was a modest increase in fracture risk for multiple complications among patients with type 2 diabetes.

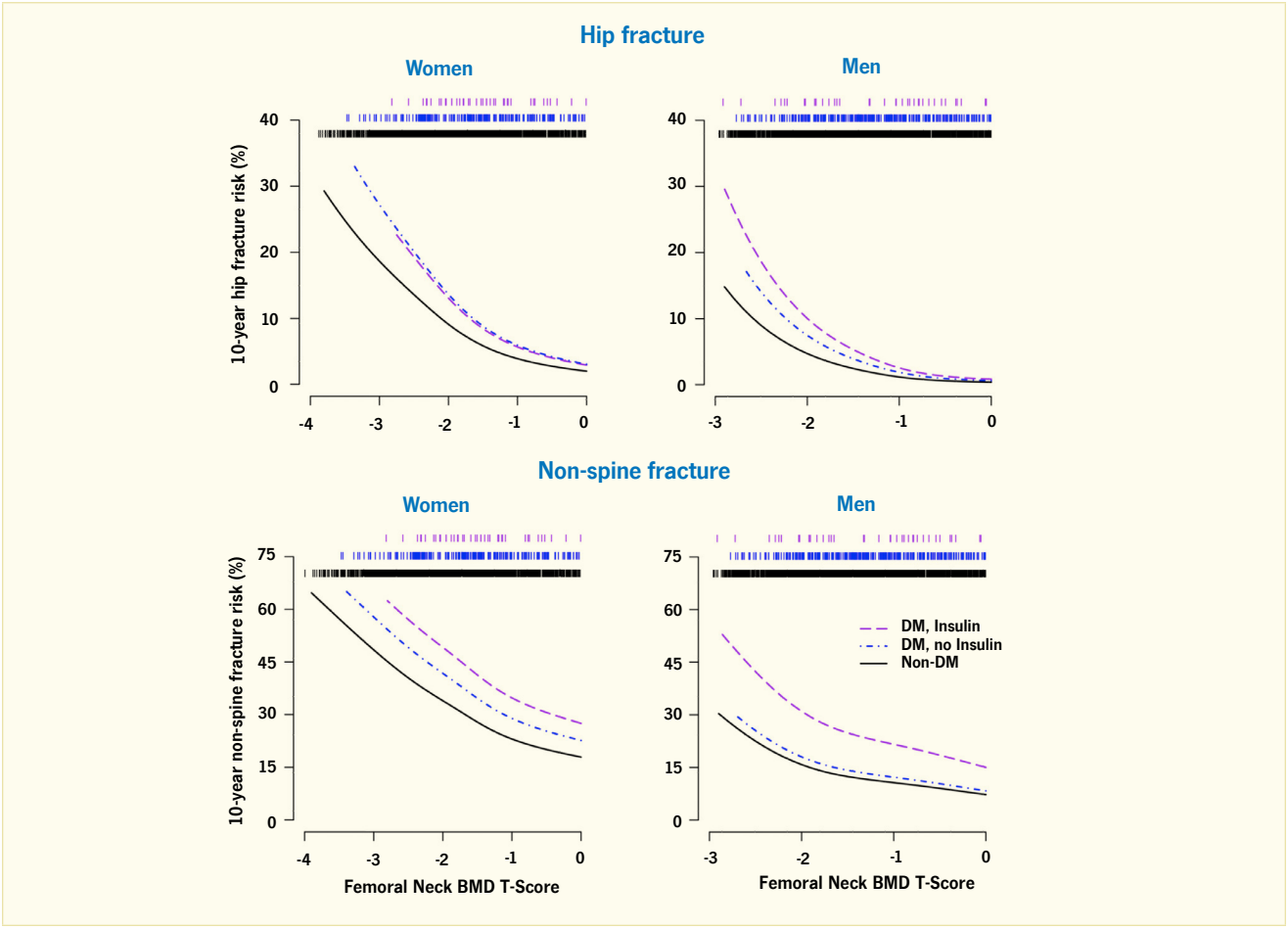
Thiazolidinediones

Thiazolidinediones (TZDs) are a class of oral diabetes medications that increase insulin sensitivity. Troglitazone, the first available TZD (1997), was withdrawn from the market in 1999 due to rare cases of liver failure. In 1999, rosiglitazone and pioglitazone were introduced in the United States. Evidence from rodent and human studies indicated that TZDs are associated with bone loss (59,60,61). The negative effect of TZDs on bone occurs, at least in part, through activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ), resulting in increased development of fat cells (adipocytes) and reduced development of bone-forming cells (osteoblasts) (59). In light of this evidence, the rate of fractures reported as adverse events in a randomized controlled trial of rosiglitazone was examined (62). The rate of clinical fractures was doubled in women using rosiglitazone compared with those using metformin or a sulfonylurea but was not increased in men. Subsequent analysis of pioglitazone trials found similar results (63). Other adverse events associated with these TZDs have led to restrictions and reduced prevalence of use in the United States. Clinicians prescribing a TZD for an older woman are advised to consider her underlying fracture risk.

Insulin Use

Insulin use appears to be associated with increased risk of fractures (Table 32.6) (21,22,40,46,64) and falls (51,65). The reasons for these associations are not clearly established. Hypoglycemic

FIGURE 32.5. Femoral Neck BMD T-Score and 10-Year Fracture Risk at Age 75 Years, by Diabetes and Insulin Use Status, SOF, MrOS, and Health ABC



Women were enrolled in the Study of Osteoporotic Fractures (SOF) or the Health, Aging and Body Composition (Health ABC) study. Men were enrolled in the Study of Osteoporosis in Men (MrOS) or Health ABC. Rug plots indicate number of participants (age 73–77 years) at each level of T-score (for women with hip fracture, n=41, 205, and 2,604, for DM with insulin use, DM without insulin use, and no DM, respectively; for women with non-spine fracture, n=41, 196, and 2,468, respectively; and for men with both hip and non-spine fracture, n=40, 306, and 1,698, respectively). BMD, bone mineral density; DM, diabetes mellitus.

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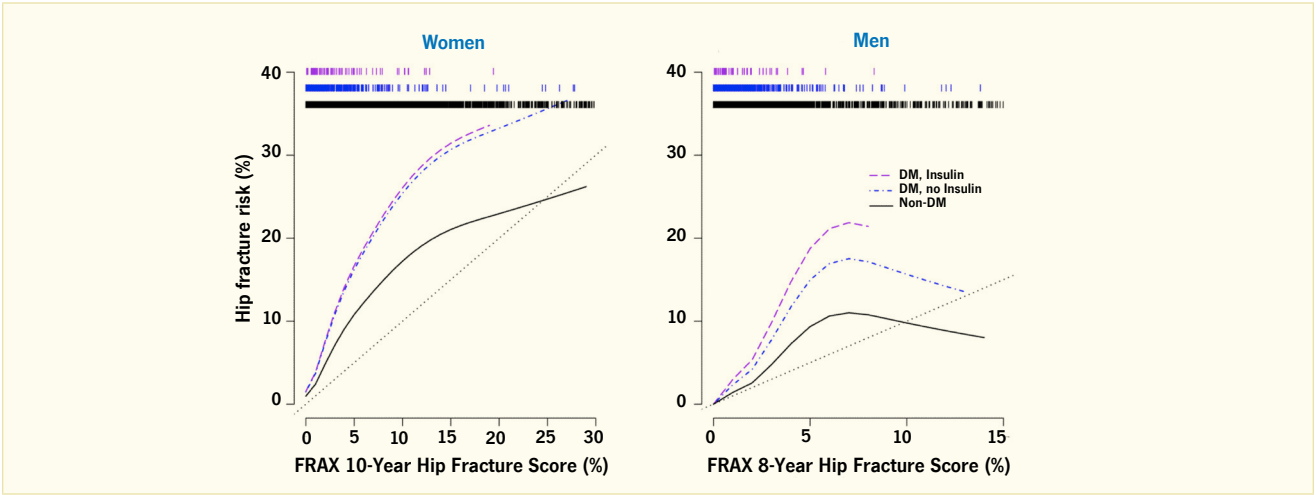
FIGURE 32.6. FRAX Hip Fracture Risk Score and Risk Estimated From Hip Fracture Experience in Women (SOF) and Men (MrOS)



Ten-year hip fracture risk based on FRAX score model versus risk estimated from hip fracture experience in the Study of Osteoporotic Fractures (women; SOF) and the 8-year hip fracture risk based on FRAX score model versus risk estimated from hip fracture experience in the Osteoporotic Fractures in Men Study (MrOS). Rug plots indicate number of participants at each level of FRAX score (for women, n=78, 442, and 7,406, and for men, n=80, 801, and 5,113, for DM with insulin, DM without insulin use, and no DM, respectively). Diagonal line is the line of equality where the FRAX predicted risk equals the estimated risk at 10 or 8 years. DM, diabetes mellitus; FRAX, Fracture Risk Assessment Tool.

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episodes associated with insulin use may increase the risk for a fall resulting in fracture. One study among Medicare patients with diabetes reported an increased risk of fall-related fractures among those with a hypoglycemic episode (66). Insulin use may be a marker for other factors that increase fracture risk, including reduced physical performance and higher prevalence of diabetic complications. Insulin use also suggests a decline in pancreatic function that may have a negative effect on bone strength.

Glycemic Control

The effects of glycemic control on the risk of fractures remain unclear. Observational studies indicate that poor glycemic control is associated with higher fracture risk (67,68). In a large randomized trial comparing intensive and standard glycemic control, no difference in the rate of fractures or falls was observed across the two treatment groups (69). However, the intensive and standard control groups achieved median A1c values of 6.4% and 7.5% (58 mmol/mol), respectively. Increased fracture risk may be confined to those with poor control.

Diabetes Duration

Longer duration of diabetes is associated with increased fracture risk (21,22,40,46,70). For example, in the Nurses' Health Study, the relative risk of hip fracture was 3.1 (95% CI 2.3–4.0) among women with duration of diabetes ≥12 years, while the relative risk was 1.7 (95% CI 1.2–2.4) among those with <5 years duration, compared with nondiabetic women (22). These results suggest that diabetes has a cumulative impact on fracture risk. With greater understanding of the characteristics of diabetes that are most important in determining fracture risk, efforts to prevent fractures in this population can be better targeted.

FRACTURE PREVENTION

Fall Prevention

Reducing falls in older adults is one aspect of fracture prevention. Effective interventions to reduce falls in older adults have been identified in broad populations, including exercise programs, home safety interventions, and multifactorial assessment and intervention programs (71). These interventions have not been tested separately among patients with diabetes, but it seems likely that they would be effective. An exercise intervention has been shown to improve balance, a risk factor for falls, among older adults with type 2 diabetes (72).

Pharmacological Therapy

In older adults with osteoporosis, pharmacological therapy may be warranted to prevent fractures. A number of effective therapies are available to reduce fracture risk in older adults with osteoporosis, defined by low BMD and/or presence of vertebral fractures, based on evidence from randomized placebo-controlled trials (73). Separate trials of these therapies have not been conducted among patients with diabetes. Very limited data are available from *post hoc* subgroup analyses of larger trials, examining efficacy in diabetic patients. In the Fracture Intervention Trial, alendronate treatment compared with placebo prevented bone loss in diabetic women as effectively as in nondiabetic women (74). Too few fracture outcomes occurred in the diabetic women to consider fracture efficacy in this subgroup. In a *post hoc* analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial of raloxifene, treatment was effective in preventing vertebral fractures in women with diabetes (75). These two trials suggest that osteoporosis therapies are likely to be effective treatments in diabetic patients with low BMD or prevalent vertebral fracture, although evidence is limited. The entry criteria for trials of osteoporosis therapy generally select participants with low BMD and/or vertebral fractures. However, diabetic patients fracture at a higher BMD on average. Thus, the efficacy of pharmacological therapy in diabetic patients with elevated fracture risk, but BMD above the threshold for osteoporosis, has not been tested.

JOINT COMPLICATIONS IN DIABETES

WHY ARTHRITIS MATTERS

The prevalence of arthritis complications in the U.S. population is high. Osteoarthritis (OA) or degenerative joint disease most frequently involves the knees, hips, hands, and spine and affects nearly 14% of individuals age ≥25 years and nearly 34% of those ≥65 years (76,77,78,79). In 2010–2012, an estimated 52.5 million adults in the United States had doctor-diagnosed arthritis (80). Arthritis was the second most common comorbid condition (16%) for adult primary care visits in 2006 (81). The economic costs associated with arthritis are high. In 2007, direct health care costs for patients with OA were over two times higher than costs for similar patients without OA (82). Medical expenditures for arthritis and joint pain in 2012 among adults age ≥65 years were an estimated $30.2 billion, exceeded only by the costs of treatment for heart conditions and for cancer (83). In 2012, knee arthroplasty and hip replacement were among the top five operating room procedures for adults age ≥45 years (84). Since the prevalence of OA increases with age, the costs are rapidly rising with the growing elderly population (85).

The impact of OA on the quality of life is high. OA of the knee is one of the five leading causes of disability among individuals living independently (86). Eighty percent of individuals with OA report some amount of movement limitation, and nearly 40% of individuals with knee OA report their health to be "poor" or "fair" (76,87).

Although research is ongoing, a few risk factors associated with OA have been established. Risk factors for OA that are not modifiable include increased age (88), sex (with women having a higher risk) (89), race/ethnicity (with African Americans having higher risk and Asians having a lower risk in hip joints) (90,91,92), and genetic predisposition (93). Modifiable risk factors include excess body weight, joint

injuries, occupations that have excess mechanical stress on joints, heavy lifting or manual labor (e.g., agriculture), structural malalignment, and muscle weakness (94,95). Other risk factors that are not as strongly associated with increased risk of lower extremity OA include estrogen deficiency, high bone mass, low vitamin C, E, and D intake, and inflammation as measured by C-reactive protein (96,97). Hand OA, especially erosive hand OA, has a strong association with genetics and is more common in women (98,99,100).

TYPE 1 DIABETES AND JOINT COMPLICATIONS

A number of studies have reported genetic/autoimmune associations with OA. Type 1 diabetes also has genetic/autoimmune associations, suggesting potential overlap in these conditions. Genetic associations include a variant allele at the *IL2-IL21* gene locus that is associated with rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus (101). A gene called *PTPN22* is highly correlated with the incidence of type 1 diabetes, as well as rheumatoid arthritis, juvenile idiopathic arthritis, and other autoimmune diseases (87,102). While genetic associations between rheumatoid arthritis and type 1 diabetes have been reported, the exact mechanism by which these allele variants increase the risk of these autoimmune diseases is not yet known.

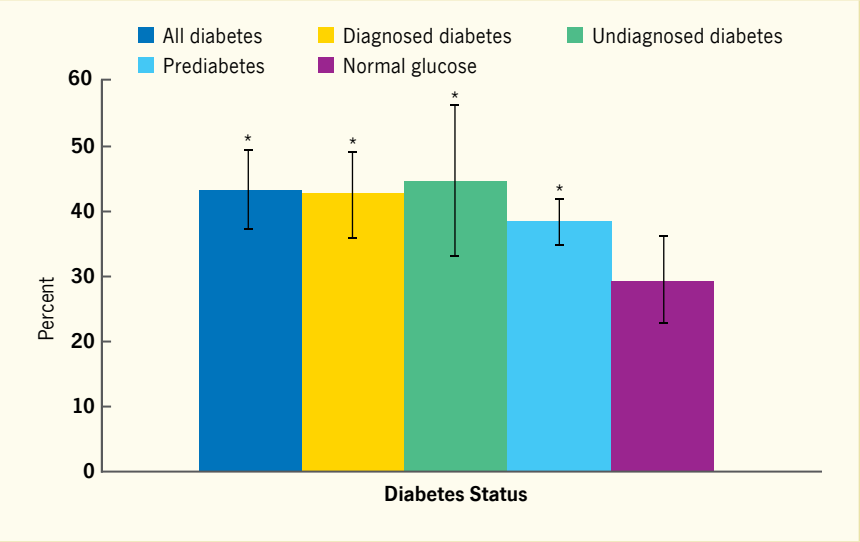
TYPE 2 DIABETES AND JOINT COMPLICATIONS

Prevalence of Osteoarthritis

In epidemiologic studies, the prevalence of OA is defined by radiographs and/or by joint pain. Radiographic knee OA requires a radiograph that has evidence of joint space narrowing, or osteophyte formation at the margin of the joints. A summary grade, usually Kellgren and Lawrence of 2 or more (scale of 0 to 4), is considered definite disease. Clinical knee OA is defined by symptoms in or around the knee on most days during the past month.

Knee OA defined by radiograph in the NHANES III (1988–1994) was 43.5% in those with diabetes and 29.3% in the normal glucose group (p<0.05) (Figure 32.7, Table 32.16), according to a new

FIGURE 32.7. Percent With Knee Osteoarthritis Among Adults Age ≥60 Years, by Diabetes Status, U.S., 1988–1994



Osteoarthritis is based on knee x-ray. Diagnosed diabetes is self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.05 compared to participants with normal glucose levels

SOURCE: National Health and Nutrition Examination Surveys III 1988–1994

TABLE 32.16. Percent With Knee Osteoarthritis Among Adults Age ≥60 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1988–1994

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	43.5 (2.95)*	42.9 (3.15)*	44.6 (5.49)*	38.6 (1.89)*	29.3 (3.26)
Age (years)					
60–74	42.9 (4.33)*	41.2 (5.29)*	46.1 (5.93)*	36.3 (2.39)*	23.2 (4.48)
≥75	44.6 (4.72)	46.2 (4.46)	40.8 (11.35)	43.7 (5.76)	47.5 (5.39)
Sex					
Men	41.9 (5.38)	43.4 (7.59)	39.4 (6.87)	25.8 (3.99)	24.4 (5.95)
Women	44.9 (2.88)*	42.5 (3.99)	50.8 (6.84)*	49.2 (3.39)*	31.5 (4.59)
Race/ethnicity					
Non-Hispanic white	42.6 (3.73)*	42.2 (4.32)	43.6 (6.35)	38.3 (2.31)*	29.0 (3.63)
Non-Hispanic black	57.4 (4.98)	54.5 (6.29)	62.4 (6.50)	47.7 (5.32)	48.8 (12.90)
Mexican American	38.8 (5.58)	35.7 (6.34)	51.7 (7.16)	35.7 (5.72)	30.9 (9.41)[1]

Osteoarthritis is based on knee x-ray. Diagnosed diabetes is self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.05 compared to participants with normal glucose levels

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys III 1988–1994

TABLE 32.17. Percent With Joint Pain Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	39.9 (2.03)	42.4 (2.10)	34.1 (3.85)	36.2 (1.71)	36.1 (1.81)
Age (years)					
50–64	41.2 (3.27)	45.0 (3.44)	33.0 (5.31)	38.4 (2.21)	37.3 (2.72)
65–74	38.7 (3.09)	39.4 (3.43)	36.9 (8.25)	33.7 (3.17)	30.4 (3.42)
≥75	38.9 (2.79)	41.2 (3.12)	32.8 (7.41)	33.3 (3.44)	38.3 (3.17)
Sex					
Men	31.4 (2.90)	35.5 (3.51)	24.0 (4.16)	31.8 (2.21)	31.7 (2.56)
Women	48.8 (2.32)*	48.7 (2.43)*	49.4 (5.44)	41.1 (2.74)	38.7 (2.08)
Race/ethnicity					
Non-Hispanic white	42.4 (2.36)	46.1 (2.44)*	35.2 (4.46)	38.9 (1.88)	36.7 (2.05)
Non-Hispanic black	34.9 (2.13)	33.7 (2.03)	39.5 (6.62)	18.1 (3.29)	29.4 (4.93)
All Hispanic	30.8 (3.21)	35.8 (3.65)	13.8 (4.89)*[1]	29.8 (5.09)	41.3 (5.72)
Mexican American	34.4 (3.71)	37.3 (3.85)	22.9 (7.27)[1]	26.1 (2.99)	38.0 (5.19)

Joint pain and diagnosed diabetes are self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* p<0.05 compared to participants with normal glucose levels

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2004

analysis conducted for *Diabetes in America*. In adults age 60–74 years, prevalence of OA in those with diabetes was 42.9% compared with 23.2% in the normal glucose group (p<0.05) but was not statistically different between the two groups for individuals age ≥75 years (44.6% vs. 47.5%). In women, OA was more prevalent in those with diabetes compared with those with normal glucose levels (44.9% vs. 31.5%, p<0.05), but OA prevalence did not differ significantly in men by diabetes status. The number of men or subjects age ≥75 years in these subgroups may be small; therefore, the power to detect significant differences was low. The prevalence of knee OA was higher among diabetic non-Hispanic whites, but not among non-Hispanic blacks or among Mexican Americans, compared to those of the same race/ethnicity with normal glucose levels.

The prevalence of self-reported joint pain from the NHANES 1999–2004 did not differ substantially by diabetes status in the overall cohort (Table 32.17), according to a new analysis. However, in women, diabetic subjects had joint pain more often than those with normal glucose levels (48.8% vs. 38.7%, p<0.05).

The SOF cohort that included 9,704 white women age ≥65 years was recruited from four centers in the United States. At baseline, hip OA defined by radiograph was present in 13.9% of subjects age 65–74 years with diabetes compared to 7.2% of those without diabetes, a nearly 80% higher rate (Table 32.18) (N. Lane, unpublished data). No difference in the prevalence of hip OA was seen in participants age ≥75 years by diabetes status.

TABLE 32.18. Percent With Hip Osteoarthritis Among Older Adults Age ≥65 Years, by Diabetes Status, Age, and Sex, in Two U.S. Cohorts

SEX AND AGE (YEARS)	PERCENT (STANDARD ERROR)	
	Diabetes	No Diabetes
Women (SOF)		
Overall	12.2 (1.75)	10.4 (0.41)
65–74	13.9 (3.92)	7.2 (0.77)
≥75	11.7 (1.95)	11.2 (0.47)
Men (MrOS)		
Overall	11.0 (1.33)	10.0 (0.51)
65–74	10.8 (2.12)	6.9 (0.72)
≥75	11.2 (1.71)	11.7 (0.69)

Hip osteoarthritis is based on radiographs, Croft ≥2. Diabetes is based on self-report in SOF and on self-report, diabetes medication use, or elevated fasting glucose (≥126 mg/dL) in MrOS. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. MrOS, Study of Osteoporosis in Men, 2000–2009; SOF, Study of Osteoporotic Fractures, 1998–2008.

SOURCE: N. Lane, unpublished analyses of the SOF and MrOS studies.

In MrOS, elderly men age ≥65 years were recruited from six centers across the United States to assess risk factors for osteoporosis and hip OA. Hip radiographs were obtained in approximately 5,000 men, of whom 11.7% had diabetes. Hip OA was more prevalent in diabetic subjects age 65–74 years (10.8%) than in men without diabetes (6.9%) (Table 32.18) (N. Lane, unpublished data). As with women, prevalence of hip OA did not differ by diabetes status in men age ≥75 years.

The research community is investigating the risk factors for both OA and diabetes. OA is a disease in which the articular cartilage degenerates, either from age or injury, and the surrounding bone reacts with new bone formation at the margins of the joints (osteophytes), thickening of the bone adjacent to the joints, and changes in the trabecular bone distal to the joint. In diabetic patients, the

increased prevalence of disease, especially in the hand and knee, may result from a low-grade inflammatory state that may increase the degradation of the cartilage or the accumulation of AGEs within the articular cartilage, which in turn reduces the ability of the cartilage to function to dissipate loads. Ultimately, the articular cartilage fails. Also, a high BMI, often observed in individuals with diabetes, is a strong risk factor for OA of the lower extremities. Lastly, in diabetic patients with neuropathy, altered loads across the joints from reduced proprioception may injure menisci and accelerate deterioration.

Prevalence of Rheumatoid Arthritis

New analyses of NHANES 1999–2010 data for *Diabetes in America* showed that the prevalence of self-reported rheumatoid arthritis was 50% higher in all diabetic subjects compared to those with normal glucose levels (12.7% vs. 8.4%, $p<0.05$); this relationship was found for all age groups (Table 32.19). Prevalence was higher in diabetic compared to nondiabetic women and non-Hispanic whites but did not differ by diabetes status in men or in non-Hispanic blacks or Hispanics. However, the prevalence of rheumatoid arthritis in the NHANES is higher than other estimates (87,102). Inflammatory OA is frequently misclassified as rheumatoid arthritis, particularly in self-reported results, and such misclassification may have inflated the estimate of rheumatoid arthritis prevalence, although this is likely to have affected those with and without diabetes. Full evaluation of differences by diabetes status will require studies with accurate ascertainment of rheumatoid arthritis status. Published data confirm a genetic/autoimmune predisposition of rheumatoid arthritis and type 1 diabetes; this association is under investigation for type 2 diabetes.

OTHER JOINT COMPLICATIONS ASSOCIATED WITH DIABETES

Other joint complications associated with type 2 diabetes are relatively rare. However, they are not thought to be rare in type 1 diabetes. Reliable data, however, are generally lacking on the prevalence of these conditions. General descriptions of these entities are provided.

Diabetic stiff hand syndrome (cheiroarthropathy) is a condition that results from excessive glycosylation of collagen in nearly all joint structures (103). The biochemical change results in a decrease in the breakdown of the collagen, and this results in thick and stiff tissues. Over time, the contraction of the fingers and a thickening and shiny appearance of the skin may resemble scleroderma. This condition has a prevalence of about 22% in individuals from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC) with longstanding type 1 diabetes (104), an estimated 45%–76% in type 2 diabetes, and 4%–20% in nondiabetic individuals (105). Cheiroarthropathy can predict development of other diabetic complications, including renal and retinal disease.

Dupuytren's contractures or "trigger fingers" are the result of tendon contractures in the hand that prevent the hand from fully extending. These contractures can be seen in diabetic patients who also have the stiff hand syndrome or may be observed by themselves. The pathogenesis is thought to be similar to the stiff hand syndrome with both increased glycosylation of collagen and increased collagen deposition within and around the tendons in the hand. While trigger fingers are common in the general population, they are more prevalent in diabetic patients, with a reported prevalence of nearly 30% (106,107,108). In the DCCT/EDIC type 1 diabetic cohort, the prevalence was 9% (104).

TABLE 32.19. Percent With Rheumatoid Arthritis Among Adults Age ≥50 Years, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)				
	All Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	Prediabetes	Normal Glucose
Overall	12.7 (0.76)*	14.0 (0.86)*	9.8 (1.58)	7.9 (0.70)	8.4 (0.77)
Age (years)					
50–64	11.9 (0.97)*	13.3 (1.23)*	9.1 (2.16)	5.9 (0.77)	8.3 (1.04)
65–74	12.9 (1.75)	13.3 (1.69)*	12.1 (4.03)[1]	9.5 (1.71)	8.4 (1.43)
≥75	14.0 (1.53)*	16.7 (1.71)*	8.2 (2.06)	11.6 (1.76)	8.6 (1.90)
Sex					
Men	9.4 (1.09)	9.9 (1.24)	8.5 (2.09)	6.8 (0.94)	9.7 (1.34)
Women	16.2 (1.11)*	17.8 (1.30)*	11.6 (2.36)	9.0 (1.04)	7.6 (0.85)
Race/ethnicity					
Non-Hispanic white	11.4 (1.04)*	12.6 (1.20)*	9.1 (1.90)	7.5 (0.82)	7.6 (0.84)
Non-Hispanic black	20.3 (1.61)	21.2 (1.87)	17.2 (3.70)	14.6 (2.24)	17.6 (2.80)
All Hispanic	12.4 (1.55)	13.8 (1.63)	8.3 (2.52)[1]	6.8 (1.12)	11.0 (2.41)
Mexican American	12.4 (1.82)	13.3 (2.03)	10.0 (3.28)[1]	9.6 (1.33)	11.8 (2.18)

Rheumatoid arthritis and diagnosed diabetes are self-reported. Undiagnosed diabetes is based on A1c ≥6.5% or FPG ≥126 mg/dL without self-report of diabetes. Prediabetes is based on A1c 5.7%–6.4% or FPG 100–125 mg/dL. Normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

* $p<0.05$ compared to participants with normal glucose levels

[1] Relative standard error >30%–40%

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

Frozen shoulder, or adhesive capsulitis, results from a stiffening of the joint that leads to contractures of the shoulder joint and can cause severe bilateral pain that is often accompanied by calcific deposits in surrounding soft tissues. It can also occur in diabetic patients with regional pain syndrome. While adhesive capsulitis can be painful in onset, in some patients, the loss of motion can be painless (105,109). In the DCCT/EDIC type 1 diabetic cohort, prevalence of adhesive capsulitis was 31% (104).

In the DCCT/EDIC, the combined prevalence of musculoskeletal disorders of the upper extremities, including stiff hand syndrome, Dupuytren's contracture, adhesive capsulitis, and carpal tunnel syndrome, was 66%. These disorders were observed more often in women, older age subjects, and those with a longer duration of diabetes (104). In addition, prevalence was associated with higher skin autofluorescence, a measure of AGEs.

Charcot joint (neuropathic arthropathy) is an infrequent condition that results from a peripheral sensory abnormality that most often affects the ankle or midfoot and results in destruction of the joints with ankylosis and deformity. The clinical presentation is rapid in onset with joint swelling and a radiograph that shows both bone fragments and new bone formation. An experienced clinician may consider an infectious etiology. The treatment of Charcot joints is unsatisfactory, and little more can be offered than splinting and bracing (105,110,111). More information about Charcot joint is provided in Chapter 20 *Peripheral Arterial Disease, Foot Ulcers, Lower Extremity Amputations, and Diabetes*.

Diffuse idiopathic skeletal hyperostosis (DISH) is a common musculoskeletal disease. DISH is characterized by proliferative calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies with relative preservation of the intervertebral disk height in the involved vertebral segments and in the absence of significant radiographic changes of degenerative disc disease. Patients with DISH often have reduced spinal mobility and may develop dysphasia due to ossifications in the cervical spine. In a well-functioning cohort of older adults (age 70–79 years), the prevalence of DISH was 13.5% (112). Among hospital and clinic patients age ≥50 years with a chest radiograph, prevalence was 25% in men and 15% in women (113). DISH is observed more often in overweight type 2 diabetic patients (114). It is also prevalent in nondiabetic patients who have abnormal insulin responses to hyperglycemia (114). Limited data suggest that prevalence is also increased in type 1 diabetes (114). Treatment of diabetes has not been shown to improve or delay DISH (105,115).

While all of these musculoskeletal conditions are more frequent in both type 1 and type 2 diabetes patients than the general population, additional studies will need to be performed to estimate the true prevalence in those with diabetes (116).

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
AGE . . . . . advanced glycation endproduct
BMD . . . . . bone mineral density
BMI . . . . . body mass index
CI. . . . . confidence interval
DCCT. . . . . Diabetes Complications and Control Trial
DISH . . . . . diffuse idiopathic skeletal hyperostosis
DXA . . . . . dual-energy x-ray absorptiometry
EDIC . . . . . Epidemiology of Diabetes Interventions and Complications study
FPG . . . . . fasting plasma glucose
FRAX . . . . . Fracture Risk Assessment Tool
Health ABC . . . Health, Aging, and Body Composition study
HR . . . . . hazard ratio
MrOS . . . . . Osteoporotic Fractures in Men study
NHANES . . . . . National Health and Nutrition Examination Survey
NNHS . . . . . National Nursing Home Survey
OA . . . . . osteoarthritis
OGTT. . . . . oral glucose tolerance test
RR . . . . . relative risk
SOF . . . . . Study of Osteoporotic Fractures
TZD . . . . . thiazolidinedione
WHI-OS . . . . . Women's Health Initiative Observational Study

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

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DUALITY OF INTEREST

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REFERENCES

1. Kanis JA, Johansson H, Oden A, Dawson-Hughes B, Melton LJ 3rd, McCloskey EV: The effects of a FRAX revision for the USA. *Osteoporos Int* 21:35–40, 2010
2. Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL: Perspective. How many women have osteoporosis? *J Bone Miner Res* 7:1005–1010, 1992
3. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B: Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. *Age Ageing* 39:203–209, 2010
4. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK: The components of excess mortality after hip fracture. *Bone* 32:468–473, 2003
5. Wolinsky FD, Fitzgerald JF, Stump TE: The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. *Am J Public Health* 87:398–403, 1997
6. Sernbo I, Johnell O: Consequences of a hip fracture: a prospective study over 1 year. *Osteoporos Int* 3:148–153, 1993
7. Reistetter TA, Graham JE, Deutsch A, Markello SJ, Granger CV, Ottenbacher KJ: Diabetes comorbidity and age influence rehabilitation outcomes after hip fracture. *Diabetes Care* 34:1375–1377, 2011
8. Kado DM, Duong T, Stone KL, Ensrud KE, Nevitt MC, Greendale GA, Cummings SR: Incident vertebral fractures and mortality in older women: a prospective study. *Osteoporos Int* 14:589–594, 2003
9. Hallberg I, Rosenqvist AM, Kartous L, Lofman O, Wahlstrom O, Toss G: Health-related quality of life after osteoporotic fractures. *Osteoporos Int* 15:834–841, 2004
10. Fink HA, Ensrud KE, Nelson DB, Kerani RP, Schreiner PJ, Zhao Y, Cummings SR, Nevitt MC: Disability after clinical fracture in postmenopausal women with low bone density: the Fracture Intervention Trial (FIT). *Osteoporos Int* 14:69–76, 2003
11. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 22:465–475, 2007
12. Youm T, Koval KJ, Kummer FJ, Zuckerman JD: Do all hip fractures result from a fall? *Am J Orthop (Belle Mead NJ)* 28:190–194, 1999
13. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR: Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 115:837–842, 1991
14. Nevitt MC: Falls in the elderly: risk factors and prevention. In *Gait Disorders of Aging: Falls and Therapeutic Strategies*. Masdeu JC, Sudarsky L, Wolfson L, Eds. Philadelphia, Lippincott-Raven, 1997, p. 13–36
15. FitzGerald G, Boonen S, Compston JE, Pfeilschifter J, LaCroix AZ, Hosmer DW, Jr., Hooven FH, Gehlbach SH; GLOW Investigators: Differing risk profiles for individual fracture sites: evidence from the Global Longitudinal Study of Osteoporosis in Women (GLOW). *J Bone Miner Res* 27:1907–1915, 2012
16. Kanis JA, Bianchi G, Bilezikian JP, Kaufman JM, Khosla S, Orwoll E, Seeman E: Towards a diagnostic and therapeutic consensus in male osteoporosis. *Osteoporos Int* 22:2789–2798, 2011
17. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S: Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on Bone Densitometry. *J Clin Densitom* 16:455–466, 2013
18. FRAX fracture risk assessment tool [article online]. Available from *http://www.sheffield.ac.uk/FRAX/*. Accessed 2008
19. Chen Z, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ, Lewis CE, Kipersztok S, Borne C, Jackson RD: Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. *Menopause* 11:264–274, 2004
20. Looker AC, Eberhardt MS, Saydah SH: Diabetes and fracture risk in older U.S. adults. *Bone* 82:9–15, 2016
21. Nicodemus KK, Folsom AR; Iowa Women's Health Study: Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care* 24:1192–1197, 2001
22. Janghorbani M, Feskanich D, Willett WC, Hu F: Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care* 29:1573–1578, 2006
23. Janghorbani M, Van Dam RM, Willett WC, Hu FB: Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 166:495–505, 2007
24. Vestergaard P, Rejnmark L, Mosekilde L: Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia* 48:1292–1299, 2005
25. Ahmed LA, Joakimsen RM, Berntsen GK, Fonnebo V, Schirmer H: Diabetes mellitus and the risk of non-vertebral fractures: the Tromso study. *Osteoporos Int* 17:495–500, 2006
26. Strotmeyer ES, Cauley JA, Orchard TJ, Steenkiste AR, Dorman JS: Middle-aged premenopausal women with type 1 diabetes have lower bone mineral density and calcaneal quantitative ultrasound than nondiabetic women. *Diabetes Care* 29:306–311, 2006
27. 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* 31:1729–1735, 2008
28. Hamilton EJ, Rakic V, Davis WA, Chubb SA, Kamber N, Prince RL, Davis TM: Prevalence and predictors of osteopenia and osteoporosis in adults with type 1 diabetes. *Diabet Med* 26:45–52, 2009
29. Vestergaard P: Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int* 18:427–444, 2007

30. Thrailkill KM, Liu L, Wahl EC, Bunn RC, Perrien DS, Cockrell GE, Skinner RA, Hogue WR, Carver AA, Fowlkes JL, Aronson J, Lumpkin CK, Jr.: Bone formation is impaired in a model of type 1 diabetes. *Diabetes* 54:2875–2881, 2005
31. McCabe LR: Understanding the pathology and mechanisms of type I diabetic bone loss. *J Cell Biochem* 102:1343–1357, 2007
32. Yamamoto M, Yamaguchi T, Yamauchi M, Yano S, Sugimoto T: Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab* 93:1013–1019, 2008
33. Shiraki M, Kuroda T, Tanaka S, Saito M, Fukunaga M, Nakamura T: Nonenzymatic collagen cross-links induced by glycoxidation (pentosidine) predicts vertebral fractures. *J Bone Miner Metab* 26:93–100, 2008
34. Schwartz AV, Garnero P, Hillier TA, Sellmeyer DE, Strotmeyer ES, Feingold KR, Resnick HE, Tylavsky FA, Black DM, Cummings SR, Harris TB, Bauer DC; Health, Aging, and Body Composition Study: Pentosidine and increased fracture risk in older adults with type 2 diabetes. *J Clin Endocrinol Metab* 94:2380–2386, 2009
35. Nevitt MC, Cummings SR, Browner WS, Seeley DG, Cauley JA, Vogt TM, Black DM: The accuracy of self-report of fractures in elderly women: evidence from a prospective study. *Am J Epidemiol* 135:490–499, 1992
36. Ismail AA, O'Neill TW, Cockerill W, Finn JD, Cannata JB, Hoszowski K, Johnell O, Matthis C, Raspe H, Raspe A, Reeve J, Silman AJ: Validity of self-report of fractures: results from a prospective study in men and women across Europe. EPOS Study Group. European Prospective Osteoporosis Study Group. *Osteoporos Int* 11:248–254, 2000
37. Siggeirsdottir K, Aspelund T, Sigurdsson G, Mogensen B, Chang M, Jonsdottir B, Eiriksdottir G, Launer LJ, Harris TB, Jonsson BY, Gudnason V: Inaccuracy in self-report of fractures may underestimate association with health outcomes when compared with medical record based fracture registry. *Eur J Epidemiol* 22:631–639, 2007
38. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, Hillier TA, Lewis CE, Barrett-Connor E, Cummings SR; Study of Osteoporotic Fractures (SOF) and Osteoporotic Fractures in Men Study (MrOS) Research Groups: High-trauma fractures and low bone mineral density in older women and men. *JAMA* 298:2381–2388, 2007
39. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL: Risk of fracture among women with type 2 diabetes: the Women's Health Initiative Observational Study. *J Clin Endocrinol Metab* 91:3404–3410, 2006
40. Melton LJ 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S: Fracture risk in type 2 diabetes: update of a population-based study. *J Bone Miner Res* 23:1334–1342, 2008
41. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A, Womack CR, Palermo L, Black DM; Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group: Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* 305:2184–2192, 2011
42. Looker AC, Melton LJ 3rd, Harris TB, Borrud LG, Shepherd JA: Prevalence and trends in low femur bone density among older US adults: NHANES 2005–2006 compared with NHANES III. *J Bone Miner Res* 25:64–71, 2010
43. Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, Yu Q, Zillikens MC, Gao X, Rivadeneira F: Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur J Epidemiol* 27:319–332, 2012
44. Barrett-Connor E, Holbrook TL: Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. *JAMA* 268:3333–3337, 1992
45. Kao WH, Kammerer CM, Schneider JL, Bauer RL, Mitchell BD: Type 2 diabetes is associated with increased bone mineral density in Mexican-American women. *Arch Med Res* 34:399–406, 2003
46. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR; Study of Osteoporotic Features Research Group: Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 86:32–38, 2001
47. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB; Health ABC Study: 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. *J Bone Miner Res* 19:1084–1091, 2004
48. Thrailkill KM, Lumpkin CK, Jr., Bunn RC, Kemp SF, Fowlkes JL: Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. *Am J Physiol Endocrinol Metab* 289:E735–E745, 2005
49. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C; Prevention of Falls Network Europe and Outcomes Consensus Group: Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc* 53:1618–1622, 2005
50. Hanlon JT, Landerman LR, Fillenbaum GG, Studenski S: Falls in African American and white community-dwelling elderly residents. *J Gerontol A Biol Sci Med Sci* 57:M473–M478, 2002
51. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, Schreiner PJ, Margolis KL, Cauley JA, Nevitt MC, Black DM, Cummings SR: Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care* 25:1749–1754, 2002
52. Yau RK, Strotmeyer ES, Resnick HE, Sellmeyer DE, Feingold KR, Cauley JA, Vittinghoff E, De Rekeneire N, Harris TB, Nevitt MC, Cummings SR, Shorr RI, Schwartz AV: Diabetes and risk of hospitalized fall injury among older adults. *Diabetes Care* 36:3985–3991, 2013
53. Maurer MS, Burcham J, Cheng H: Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. *J Gerontol A Biol Sci Med Sci* 60:1157–1162, 2005
54. National Osteoporosis Foundation: *Clinician's Guide to Prevention and Treatment of Osteoporosis*. Washington, DC: National Osteoporosis Foundation, 2010
55. Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA: FRAX underestimates fracture risk in patients with diabetes. *J Bone Miner Res* 27:301–308, 2012
56. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB: Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the Health, Aging, and Body Composition Study. *Arch Intern Med* 165:1612–1617, 2005
57. Patsch JM, Burghardt AJ, Yap SP, Baum T, Schwartz AV, Joseph GB, Link TM: Increased cortical porosity in type 2

diabetic postmenopausal women with fragility fractures. *J Bone Miner Res* 28:313–324, 2013
58. Vestergaard P, Rejnmark L, Mosekilde L: Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes. *Calcif Tissue Int* 84:45–55, 2009
59. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B: Bone is a target for the antidiabetic compound rosiglitazone. *Endocrinology* 145:401–406, 2004
60. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR: Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 91:3349–3354, 2006
61. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR: The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab* 92:1305–1310, 2007
62. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, Heise MA, Aftring RP, Viberti G; Diabetes Outcome Progression Trial (ADOPT) Study Group: Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 31:845–851, 2008
63. Loke YK, Singh S, Furberg CD: Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 180:32–39, 2009
64. Napoli N, Strotmeyer ES, Ensrud KE, Sellmeyer DE, Bauer DC, Hoffman AR, Dam TT, Barrett-Connor E, Palermo L, Orwoll ES, Cummings SR, Black DM, Schwartz AV: Fracture risk in diabetic elderly men: the MrOS study. *Diabetologia* 57:2057–2065, 2014
65. Volpato S, Leveille SG, Blaum C, Fried LP, Guralnik JM: Risk factors for falls in older disabled women with diabetes: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci* 60:1539–1545, 2005
66. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J: Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes Obes Metab* 14:634–643, 2012
67. Oei L, Zillikens MC, Dehghan A, Buitendijk GH, Castano-Betancourt MC, Estrada K, Stolk L, Oei EH, van Meurs JB, Janssen JA, Hofman A, van Leeuwen JP, Witteman JC, Pols HA, Uitterlinden AG, Klaver CC, Franco OH, Rivadeneira F: High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. *Diabetes Care* 36:1619–1628, 2013
68. Schneider AL, Williams EK, Brancati FL, Blecker S, Coresh J, Selvin E: Diabetes and risk of fracture-related hospitalization: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 36:1153–1158, 2012
69. Schwartz AV, Margolis KL, Sellmeyer DE, Vittinghoff E, Ambrosius WT, Bonds DE, Josse RG, Schnall AM, Simmons DL, Hue TF, Palermo L, Hamilton BP, Green JB, Atkinson HH, O'Connor PJ, Force RW, Bauer DC: Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. *Diabetes Care* 35:1525–1531, 2012
70. Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J: Biphasic fracture risk in diabetes: a population-based study. *Bone* 40:1595–1601, 2007
71. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE: Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 9:CD007146, 2012
72. Morrison S, Colberg SR, Mariano M, Parson HK, Vinik AI: Balance training reduces falls risk in older individuals with type 2 diabetes. *Diabetes Care* 33:748–750, 2010
73. Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, Abu Elnour NO, Erwin PJ, Hazem A, Puhan MA, Li T, Montori VM: Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 97:1871–1880, 2012
74. Keegan TH, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL; Fracture Intervention Trial: Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the Fracture Intervention Trial. *Diabetes Care* 27:1547–1553, 2004
75. Johnell O, Kanis JA, Black DM, Balogh A, Poor G, Sarkar S, Zhou C, Pavo I: Associations between baseline risk factors and vertebral fracture risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. *J Bone Miner Res* 19:764–772, 2004
76. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 58:26–35, 2008
77. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF: The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 30:914–918, 1987
78. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, Fang F, Schwartz TA, Abbate LM, Callahan LF, Kalsbeek WD, Hochberg MC: Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol* 34:172–180, 2007
79. Dillon CF, Hirsch R, Rasch EK, Gu Q: Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991–1994. *Am J Phys Med Rehabil* 86:12–21, 2007
80. Centers for Disease Control and Prevention (CDC): Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2010–2012. *MMWR Morb Mortal Wkly Rep* 62:869–873, 2013
81. Cherry DK, Hing E, Woodwell DA, Rechtsteiner EA: National Ambulatory Medical Care Survey: 2006 summary. *Natl Health Stat Report* 1–39, 2008
82. Le TK, Curtis B, Kahle-Wrobleski K, Johnston J, Haldane D, Melfi C: Treatment patterns and resource use among patients with comorbid diabetes mellitus and major depressive disorder. *J Med Econ* 14:440–447, 2011
83. Agency for Healthcare Research and Quality: *Top Five Most Costly Conditions Among Adults Age 18 and Older, 2012: Estimates For the U.S. Civilian Noninstitutionalized Population*. MEPS Statistical Brief #471. Rockville, MD: U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality, 2015
84. Agency for Healthcare Research and Quality: *Most Frequent Operating Room Procedures Performed in U.S. Hospitals, 2003–2012*. HCUP-US Statistical Brief #186. Rockville, MD: U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality, 2014
85. Cisternas MG, Murphy LB, Yelin EH, Foreman AJ, Pasta DJ, Helmick CG: Trends in medical care expenditures of US

adults with arthritis and other rheumatic conditions 1997 to 2005. *J Rheumatol* 36:2531–2538, 2009
86. Centers for Disease Control and Prevention (CDC): Prevalence and most common causes of disability among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep* 58:421–426, 2009
87. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH; National Arthritis Data Workgroup: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 58:15–25, 2008
88. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM: Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* 38:1134–1141, 1995
89. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, Levy D: The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 38:1500–1505, 1995
90. Dillon CF, Rasch EK, Gu Q, Hirsch R: Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991–94. *J Rheumatol* 33:2271–2279, 2006
91. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM: Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 59:1207–1213, 2008
92. Felson DT, Nevitt MC, Zhang Y, Aliabadi P, Baumer B, Gale D, Li W, Yu W, Xu L: High prevalence of lateral knee osteoarthritis in Beijing Chinese compared with Framingham Caucasian subjects. *Arthritis Rheum* 46:1217–1222, 2002
93. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D: Genetic influences on osteoarthritis in women: a twin study. *BMJ* 312:940–943, 1996
94. Rossignol M, Leclerc A, Allaert FA, Rozenberg S, Valat JP, Avouac B, Coste P, Litvak E, Hilliquin P: Primary osteoarthritis of hip, knee, and hand in relation to occupational exposure. *Occup Environ Med* 62:772–777, 2005
95. Toivanen AT, Heliovaara M, Impivaara O, Arokoski JP, Knekt P, Lauren H, Kroger H: Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis—a population-based study with a follow-up of 22 years. *Rheumatology (Oxford)* 49:308–314, 2010
96. Felson DT, Zhang Y: An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 41:1343–1355, 1998
97. Felson DT: Risk factors for osteoarthritis: understanding joint vulnerability. *Clin Orthop Relat Res* 427(Suppl):S16–S21, 2004
98. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA: Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. *Am J Epidemiol* 139:119–129, 1994
99. Kalichman L, Kobyliansky E, Malkin I, Yakovenko K, Livshits G: Search for linkage between hand osteoarthritis and 11q 12-13 chromosomal segment. *Osteoarthritis Cartilage* 11:561–568, 2003
100. Bijsterbosch J, Kloppenburg M, Reijnierse M, Rosendaal FR, Huizinga TW, Slagboom PE, Meulenbelt I: Association study of candidate genes for the progression of hand osteoarthritis. *Osteoarthritis Cartilage* 21:565–569, 2013
101. Maiti AK, Kim-Howard X, Viswanathan P, Guillen L, Rojas-Villarraga A, Deshmukh H, Direskeneli H, Saruhan-Direskeneli G, Canas C, Tobon GJ, Sawalha AH, Chernavsky AC, Anaya JM, Nath SK: Confirmation of an association between rs6822844 at the Il2-Il21 region and multiple autoimmune diseases: evidence of a general susceptibility locus. *Arthritis Rheum* 62:323–329, 2010
102. Simard JF, Mittleman MA: Prevalent rheumatoid arthritis and diabetes among NHANES III participants aged 60 and older. *J Rheumatol* 34:469–473, 2007
103. Sugrue D, McEvoy M, Dempsey J, Fitzgerald G, Drury MI: Diabetic stiff hand syndrome. *Ir J Med Sci* 152:152–156, 1983
104. Larkin ME, Barnie A, Braffett BH, Cleary PA, Diminick L, Harth J, Gatcomb P, Golden E, Lipps J, Lorenzi G, Mahony C, Nathan DM; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Musculoskeletal complications in type 1 diabetes. *Diabetes Care* 37:1863–1869, 2014
105. Al-Homood IA: Rheumatic conditions in patients with diabetes mellitus. *Clin Rheumatol* 32:527–533, 2013
106. Sergent J: Arthritis accompanying endocrine and metabolic disorders. In *Kelley's Textbook of Rheumatology*. 8th ed. Firestein GS, Budd RC, Harris ED, Jr., McInnes IB, Ruddy S, Sergent JS, Eds. Saunders/Elsevier, 2009, p. 1833–1840
107. Chammas M, Bousquet P, Renard E, Poirier JL, Jaffiol C, Allieu Y: Dupuytren's disease, carpal tunnel syndrome, trigger finger, and diabetes mellitus. *J Hand Surg Am* 20:109–114, 1995
108. Rosenbloom AL, Silverstein JH: Connective tissue and joint disease in diabetes mellitus. *Endocrinol Metab Clin North Am* 25:473–483, 1996
109. Huang YP, Fann CY, Chiu YH, Yen MF, Chen LS, Chen HH, Pan SL: Association of diabetes mellitus with the risk of developing adhesive capsulitis of the shoulder: a longitudinal population-based followup study. *Arthritis Care Res (Hoboken)* 65:1197–1202, 2013
110. Sinacore DR, Withrington NC: Recognition and management of acute neuropathic (Charcot) arthropathies of the foot and ankle. *J Orthop Sports Phys Ther* 29:736–746, 1999
111. Sinacore DR, Hastings MK, Bohnert KL, Fielder FA, Villareal DT, Blair VP 3rd, Johnson JE: Inflammatory osteolysis in diabetic neuropathic (charcot) arthropathies of the foot. *Phys Ther* 88:1399–1407, 2008
112. Nardo L, Lane NE, Parimi N, Cawthon PM, Fan B, Shepherd J, Cauley J, Zucker-Levin A, Murphy RA, Katzman WB: Diffuse idiopathic skeletal hyperostosis association with thoracic spine kyphosis: a cross-sectional study for the Health Aging and Body Composition Study. *Spine (Phila Pa 1976)* 39:E1418–E1424, 2014
113. Weinfeld RM, Olson PN, Maki DD, Griffiths HJ: The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. *Skeletal Radiol* 26:222–225, 1997
114. Pillai S, Littlejohn G: Metabolic factors in diffuse idiopathic skeletal hyperostosis—a review of clinical data. *Open Rheumatol J* 8:116–128, 2014
115. Mader R, Lavi I: Diabetes mellitus and hypertension as risk factors for early diffuse idiopathic skeletal hyperostosis (DISH). *Osteoarthritis Cartilage* 17:825–828, 2009
116. *Pocket Primer on the Rheumatic Diseases*. 2nd ed. Klippel JH, Stone JH, Crofford LJ, White PH, Eds. London, UK, Springer-Verlag, 2010