ABSTRACT. Care of patients with diabetes should include assessment of bone health. The extension of the average life expectancy of people with diabetes, which has accompanied improvements in medical care, has also increased the significance of osteoporosis. In addition to the usual causes of osteoporosis associated with aging, bone health is also compromised by diabetes. Studies on bone involvement in patients with diabetes mellitus have generated conflicting results, largely because of the pathogenetic complexity of the condition. It is now clear that patients with type 1 diabetes have lower bone mineral density (BMD) and a higher risk of fractures. Evidence is emerging that patients with type 2 diabetes who have complications are also at increased risk of certain types of osteoporotic fractures, despite having a higher BMD when compared to patients with type 1 diabetes. Although many factors, including number and type of falls, visual impairment, neuropathy, and reduced muscle strength, influence the probability of fractures, the most significant factor seems to be the strength of the bone itself. Thus, sarcopenia, a reduction in muscle mass and muscle strength, is considered one of the main determinants of bone fragility. The aim of this review is to examine the occurrence of osteoporosis in type 1 and type 2 diabetes.

INTRODUCTION

The prevalence rates of diabetes and osteoporosis are increasing, mainly because of population aging and the extended life expectancy of patients with diabetes. These trends also lead to the higher prevalence of the co-existence of chronic diseases.

The number of people with diabetes in the world is expected approximately to double between 2000 and 2030 (1-3), not only due to population aging. The global incidence of type 1 diabetes in children and adolescents is also increasing, at an estimated overall annual rate of around 3% (4-6). Several European studies have suggested that, in relative terms, increases are greatest in young children (7-9). Although type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population (95% of diabetic patients have type 2), it is the predominant form in younger age groups in most developed countries. However, reports from several research centers indicate that type 2 diabetes in this population is now as common as type 1, particularly in Hispanic and black groups (10). Type 1 results from the autoimmune destruction of insulin-producing β-cells in the pancreas. Genetic and as yet undefined environmental factors act together to precipitate the disease. Type 2 has become common, conveying substantial morbidity and premature mortality. More than 5% of the total population in the United States have diabetes, with prevalence rates rising from 1% in those aged 20-39 years to 13% in those aged 60 and older. In Europe, an average prevalence rate of 7.8% of type 2 diabetes in the population between 20-79 (48.4 million persons) was estimated in 2003 (11). This high rate is partly a consequence of the relatively older population compared with other regions worldwide. Currently, about one-third of the European population is over 50 years of age, and this figure is expected to increase to over 40% by 2050 (11).

Osteoporosis is the most prevalent metabolic bone disease, characterized by low bone mass, increased fragility, decreased bone quality, and increased fracture risk (12). Data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that 13-18% of women over 50 in the United States have osteoporosis, and 37-50% have low bone mass at the hip (13). The disease results in more than 350,000 hip fractures a year in the United States, and the annual number of fractures is expected to double by 2025 (14-16).

In Italy, high life expectancy combined with low natality has increased the elderly population, so that this country represents an interesting case study for aging-related
diabetes. The Epidemiology Study on the Prevalence of Osteoporosis (ESOPO) (17) recently shaved that 40% of Italian women aged 60 and older (almost 4 million women) have osteoporosis and therefore an increased risk of femoral fracture. About 18,000 persons in Italy each year become permanently disabled as a result of femoral fractures. However, their real long-term effects of femoral fractures in Italy has not been sufficiently evaluated, and is probably underestimated (18).

Albright and Reifenstein (19) first reported the higher occurrence of osteoporosis in patients with diabetes mellitus in 1948, and in 1967 Meema and Meema (20) claimed that diabetes is an antiosteoporotic condition. These historical statements have reflected the confusion until the present day: the heterogeneity of results may be explained by the heterogeneity of diabetes and its complications, and also by methodological aspects (e.g., differences in recruiting patients, assessing diabetes and osteoporosis, etc.).

In the last decade, several authors have reported a strong correlation between type 1 diabetes and lower bone mineral density (BMD) and a higher risk of fractures. Evidence is emerging that patients with type 2 diabetes with complications have an increased risk of certain types of osteoporotic fractures, although they have higher BMD.

In this article, we review the occurrence of osteoporosis in type 1 and type 2 diabetes and the potential pathophysiological mechanisms for their association.

**TYPE 1 DIABETES**

Epidemiology

People with type 1 diabetes have been reported to have high rates of bone turnover and resorption, attributed to the effects of secondary hyperparathyroidism, hypomagnesemia, and decreased levels of 1-25-hydroxycholecalciferol (21-23).

Some researchers have reported that the longer duration of type 1 diabetes seems to be correlated with a decrease in BMD (21, 24). Other studies did not find any association between loss of bone mass and duration of type 1 diabetes (25). The two largest pediatric studies, which evaluated 55 children with a mean age of 10-11 years (26) and girls with a mean age of 16 years (27), showed no adverse effect of type 1 diabetes on BMD in a population that has yet to reach peak bone mass. In these studies, there was no correlation between BMD and the short duration of disease (3 and 7 years) or glycemic control as determined by glycosylated hemoglobin (HbA1c) serum levels. In young adults who have reached peak bone mass and have stable type 1 diabetes of intermediate duration, the findings are somewhat heterogeneous, although the majority of studies point toward the negative effect of type 1 diabetes on BMD. Two studies that evaluated patients in their forties with a mean duration of type 1 diabetes of 33 and 20 years, respectively, detected nonsignificant BMD differences at the lumbar spine and femoral neck (28) or diastal radius (29), compared with closely matched healthy controls. Other studies on between 31 and 56 patients with type 1 diabetes demonstrated lower BMD values at the lumbar spine (30, 31) and femoral neck (30-33).

Osteopenia, in the absence of clinical signs detected by dual-energy X-ray absorptiometry (DXA), was initially described in adolescents with diabetes, 50% of whom were found to have decreased cortical and trabecular forearm BMD (25). Several subsequent studies found that forearm BMD in children with only 4-6 years of type 1 diabetes was 20-50% lower than that in control subjects (34). One study examining vertebral BMD found decreased cortical but not trabecular BMD in diabetic children (35). Therefore, most studies in children and adults confirm that BMD is lower in patients with type 1 diabetes than in subjects without diabetes. Until recently, it was unclear whether lower BMD was associated with increased fracture rates in type 1 diabetes. The Nord-Trondelag Health Survey from Norway showed a significantly increased risk of hip fracture in women with type 1 diabetes, compared with women without diabetes [relative risk (RR) 6.9; 95% confidence interval (95% CI) 2.2-21.6] (36).

The Blue Mountain Eye Study (37) assessed 3654 subjects aged 49 years and older with all type of diabetes and, after 2 years of follow-up, found that several diabetes-related factors were significantly associated with increased risk of all fractures combined, including the presence of diabetic retinopathy (adjusted RR 5.4; 95% CI 2.7-10.8), diabetes duration ≥10 years (RR 3.3; 95% CI 1.3-8.2), cortical cataract involving ≥25% of the lens area (RR 2.5; 95% CI 1.3-4.7) and insulin treatment (RR 5.9; 95% CI 2.6-13.5). Diabetic retinopathy (RR 10.3; 95% CI 2.2-48.0), diabetes duration ≥10 years duration; RR 11.3; 95% CI 2.4-54.2) and insulin treatment (RR 18.8; 95% CI 4.0-88.7) were all associated with proximal humerus fracture. A case-control study found that the prevalence of fractures of the hip and distal arm in insulin-treated diabetic women, of whom 33% had type 1 diabetes, was lower than in women without type 1 diabetes (38). An excess of patients with diabetes was also found in patients with hip fractures, suggesting at least a twofold relative risk in all diabetic patients (39). In addition, in two other studies, women with type 1 diabetes had a 6.9 to 12-fold relative risk of hip fractures compared with women without diabetes (36, 40).

Pathophysiology

The distinctive finding of osteopenia and osteoporosis in young patients with type 1 diabetes, even shortly after the onset of the disease, has led to the hypothesis that insulin is a bone-anabolic factor (41). Because type 1 dia-