Osteoporosis among patients with type 1 and type 2 diabetes

A. Räkel\textsuperscript{a,b}, O. Sheehy\textsuperscript{a}, E. Rahme\textsuperscript{b}, J. LeLorier\textsuperscript{a,*}

\textsuperscript{a} Research Group in Pharmacoepidemiology and Pharmacoeconomics, Research Centre, centre hospitalier de l’université de Montréal (CHUM), Hôtel-Dieu, 3850, rue St-Urbain, H2W 1T7, Montréal, Québec, Canada

\textsuperscript{b} Division of Clinical Epidemiology, McGill University Health Centre, Montréal, Québec, Canada

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Abstract

Both diabetes and fractures are prevalent in adults. The relationship between diabetes and osteoporosis is complex and, although it has been investigated extensively, the subject remains controversial. While low bone mineral density (BMD) is consistently observed in type 1 diabetes, the relationship is less clear in type 2 diabetes, with some studies reporting modestly increased or unchanged BMD. Both type 1 and type 2 diabetes have been associated with a higher risk of fractures. Despite discrepancies between BMD and fracture rates, clinical trials uniformly support the fact that new bone formation and bone microarchitecture and, thus, bone quality, are altered in both types of diabetes. Although a causal association between diabetes and osteoporosis cannot be established on the basis of existing data, it is possible to conclude from many studies and from a better understanding of the physiopathology of diabetes that it can increase the risk of fractures through skeletal (decreased BMD and bone quality) and extraskeletal (increased risk of falls) factors. Even though osteoporosis screening or prophylactic treatment in all patients with type 1 and type 2 diabetes is not being recommended at present, such patient populations should be given general guidelines regarding calcium and vitamin D intakes, exercise and the avoidance of potential risk factors for osteoporosis. The extent of diagnostic and therapeutic interventions should be based on the individual’s risk profile for fractures.

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Résumé

Osteoporose et diabète de type 1 et 2.

Le diabète et les fractures sont deux problèmes prévalents dans la population adulte. Bien que plusieurs études se soient penchées sur la relation entre l’ostéoporose et le diabète, elle demeure controversée. Alors qu’une densité minérale osseuse (DMO) basse est uniformément observée chez les diabétiques de type 1, la situation est plus complexe chez le diabétique de type 2 où des DMO légèrement augmentées ou normales ont été observées. Le risque de fractures est quant à lui augmenté tant chez les diabétiques de type 1 que de type 2. Malgré cette discordance entre la DMO et le risque de fractures, toutes les études cliniques soutiennent que chez les diabétiques de type 1 et de type 2, la qualité osseuse est altérée en raison d’anomalies au niveau de la formation osseuse et de la microarchitecture osseuse. Bien qu’une association causale ne puisse être établie entre l’ostéoporose et le diabète sur la base de la connaissance actuelle, on peut affirmer grâce à plusieurs études et à notre meilleure compréhension de la physiopathologie du diabète que ce dernier est associé à un risque accru de fractures en raison de facteurs squelettiques (tels que la diminution de la DMO et de la qualité osseuse) et de facteurs extrasquelettiques (tels qu’une augmentation du risque de chutes). Bien qu’il ne soit pas encore recommandé de dépister ou de traiter de façon préventive pour l’ostéoporose tous les patients diabétiques, ces derniers devraient être informés d’éviter certains comportements à risque pour l’ostéoporose et devraient recevoir des recommandations au sujet de leur apport en calcium et en vitamine D et de l’exercice. L’ampleur des interventions diagnostiques et thérapeutiques devraient tenir compte du profil de risque de fracture individuel.

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Keywords: Diabetes mellitus type 1 and type 2; Osteoporosis; Osteopenia; Fractures; Bone mineral density; Review

Mots clés : Diabète de type 1 et de type 2 ; Ostéoporose ; Ostéopénie ; Fractures ; DMO ; Revue

* Corresponding author.

E-mail address: massicoa@umontreal.ca (J. LeLorier).

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Patients with diabetes have multiple skeletal disorders, including osteopenia, osteoporosis, Charcot’s disease and diffuse idiopathic skeletal hyperostosis (DISH). This review will focus on osteopenia and osteoporosis in patients with diabetes. More than 50 years ago, Albright and Reifenstein demonstrated that diabetes mellitus could be associated with a loss of bone mass leading to osteoporosis [1]. This finding has since received a great deal of attention and been investigated by a number of researchers [1–10], as osteoporosis is a major health problem, and its occurrence among patients who have diabetes further increases their burden of disease. However, in spite of numerous studies, the relationship between diabetes and osteoporosis remains controversial [11–13]. Moreover, conditions such as Cushing’s syndrome, pancreatic insufficiency, polyglandular autoimmune syndrome type 2, post-transplantation state or hereditary hemochromatosis can lead to secondary diabetes. These conditions are also associated with an increased risk of osteoporosis. Although the association between secondary diabetes and osteoporosis is not addressed in this review, it nevertheless requires careful clinical assessment and care from clinicians. The results of published studies that have assessed the association between type 1 and type 2 diabetes and osteopenia and/or osteoporosis is reviewed first, followed by a summary of the studies assessing the association between diabetes and fractures, and a review of the various hypotheses for the pathophysiology of this association. Finally, general suggestions are offered regarding the care that diabetic patients should receive to protect their bones.

1. Bone mass density and diabetes mellitus

1.1. Bone mass density and type 1 diabetes mellitus

Several historical studies have demonstrated that osteopenia and osteoporosis are frequent complications of type 1 diabetes in both children and adults [14–16]. Earlier investigations were carried out using older technologies such as single- or dual-photon absorptiometry, and focused on the appendicular skeleton. BMD analysis is now typically performed using dual X-ray absorptiometry (DXA), a more precise method. The majority of recent studies has confirmed the association between type 1 diabetes and decreased BMD in adults [2,7,8,17–27] as well as in children [3,20,28–32] (Table 1). BMD appears to be decreased in both the spine and hip in type 1 diabetes. Using DXA, osteopenia is found in about 50–60% of patients with type 1 diabetes [21,25] while osteoporosis is seen in around 14–20% of cases [23,25]. A meta-analysis of 80 papers by Vestergaard, assessing the BMD and fracture risk in patients with type 1 or type 2 diabetes, concludes that BMD is decreased in type 1 diabetes [33]. Although the vast majority of studies were cross-sectional, limiting the capacity to establish a causal association, many arguments support such an association, including replication of the findings, the strength of the association, the ‘dose–response’ relationship (in terms of duration of diabetes) and biological plausibility.

1.2. Bone mass density and type 2 diabetes mellitus

Earlier studies have given discrepant results for type 1 and type 2 diabetes, with a decreased BMD in patients with type 1 diabetes, but a normal-to-increased BMD in type 2 diabetes. Measurements of vertebral or femoral neck BMD by DXA have revealed increased BMD in most patients with type 2 diabetes, compared with age-matched subjects without diabetes [2,5,9,10,34–43] (Table 2); the BMD increment persisted even after correction for body weight or body composition and the use of estrogens [9]. It should be noted, however, that the majority of these studies involved postmenopausal women. The meta-analysis by Vestergaard also concluded that BMD was increased in type 2 diabetes [33]. Also, body mass index (BMI) appeared to be one of the main determinants of BMD in type 2 diabetes. Nevertheless, the meta-analysis was limited, as information on BMI was missing in a significant number of studies reviewed. Other publications have reported normal or lower BMD among individuals with type 2 diabetes [4,27,44–47]. Any discrepancy between the results of these studies and those previously mentioned may be due to differences in the duration, severity and treatment of diabetes, and perhaps also due to the different methods used to measure BMD. Authors have also suggested that an increased BMD, at least in some subgroups of patients with type 2 diabetes, could be related to the presence of Forestier’s disease (DISH) at the spinal level [48].

The associations between type 1 and type 2 diabetes and BMD are not clear. Nevertheless, patients with type 1 or type 2 diabetes are at high risk for bone fractures. The literature discussing the link between type 1 and type 2 diabetes and bone fractures is reviewed below.

2. Diabetes mellitus and fractures

2.1. Type 1 diabetes mellitus and fractures

The reviewed studies reported a trend towards increased fracture risks at most skeletal sites among patients with type 1 diabetes (Table 3).

Humeral fractures: Kelsey et al. determined that, in a prospective cohort of 9704 women aged 65 years or older and enrolled in the Study of Osteoporotic Fractures, those with insulin-dependent or insulin-treated diabetes (the two terms are used synonymously by the authors) had an increased rate of fractures of the proximal humerus [relative risk (RR) 3.79; 95% confidence interval (CI): 1.16–12.36] compared with women without insulin-dependent diabetes [49]. It must be noted, however, that confusion is possible because insulin-treated diabetes per se does not necessarily mean type 1 diabetes. Therefore, the association between humeral fractures and type 1 diabetes is not clear.

Hip fractures: type 1 diabetes has been associated with an increased risk of hip fractures with RRs ranging from 6.9 to 12.25. For example, Forsen et al. reported that the rate of hip fractures was significantly increased in women with type 1 diabetes, aged 50–74 years, compared with non-diabetic women of similar age (RR 6.9; 95% CI: 2.2–21.6). The increased rate of hip fractures among diabetic men in that study was not signifi-
<table>
<thead>
<tr>
<th>Study population</th>
<th>Site</th>
<th>BMD</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of patients (F/M)</td>
<td>Age</td>
<td>Controls</td>
<td>Duration of diabetes (years)</td>
</tr>
<tr>
<td>Forst et al. [19]</td>
<td>1995</td>
<td>41 (21/20)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Krakauer et al. [7]</td>
<td>1995</td>
<td>46</td>
<td>51.7 ± 11.3 to 55.9 ± 11.5</td>
</tr>
<tr>
<td>Lettgen et al. [29]</td>
<td>1995</td>
<td>21 (8/13)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Munoz-Torres et al. [23]</td>
<td>1996</td>
<td>94 (49/45)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Gunczler et al. [20]</td>
<td>1998</td>
<td>26 (11/15)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Miazgowski et al. [8]</td>
<td>1998</td>
<td>54 (23/31)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Kemink et al. [25]</td>
<td>2000</td>
<td>35 (14/21)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Gunczler et al. [3]</td>
<td>2001</td>
<td>23 (16/7)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Lopez-Ibarra et al. [26]</td>
<td>2001</td>
<td>32 (10/22)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Valerio et al. [32]</td>
<td>2002</td>
<td>32 (12/15)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Liu et al. [31]</td>
<td>2003</td>
<td>72 (F)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Heap et al. [30]</td>
<td>2004</td>
<td>55 (25/30)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>DeSchepper et al. [18]</td>
<td>1998</td>
<td>23 (8/15)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Hampson et al. [4]</td>
<td>1998</td>
<td>31 F</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Pasqual et al. [20]</td>
<td>1998</td>
<td>55 (29/26)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Lunt et al. [40]</td>
<td>2001</td>
<td>99 F</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>Inghberg et al. [121]</td>
<td>2004</td>
<td>38 (20/18)</td>
<td>Age-matched controls</td>
</tr>
<tr>
<td>© 2018 Elsevier Masson SAS. Tous droits réservés. Document téléchargé le 24/11/2018 Il est interdit et illégal de diffuser ce document. BMD, bone mineral density; bx, biopsy; CB, cortical bone; CS, cross-sectional; DL, distal lower limb; DFx, dual-photon absorptiometry; DXA, dual X-ray absorptiometry; F, female; FN, femoral neck; IDDM, insulin-dependent diabetes mellitus; LS, lumbar spine; M, male; NS, not significant; post-m, postmenopausal; pQCT, peripheral quantitative tomography; pre-m, premenopausal; Prosp, prospective; SPA, single-photon absorptiometry; T, total bone; TB, trabecular bone; TBMC, total body mineral content; WT, Ward’s triangle.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Number of patients (F/M)</td>
<td>Age (years)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>Barrett-Connor et al.</td>
<td>1992</td>
<td>39/41</td>
<td>72 (55–88)</td>
</tr>
<tr>
<td>Krakauer et al.</td>
<td>1995</td>
<td>63</td>
<td>51.7 ± 11.3 to 55.9 ± 11.5</td>
</tr>
<tr>
<td>van Daele et al.</td>
<td>1995</td>
<td>335/243</td>
<td>≥ 55</td>
</tr>
<tr>
<td>Rishaug et al.</td>
<td>1995</td>
<td>15/21</td>
<td>40–65</td>
</tr>
<tr>
<td>Kwon et al.</td>
<td>1996</td>
<td>185 F</td>
<td>35–74</td>
</tr>
<tr>
<td>Isaia et al.</td>
<td>1999</td>
<td>66F</td>
<td>63.2 ± 7.4</td>
</tr>
<tr>
<td>Christensen et al.</td>
<td>1999</td>
<td>32/33</td>
<td>11 pre-norm,</td>
</tr>
<tr>
<td>el Miedany et al.</td>
<td>1999</td>
<td>40/20</td>
<td>post-m</td>
</tr>
<tr>
<td>Sahin et al.</td>
<td>2001</td>
<td>161 F</td>
<td>post-m</td>
</tr>
<tr>
<td>Lunt et al.</td>
<td>2001</td>
<td>4000</td>
<td>50–80</td>
</tr>
<tr>
<td>Sert et al.</td>
<td>2003</td>
<td>176/101</td>
<td>30–60</td>
</tr>
<tr>
<td>Kao et al.</td>
<td>2003</td>
<td>98/55</td>
<td>54.8 ± 12.5 (F)</td>
</tr>
<tr>
<td>Strotmeyer et al.</td>
<td>2004</td>
<td>243/323</td>
<td>70–79</td>
</tr>
<tr>
<td>Dennison et al.</td>
<td>2004</td>
<td>32/33</td>
<td>59–71</td>
</tr>
<tr>
<td>de Liefde et al.</td>
<td>2005</td>
<td>3964/2691</td>
<td>73.8 ± 9.2</td>
</tr>
<tr>
<td>Gerdem et al.</td>
<td>2005</td>
<td>67 (F)</td>
<td>75</td>
</tr>
<tr>
<td>Sosa et al.</td>
<td>1996</td>
<td>47F</td>
<td>61.3 ± 7</td>
</tr>
<tr>
<td>Hampson et al.</td>
<td>1998</td>
<td>21F</td>
<td>42.5 ± 5.5</td>
</tr>
<tr>
<td>Tsuimam et al.</td>
<td>1999</td>
<td>68 (34/34)</td>
<td>52–72</td>
</tr>
<tr>
<td>Majima et al.</td>
<td>2005</td>
<td>145 (81/64)</td>
<td>63 (F)</td>
</tr>
<tr>
<td>Bridges et al.</td>
<td>2005</td>
<td>90 (M)</td>
<td>63</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; BMI, body mass index; bx, biopsy; CB, cortical bone; CS, cross-sectional; DL, distal lower limb; DM, diabetes mellitus; DPA, dual-photon absorptiometry; DR, distal radius; dx, diagnosis; DXA, dual X-ray absorptiometry; F, female; FN, femoral neck; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; LS, lumbar spine; M, male; na, not available; NGT, normal glucose tolerance; NS, not significant; post-m, postmenopausal; pQCT, peripheral quantitative tomography; pre-m, premenopausal; Prosp, prospective; SPA, single-photon absorptiometry; T, total bone; TB, trabecular bone; TBMC, total body mineral content; US, ultrasound; WT, Ward’s triangle.

Table 3  
Fracture rate in patients with type 1 and type 2 diabetes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>DM type</th>
<th>Population</th>
<th>Type of study</th>
<th>Site</th>
<th>Fracture rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelsey et al. [49]</td>
<td>1992</td>
<td>1 &amp; 2</td>
<td>9704 women 65 years &amp; older</td>
<td>Prosp</td>
<td>Proximal humerus</td>
<td>↑</td>
</tr>
<tr>
<td>Forsen et al. [50]</td>
<td>1999</td>
<td>1 &amp; 2</td>
<td>35,444 people 50 years &amp; older (18,596 F; 16,848 M)</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Nicodemus et al. [51]</td>
<td>2001</td>
<td>1 &amp; 2</td>
<td>32,096 postmenopausal women</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Schwartz et al. [55]</td>
<td>2001</td>
<td>Insulin-treated DM &amp; non-insulin-treated DM</td>
<td>9654 women 65 years &amp; older</td>
<td>Prosp</td>
<td>Insulin No insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ottenbacher et al. [56]</td>
<td>2002</td>
<td>2</td>
<td>1213 M; 1671 F 65 years &amp; older</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Taylor et al. [57]</td>
<td>2004</td>
<td>2</td>
<td>6787 women 66 years &amp; older</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Miao et al. [52]</td>
<td>2005</td>
<td>1</td>
<td>12,551 M; 12,054 F</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Strotmeyer et al. [59]</td>
<td>2005</td>
<td>2</td>
<td>1456 M; 1523 F aged 70–79 years</td>
<td>Prosp</td>
<td>Any</td>
<td>↑</td>
</tr>
<tr>
<td>Vestergaard et al. [54]</td>
<td>2005</td>
<td>1 &amp; 2</td>
<td>124,655 fractures (cases) 373,962 controls</td>
<td>Case-control</td>
<td>Any</td>
<td>Type 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Type 2</td>
</tr>
<tr>
<td>de Liefde et al. [35]</td>
<td>2005</td>
<td>2</td>
<td>3964 F; 2691 M</td>
<td>Prosp</td>
<td>Non-vertebral</td>
<td>↑</td>
</tr>
<tr>
<td>Dobnig et al. [58]</td>
<td>2006</td>
<td>2</td>
<td>1664 elderly women</td>
<td>Prosp</td>
<td>Hip</td>
<td>↔</td>
</tr>
<tr>
<td>Janghorbani et al. [53]</td>
<td>2006</td>
<td>1 &amp; 2</td>
<td>1398 women 34–59 years old</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
<tr>
<td>Bonds et al. [60]</td>
<td>2006</td>
<td>2</td>
<td>93,676 women</td>
<td>Prosp</td>
<td>Hip</td>
<td>↑</td>
</tr>
</tbody>
</table>

Prosp, prospective; F, female; M, male; DM, diabetes mellitus.

cant [50]. Nicodemus et al. demonstrated that postmenopausal women with type 1 diabetes were 12.25 times more likely (95% CI: 5.0–29.7) to report a hip-fracture incident than women without diabetes [51]. Miao et al. also showed that, in comparison to the general population, Swedish men and women hospitalized for type 1 diabetes at least once before age 31 had increased hip-fracture risks, with standardized hospitalization ratios (SHR) of 7.6 (95% CI: 5.9–9.6) among men and 9.8 (95% CI: 7.3–12.9) among women [52]. The SHR is defined as the ratio of the observed to the expected numbers of first hospitalizations. Recently, in the Nurses’ Health Study cohort, Janghorbani et al. documented that women with type 1 diabetes had a greater risk of hip fractures compared with women without diabetes (RR 7.1; 95% CI: 4.4–11.4) [53]. In the meta-analysis by Vestergaard, most of the reviewed studies only assessed the association between type 1 diabetes and hip fractures [33], and found a significant increase in hip fracture risk (RR 6.94; 95% CI: 3.25–14.78) associated with type 1 diabetes.

Any fractures: adopting a case-control design, Vestergaard et al. found that type 1 diabetes was associated with an increased risk of fractures at all sites. The odds ratios (ORs) and 95% CI reported by the authors in patients with type 1 diabetes versus those with no diabetes were: any fracture 1.3, 1.2–1.5; hip fracture 1.7, 1.3–4.6; and spinal fracture 2.5, 1.3–4.6; respectively [54].

2.2. Type 2 diabetes mellitus and fractures

Type 2 diabetes has also been associated with an increased risk of fractures at any skeletal site (Table 3).

Hip fractures: as in type 1 diabetes, the risk of hip fractures is increased in type 2 diabetes, although to a lesser magnitude, with risks varying from 1.5- to 2.8-fold. Forsen et al. found a non-significant increase in the rate of hip fractures in women with type 2 diabetes, 50–74 years of age, compared with non-diabetic women in the same age group [50]. The crude RRs and 95% CI for these female patients were 1.8 and 1.1–2.9, respectively. However, this increase was no longer statistically significant after adjustment for complications of diabetes such as impaired vision and motor abilities, although the point estimate...
remained higher than 1 (adjusted RR: 1.5; 95% CI: 0.9–2.5) [50]. In the study by Nicodemus et al., postmenopausal women with type 2 diabetes had a 1.7-fold higher risk (95% CI: 1.2–2.4) of hip fracture than women without diabetes. In addition, a longer duration of diabetes and the use of insulin or oral diabetes medications in women with type 2 diabetes were associated with a higher hip-fracture rate [51]. Schwartz et al. suggested that older women with type 2 diabetes had an increased risk of hip fracture (RR 1.82; 95% CI: 1.24–2.69) in comparison to women without type 2 diabetes [55]. This was also demonstrated for hip fractures in older Mexican-Americans by Ottenbacher et al. [hazard ratio (HR) 1.57; 95% CI: 1.03–2.39 for patients with diabetes versus subjects without diabetes], particularly in those with diabetes taking insulin compared with non-diabetic subjects (HR 2.84; 95% CI: 1.49–5.43) [56]. Taylor et al. reported that type 2 diabetes was associated with a 68% increase in the risk of hip fractures [adjusted HR in those with type 2 diabetes versus those without type 2 diabetes 1.68 (95% CI 1.23–2.3)] [57]. In nursing-home patients, despite decreased bone turnover and higher bone mass among women with type 2 diabetes, hip-fracture risk was similar between women with and without diabetes. This finding could perhaps be explained by the fact that the study population was frail and had many significant risk factors for fracture that may have overwhelmed those of diabetes [58].

Humeral fractures: Schwartz et al. suggested that women with type 2 diabetes had an increased risk of proximal humerus fracture (RR 1.94; 95% CI: 1.24–3.02) in comparison to women without the disease [55]. Any fractures: in the Health ABC Study, type 2 diabetes was associated with an elevated fracture risk (RR 1.64; 95% CI: 1.07–2.5) [59]. In the Women’s Health Initiative Study, although women with type 2 diabetes had higher BMD levels compared with women without type 2 diabetes at baseline, they had an increased risk of fractures at the seven-year follow-up (RR 1.2; 95% CI: 1.1–1.3). This trend was also evident among black women with type 2 diabetes compared with non-diabetics (RR 1.3; 95% CI: 1–1.8) [60]. In the Rotterdam Study, even when patients with diabetes had a higher BMD at baseline, they had an increased risk of non-vertebral fractures (HR 1.33; 95% CI: 1.00–1.77). In a subgroup analysis, the increased risk appeared to be restricted to diabetic patients receiving pharmacological treatment (HR 1.69; 95% CI: 1.16–2.46). The Nurses’ Health Study also revealed a slight increase in fracture risk in women with type 2 diabetes in comparison to their counterparts without the disease (RR 2.2; 95% CI: 1.8–2.7). This observation was stronger among women with a longer diabetes duration compared with non-diabetic women [53]. Vestergaard et al. showed that patients with type 2 diabetes, in comparison to non-type-2 diabetics, were at increased risk of: any fracture (OR 1.2; 95% CI: 1.1–1.3); hip fracture (OR 1.4; 95% CI: 1.2–1.6); and forearm fracture (OR 1.2; 95% CI: 1.3–4.6) [54]. Finally, Vestergaard’s meta-analysis revealed a significant association between diabetes and hip-fracture risk (RR 1.38; 95% CI: 1.25–1.53). The risk of wrist fracture was also slightly increased among patients with diabetes compared with non-diabetic controls (RR 1.19; 95% CI 1.01–1.41). However, this was not the case for spine fractures (RR 0.93; 95% CI: 0.63–1.37). The risk of hip fracture was significantly higher in type 1 than in type 2 diabetes [33].

In summary, the reviewed literature suggests an increase in fracture risks in both type 1 and type 2 diabetes. The fracture-risk point estimates described in type 1 diabetes are considerably higher than in type 2 diabetes. It is, therefore, possible that the increased BMD in type 2 diabetes is protective against fractures, and that longstanding type 2 diabetes may increase the risk of falls and, thus, the risk of fractures, despite greater BMD. The pathophysiological explanations for increased fracture risks are discussed below. Skeletal factors, such as decreased BMD and poor bone quality, are addressed first, followed by the extraskeletal factors that may contribute to the increased risk of fractures in diabetes, such as the propensity to fall.

3. Pathophysiology of the increased fracture risks in diabetes mellitus

3.1. Skeletal factors

3.1.1. Decreased bone mass density

3.1.1.1. Low peak bone mass. Insufficient skeletal mineralization during puberty has been implicated as a mechanism that might explain the lower BMD in patients with type 1 diabetes. In a newly diagnosed population of type 1 diabetes patients, BMD was lower in comparison to healthy controls. Osteopenia at the onset of type 1 diabetes indicates the presence of active mechanisms before the appearance of diabetes symptoms. Some authors have proposed that autoimmune and autoinflammatory mechanisms, present before the onset of diabetes, may play a role in bone loss or altered bone mineralization during puberty.

Recently, a one-year follow-up prospective study has confirmed that teenagers with type 1 diabetes have lower bone mass and smaller bone size despite normal growth and maturation. Bone mineral acquisition, although driven by puberty, was lower and inversely correlated with glycosylated haemoglobin (HbA1c) levels [61].

3.1.1.2. Diabetic complications. It has been hypothesized that microangiopathy [62] and macroangiopathy [63] may be contributing to osteoporosis and might predict low BMD in patients with type 1 diabetes.

Retinopathy may also be associated with lower BMD because it prevents exercise and is, therefore, linked to lower muscle strength. Munoz-Torres et al. found that patients with diabetes showed reduced BMD in all sites, and that it correlated with the presence and extent of diabetic complications [23]. In a study by Rozadilla et al. of patients with type 1 diabetes, with a mean age of 29 years and a mean disease duration of 11 ± 6.4 years, those with retinopathy also had lower lumbar spine BMD values than patients without retinopathy. However, this difference was no longer evident after adjustment for age and disease duration [24]. Campos Pastor et al. demonstrated that patients with retinopathy were at higher risk of osteopenia or osteoporosis than patients without retinopathy (RR: 3.2) [17].
In addition, nephropathy has been associated with low BMD in patients with type 1 diabetes. Clausen et al. examined the relationship between BMD and renal function in men with type 1 diabetes: BMD was normal in those with a normal urinary albumin-excretion rate, but was reduced in the femoral neck, the trochanter major and Ward’s triangle in patients with an increased urinary albumin-excretion rate [64]. It has been suggested that, in diabetic patients with chronic kidney disease, bone loss is detectable and progressive during follow-up, and apparently more severe at the femoral neck [65]. One of the mechanisms suggested to explain the lower BMD levels in diabetic patients with altered renal function is increased bone resorption. In fact, hydroxyproline excretion is increased in those with diabetes and microalbuminuria [66]. Furthermore, in patients with chronic kidney disease stage 5, those who were also diabetic were at greater risk of 25-hydroxyvitamin-D deficiency, and there was a positive association between 25-hydroxyvitamin D levels and BMD Z scores [67]. Moreover, advanced chronic renal failure is known to be associated with four possible types of bone disease, grouped under the term ‘renal osteodystrophy’: osteitis fibrosa cystica; osteomalacia; adynamic bone disease; and mixed uremic osteodystrophy. In fact, diabetes is the most common cause of end-stage renal disease. In diabetic patients on dialysis, low-turnover bone disorders (osteomalacia and adynamic bone disease) are especially prevalent [68]. However, the value of BMD measurement in the assessment of renal osteodystrophy is unclear. BMD at the distal radius may be more useful than lumbar BMD for evaluating patients on hemodialysis [69]. By comparison, BMD measurement at the hip or spine may be misleading, resulting in the inappropriate administration of antosteoporotic therapy.

In type 1 diabetes, Rix et al. demonstrated that peripheral neuropathy may be an independent risk factor for reduced BMD in the affected limbs as well as in the skeleton in general, thereby suggesting a systemic effect of peripheral neuropathy or factors associated with peripheral neuropathy such as microangiopathy [70]. In the Health ABC Study, diabetic patients who had sustained a fracture had more peripheral neuropathy than those without fractures [59]. In the Swedish population-based cohort referred to above, diabetic patients with neurological complications had an SHR of 32.6 (95% CI 22.3–46.0) compared with the general population. Patients with diabetes without neurological complications had an SHR of 4.6 (95% CI 3.3–6.4) in comparison to the general population [52].

Peripheral vascular disease was negatively associated with femoral neck BMD in women with longstanding type 1 diabetes [22] and in diabetic women with normal menstrual cycles [6,23].

3.1.1.3. Phosphocalcic balance. For some time, hypercalciuria has been considered a potential risk factor for osteoporosis in patients with poorly controlled type 1 [71] or type 2 [72] diabetes, but glycemic control can reduce hypercalciuria [71]. In diabetic rats, hypercalciuria presented as a raised glomerular filtration rate, reduced calcium reabsorption and impaired bone deposition. Also, the inclusion of patients with celiac disease as well as type 1 diabetes could partially explain the decreased calcium absorption seen in diabetes [40]. Hypercalciuria and reduced intestinal calcium absorption should, in theory, lead to a compensatory increase in parathyroid hormone (PTH). Most studies, however, have shown normal or even lower-than-expected PTH levels [25,73,74]. Magnesium deficiency has been incriminated in this functional hypoparathyroidism, and could partially explain the low bone turnover [75]. Finally, vitamin D deficiency is common in patients with type 2 diabetes, and needs to be taken into account in the dietary recommendations offered to patients.

3.1.1.4. Insulin and insulin-like growth factor-1. Insulin has been looked at as a potential mechanism to explain the lower BMD in type 1 diabetics. Tuominen et al. measured BMD in middle-aged and elderly men and women who developed type 1 or type 2 diabetes after age 30, and were treated with insulin [27]. For both men and women, BMD was significantly lower in those with type 1 diabetes compared with patients with type 2 diabetes and the control subjects. The authors concluded that this finding was probably due to the more rapid bone loss after the onset of type 1 diabetes. They also suggested that the lower BMD in type 1 diabetes was not the result of insulin treatment as patients with either type of diabetes received insulin.

Insulin-like growth factor-1 (IGF-1), a polypeptide protein hormone similar in molecular structure to insulin, plays an important role in childhood growth and continues to have anabolic effects in adults [76]. Indeed, it has been proven that osteoblasts (OB; bone-forming cells) have receptors for both insulin and IGF-1 [77]. IGF-1 and insulin growth factor-binding protein-3 (IGFBP-3) serum levels in patients with type 1 diabetes are known to be lower than those in type 2 diabetics and non-diabetics. Furthermore, a positive correlation has been found between IGF-1, IGFBP-3 and BMD [78].

3.1.1.5. Leptin. Leptin is a protein hormone that plays a key role in regulating energy expenditure. Although the data remain conflicting, a few studies in non-diabetics have concluded that leptin may be involved in bone strength [79,80]. A positive correlation has been observed between leptin and BMD in non-diabetic subjects, whereas there is a negative correlation between leptin and markers of bone remodeling in diabetic patients [81]. Leptin may also reduce osteoclastogenesis by inhibiting the expression of the cytokines that regulate it [82]. More studies are needed in this area.

3.1.1.6. Peroxisome proliferator-activated receptor-gamma. The decrease of bone volume in age-related osteoporosis is shown to be accompanied by an increase in marrow adipose tissue [83,84]. In fact, OB and adipocytes share a common progenitor: mesenchymal stem cells (MSC), which give rise to OB, adipocytes and other cell types [85]. Several transcription factors involved in adipocyte differentiation have been identified, including peroxisome proliferator-activated receptor-gamma (PPARγ). The overexpression of PPARγ induces adipogenesis over osteoblastogenesis in pluripotent cells [86]. Moreover, PPARγ haploinsufficiency has been found to increase bone mass by stimulating osteoblastogenesis by bone marrow progenitors [87]. Changes in marrow composition with increased bone
adiposity, decreased mature OB and increased PPARγ expression have all been detected in type 1 diabetic mice, suggesting that insulin-dependent diabetes contributes to bone loss through modifications in marrow composition, thereby resulting in fewer mature OB and more adipose accumulation [88]. Medications that activate PPARγ—thiazolidinediones (TZDs)—have been marketed as insulin sensitizers. Studies in vitro have demonstrated that the TZD rosiglitazone converts cells of OB lineage into terminally differentiated adipocytes while simultaneously and irreversibly suppressing the OB phenotype [86,89]. It has also been demonstrated in murine in vivo bone studies that rosiglitazone therapy poses a significant risk of adverse skeletal effects by reducing the rate of bone formation and, thus, leading to bone loss [90–92]. These effects appear to be shared by the whole class of TZD drugs. Darglitazone and netoglitazone (two other PPARγ agonists) have also been shown to have antosteoblastic and proadipocytic effects in vivo [93,94]. To date, reports of the outcomes of TZD intake on bone in humans are limited. An analysis of the data from the Health, Aging and Body Composition cohort studies disclosed that the intake of a TZD (rosiglitazone or pioglitazone) for more than 24 months by elderly (70- to 79-year-old) diabetic patients decreased BMD in the femoral neck and hip [95]. More recently, in the A Diabetes Outcome Progression Trial (ADOPT), women receiving rosiglitazone had a higher rate of fractures in comparison to women taking metformin or glyburide [96]. Given the reported deleterious effects of PPARγ agonists on bone in animal models, more research is needed to confirm whether this occurs in humans, and studies of fractures per se are also required.

3.1.1.7. Bone turnover in diabetes. Most studies assessing bone turnover in diabetes have involved only small numbers of patients. Overall, studies conducted with animals as well as those with humans have shown normal or low serum levels of osteocalcin in the presence of diabetes [25,38,76,97,98]. Kemink et al. reported that patients who had lower BMD also had decreased levels of alkaline phosphatase [25]. In the study by Dobnig et al., mean serum PTH and osteocalcin levels were significantly lower in treated type 2 diabetic patients [58]. Achemlal et al. showed that men with type 2 diabetes had lower osteocalcin levels than their controls [99]. Therefore, bone formation appears to be decreased in diabetes.

On the other hand, in the study by Isaia et al. [38] with female postmenopausal diabetic patients, higher levels of some markers of bone resorption (urinary calcium, hydroxyproline and telopeptide) were found in the diabetics, while urinary crosslinks were higher in the controls. Dobnig et al. [58] and Achemlal et al. [99] both found that C-terminal cross-linked telopeptide (CTX) did not differ in diabetic patients compared with the controls. The latter investigations also indicated that bone resorption was not altered.

Most reviewed studies showed decreased bone formation with normal bone resorption and normal mineralization in patients with diabetes. This corresponds to a state of low bone turnover or mild adynamic bone. This low bone-turnover state is also supported by the observation that fractures take longer to heal in diabetics [100]. As for patients with type 2 diabetes, some suggest that low bone turnover could slow bone loss and explain the higher BMD seen in these patients, while others postulate that it could increase bone fragility, independently of BMD, through the accumulation of fatigue damage [101].

Given that bone strength reflects the integration of BMD and bone quality, the pathophysiology of decreased bone quality in diabetes is reviewed below.

3.1.2. Decreased bone quality

3.1.2.1. Histomorphometry and diabetes. Histomorphometric studies in diabetes have described low recruitment of OB and diminished mineral apposition rates with no mineralization defects [102,103]. Histomorphometry is rarely undertaken in humans because it requires bone biopsy, which is invasive. However, animal studies have demonstrated that bone formation is impaired in a type 1 diabetic mouse model during tibial distraction osteogenesis [13]. In a bacteria-stimulated bone-loss mouse model, diabetes also caused decreased osteoclastogenesis, reduced bone formation and enhanced OB apoptosis [104].

3.1.2.2. Insulin and bone metabolism. Evidence of a direct link between insulin action and bone formation in vivo is weak. Insulin receptor substrate-1 (IRS-1) knockout mice have impaired bone healing [105]. IRS-2 knockout mice appear to develop normally, but have osteopenia with decreased bone formation and increased bone resorption [106]. Insulin receptors (IR) have also been found on osteoclasts (OCs), while insulin has been shown to inhibit OC activity in vitro [107]. This has led some authors to suggest that insulin is an anabolic agent for bone [13].

Insulin deficiency has detrimental effects on the biomechanical properties of bone. In the untreated insulin-deficient state, decreased bone strength [108], deficit in mineralized surface area, decrement in the rate of mineral apposition, decreased osteoid surface, decreased OB activity and fewer OCs have all been observed [109]. Insulin administration reverses these abnormalities and improves bone strength [108].

3.1.2.3. Advanced glycation end-products. Hyperglycemia is known to generate a higher concentration of advanced glycation end-products (AGE) in collagen that may reduce bone strength [110]. AGE accumulate in diabetic and older individuals, and may inhibit the phenotypic expression of OB [111] and promote OB apoptosis, thereby contributing to deficient bone formation [112]. AGE also increase OC-induced bone resorption [113]. AGE are specifically recognized by AGE receptors (RAGE). AGE–RAGE interaction induces activation of cytokines in RAGE-bearing cells, which contributes to altered bone healing and bone turnover [114].

3.1.2.4. Osteoproegerin. Osteoprotegerin (OPG) and its ligand, also known as RANKL (receptor activator of NF-kappaB ligand), are cytokines that regulate osteoclastogenesis [115]. OPG neutralizes RANKL, which has the effect of decreasing OCs and resorption. Galluzzi et al. demonstrated that prepuberal children with type 1 diabetes had a significant increase in...
OPG levels, which was negatively correlated with bone quality [116]. Alexopoulos et al. detected a trend toward elevated OPG levels in patients with type 1 diabetes [81]. In a study by Browner et al., OPG levels were also increased in elderly women with diabetes, and were associated with an increase in hip fractures, but not wrist fractures. No association has been found between BMD and OPG levels [117]. In spite of the increased OPG levels among diabetics, it remains difficult to conclude that the increased OPG is the cause of the altered bone quality among diabetics. OPG could simply be a marker of decreased bone quality.

The risk of fracture is also increased by the propensity to fall. The reasons why diabetics may be at increased risk of falls is now reviewed.

3.2. Extraskeletal factors

One mechanism that could explain the increased risk of fractures in diabetes could be the propensity to fall, mediated through impaired vision, impaired proprioception due to polyneuropathy and/or frequent nocturia. Forsen et al. showed that the effects of diabetes appear to be reduced when controlling for complications predisposing to trauma (such as retinopathy, cerebral stroke, peripheral neuropathy and muscle strength), with a RR of 1.8 (95% CI 1.1–2.9) decreasing to 1.5 (95% CI 0.9–2.5) after adjustment [50]. In the study by Schwartz et al., falls, poor vision, less exercise, limitations in functional ability and use of long-acting benzodiazepines accounted for a small portion of the association between diabetes and fracture risks [55]. In the Health ABC Study, there were more recurrent falls in patients with diabetes who sustained fractures than in those without fractures [59]. In the Women’s Health Initiative–Observational Study (WHI–OS) cohort, more women with diabetes reported fractures [54]. In the Blue Mountains Eye Study by Ivers et al. revealed that, in a population-based sample of older Australians, those with diabetic retinopathy were at greater risk for all fractures combined (RR 5.4; 95% CI: 2.7–10.8) compared with those without diabetic retinopathy. Furthermore, patients with cataracts involving greater or equal to 25% of the lens area had a 2.5-fold higher risk (95% CI: 1.3–4.7) of all fractures combined compared with subjects without cataracts [118]. However, in the study by Ottenbacher et al. of older Mexican-American adults, vision impairment was not associated with increased risk of fractures in the diabetic group [56]. In the Health ABC study, retinopathy and cataracts also did not appear to explain the increased fracture rate in those with diabetes [59]. In the WHI–OS cohort, more women with diabetes reported moderate or severe eyesight problems at baseline compared with those without diabetes (11% versus 5%). Diabetes remained a risk factor for fracture among these women even after adjustment for impaired vision [60]. In a population of Swedish patients hospitalized at least once for type 1 diabetes before age 31 years, those who had ophthalmic complications had a SHR of 17.4 (95% CI: 12.5–23.5) while those without ophthalmic complications had a SHR of 4.1 (95% CI: 2.7–6.0) compared with the general population [52]. Therefore, impaired vision very likely contributes to the risk of fractures in diabetes, although it has not been uniformly demonstrated in all studies.

3.2.3. Nocturnal polyuria and falls

Although nocturnal polyuria is often cited in the literature as a potential risk factor for fractures, and an association between nocturnal polyuria and fracture risk appears plausible, to date, the connection has never been confirmed in diabetic patients.

4. Medical care

At present, although patients with type 1 or type 2 diabetes may be at greater risk of fractures, routine screening or initiation of preventative medications for osteoporosis is not recommended. However, bone health should be part of the evaluation of all diabetic patients. A patient-specific approach should be taken when evaluating, preventing or treating osteoporosis in diabetes. These patients should first be evaluated according to the Canadian guidelines for the diagnosis and management of osteoporosis [119] for all ‘classical’ major and minor risk factors of osteoporosis. Major risk factors include age greater or equal to 65 years, personal history of fracture as an adult, history of fragility fracture in a first-degree relative, personal history of fragility fracture after age 40, systemic glucocorticoid therapy for more than three months, malabsorption syndrome, primary hyperparathyroidism, propensity to falls, osteopenia on plain X-ray, hypogonadism and early menopause (before age 45). Minor risk factors include rheumatoid arthritis, past hyperthyroidism, chronic anticonvulsant therapy, low dietary calcium intake, low body weight (less than 57 kg), current cigarette-smoking, alcoholism, excessive caffeine intake, weight loss greater than 10% of weight at age 25 and chronic hepatic therapy [119]. Also, retinopathy, nephropathy, neuropathy and vascular disease should be verified to identify additional risk factors for low BMD and falls. It is also important to remember that patients with type 1 diabetes are at high risk of other autoimmune diseases such as celiac disease and autoimmune thyroid disease, which can contribute to low BMD. Common sense suggests BMD screening of type 1 or type 2 diabetes patients who have any complications. However, in type 2 diabetes, normal BMD measurements may be misleading in the assessment of fracture risk because of poor bone quality. As regards to treatment, evidence-based recommendations for osteoporosis in diabetes are not available. However, glycemic control is crucial for preventing diabetic complica-
tions and limiting bone fragility. Furthermore, according to Canadian guidelines for osteoporosis, all adults—diabetic or not—aged between 19 and 50 years should receive 1000 mg of elemental calcium and 400 IU of vitamin D3 daily, and all those aged over 50 should take 1500 mg of elemental calcium and 800 IU of vitamin D3 daily [119]. This can be achieved through a calcium- and vitamin D-adequate diet. Dietary supplements are also helpful for meeting the recommendations for calcium and vitamin D levels. Exercise should be promoted for successful weight management as well as improvements in bone and muscle mass, which are important in preventing falls. Patients with low-impact fractures or osteoporosis should be offered the same pharmacological treatment as those without diabetes, including bisphosphonates, raloxifen and calcitomin as first-line treatments. It remains to be verified, however, if these drugs have the same beneficial effects in patients with diabetes as in non-diabetics.

5. Summary and conclusion

Patients with type 1 diabetes are at greater risk of fractures because of lower BMD and an increased risk of falls. Lower BMD is explained by insulinopenia and hyperglycemia, which impair bone formation. Furthermore, poor long-term glycemic control induces retinopathy, neuropathy and nephropathy, which are associated with lower bone mass. In addition, retinopathy and neuropathy put all patients at increased risk of falls. On the other hand, patients with type 2 diabetes also have an increased risk of fractures in spite of higher BMD. The increased BMD persists even after adjustment for BMI, suggesting that the low bone turnover is responsible for the decreased age-related bone loss in type 2 diabetes. In these patients, the main mechanism to explain the increased risk of fractures is the propensity to falls. Thus, adequate glycemic control, and calcium and vitamin D intakes, screening for low BMD, and the prevention and treatment of diabetic complications are key elements in the elimination of osteoporosis in both types of diabetes. Patients with osteoporosis and diabetes should be offered the same pharmacological treatments as non-diabetics.

Future studies need to be prospective, and include the evaluation of bone quality, BMI, diabetes duration, falls, HbA1C, complications and BMD, to clarify the association between diabetes and fractures. Additional studies are also required to determine whether TZD drugs increase the risk of fractures in patients. Finally, osteoporosis trials need to include subgroups of diabetic patients with enough power to provide evidence-based guidelines for osteoporosis management in diabetes mellitus.

Conflict of interest

All of the authors have no conflicts of interest.

References


