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Review

Orthopedic complications in diabetes

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ABSTRACT

Diabetes is associated with a number of lower extremity orthopedic conditions and complications including fractures, Charcot neuroarthropathy, plantar ulcers, and infection. These complications are of significant clinical concern in terms of morbidity, mortality, and socioeconomic costs. A review of each condition is discussed, with particular emphasis on the clinical importance, diagnostic considerations, and orthopedic treatment recommendations. The goal of the article is to provide a clinical picture of the challenges that orthopedic surgeons confront, and highlight the need for specific clinical guidelines in diabetic patients.

Contents

1. Introduction

A number of clinical and pre-clinical studies indicate that diabetes affects bone quality, which results in increased fracture rates [1]. Unique morphological and architectural changes of bone including increased porosity, smaller cortical area and decreased strength may contribute to increased fragility in diabetes [2,3]. Although the exact etiology is not known, low bone turnover and accumulation of advanced glycation end products (AGEs), which alter bone biomechanical properties, are emerging as major contributors [4–6]. It is well recognized that parallel to the increased diabetes epidemic, there is an increase in the number of diabetic patients undergoing orthopedic procedures, and that the rate of complications in these patients is high.

Besides a contribution of the aforementioned abnormalities in bone homeostasis, the clinical practice point of view recognizes the obvious connection to complications of chronic hyperglycemia, and its impact

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on microvascular, neurological, and immunological body functions [7,8]. Hip fractures have a higher incidence in patients with diabetes, and higher rates of complications and mortality [9,10]. Ankle fractures have higher rates of adverse outcomes in diabetic patients, and are therefore treated differently than in non-diabetic patients [11–14]. Charcot neuroarthropathy is a disorder associated with diabetic neuropathy, for which the underlying mechanisms are not yet completely understood, early diagnosis is sometimes difficult, and the success of treatment not completely known [15]. Plantar ulcers are costly to treat and have poor outcomes on the whole [16,17]. Finally, although infections are found in any group of patients, diabetic patients have higher risks of infection, which increase the risks of overall poorer outcomes [18,19].

We focused this article on the clinically significant lower extremity conditions in orthopedics that are associated with diabetes. The upper extremity associations including adhesive capsulitis, trigger finger, carpal tunnel syndrome, and Dupuytren's disease are not discussed. Although important, these conditions have less significance in mortality, morbidity, and economic considerations [20–29]. This review provides a clinical outlook of orthopedic complications in diabetes, which may be sometimes overlooked in basic science. We believe that it will also contribute to an increased awareness for a need to develop specific guidelines for preventing and treating diabetic orthopedic conditions and complications.

1.1. Hip fracture

Hip fractures have an incidence of up to 1% per year in the United States [30,31], and the overall incidence has been estimated to be increasing as a quadratic curve [32]. In diabetic patients, the incidence is higher for somewhat unexplained reasons [10,33–43]. Type I diabetes (T1D) has a 6–7 fold increase, while type II diabetes (T2D) has a 1.4–1.8 fold increase in risk [44–46]. In contrast to T2D, up to 7% of T1D patients will have hip fractures prior to age 65, emphasizing that this specific disease process affects younger individuals [47]. In terms of costs, treatment of a non-complicated hip fracture is estimated at $19,000–$23,000 for one year of treatment [48–50]. These costs are certainly higher on average in diabetic patients because they have a higher complication rate, especially of surgical site infection (SSI), cardiovascular problems, and mortality [9,43,47,51–58]. On the whole, the functional outcomes of patients with diabetes are also less successful [54,59]. Because a hip fracture has an unexpected timing, complete optimization of a patient's medical issues is not always possible to attempt to reduce the perioperative complication risks.

With regards to mortality, patients with diabetes and hip fracture have a 1.4–1.5-fold increase in mortality versus non-diabetic patients [9,51,57]. However, the presence of diabetes alone probably does not increase the risk; rather the complications that occur in the treatment of hip fractures that are associated with diabetes are more likely the cause of increased mortality [57]. In the population as a whole, mortality rates after hip fracture at one year range from 18–33% [51,52,55,56,60–63], and the rates remain higher than the general public for at least ten years postoperatively. An analysis in the Danish registry noted that the one year mortality is nearly double that of those without hip fracture, and that the excess mortality is approximately 1.8% increased each year after [57,58]. At 20 years follow-up, the survival is 57% of what would be expected from the control group [57]. An analysis of mortality after hip fracture that subdivided the fracture types do show a trend to less in-hospital and one-year mortality in femoral neck fractures than with intertrochanteric (IT) fractures, but the difference does not reach statistical significance [59,63,64].

1.2. Hip fracture potential etiologies

Falls are of considerable concern in patients with diabetes, as the incidence of falling has been shown to be increased. In addition, diabetes-related renal dysfunction, peripheral neuropathy, and tight glucose control with insulin are also associated with increased incidence of falls [7,65,66]. Falling more than one time per year in women older than 65 is reported at 17% in non-diabetic, 25.7% in non-insulin treated diabetic, and 35.4% in insulin-treated diabetic persons [66]. Some clinical targets for fall reduction are reducing polypharmacy and improving overall physical function [67–71]. However, other than hypoglycemia, peripheral neuropathy, and nephropathy, there are many other reasons for falls, and it may be difficult to practically reduce falls significantly in order to decrease the risk of fractures [72]. Additionally, some hip fractures have already occurred prior to the fall, and are the actual reason for the fall [73].

Anti-diabetic medication use has been suggested as a risk factor for hip fractures, both as a source for hypoglycemia and falls, and as a mechanism in which bone quality is altered. Indeed, hypoglycemia in patients on insulin or sulphonylurea therapy is proposed as a causal factor for increased fracture risk, because of a possible increased incidence of falls, but the data to support the hypothesis is mixed. In some studies, therapy with insulin correlates strongly with increased risk of non-vertebral fractures [74,75], however other studies do not confirm this association [76]. Similarly, sulphonylureas have been associated with even a protective effect with a relative risk of 0.77 in the hip [10], while others see no effect on fracture incidence [77]. New therapies with GLP-1 receptor agonists and DPP-4 inhibitors, which are not associated with hypoglycemia, either have no effect or may possibly reduce the risk of bone fractures [78,79]. In preclinical studies, GLP-1 analog exendin-4 prevented bone loss in a rat model of estrogen deficiency and increased BMD in a rat model of diabetes [80,81]. Although some of the data is mixed on other antidiabetic medications, it is clear that long-term use of thiazolidinediones (TZD) increases the fracture odds ratio up to 1.94 in women, but not in men [77,82,83]. In terms of bone quantity, a 1.2% reduction in BMD of the hip was shown in women with use of TZD [84]. These effects on bone are thought to be potentiated through a change in precursor mesenchymal cell differentiation. A number of clinical and preclinical studies indicate that TZDs decrease osteoblast differentiation and affect function, while increasing osteoclast differentiation, which leads to unbalanced bone remodeling, loss of bone mass, and poorer bone quality [85]. In animal models, TZDs effect bone regeneration as well, which may suggest that healing complications of orthopedic treatment may also be increased [86].

The impact of BMD is confusing in diabetic patients, as the BMD is decreased in T1D and increased in T2D over controls, yet there is an increased fracture risk in both groups. T1D patients have an average decrease in BMD that accounts for only 1.4 times increase in risk for fracture versus controls [44,87], despite having up to a 6–7 times risk increase. In patients with T2D, BMD is increased on average, and therefore is a paradoxical increase in fracture risk as compared to non-diabetic counterparts [35,36,42,44,87]. Taken together, bone mineralization quantity in diabetes does not adequately explain the risk of fracture in either T1D or T2D.

How T1D influences fracture risk specific to the hip is not fully known. However, two T1D rat models suggest that trabecular volume, number, and thickness in the proximal tibia are all significantly decreased, and the volume is less than 50% as compared to controls. In addition, cortical bone area is decreased in the femur. Furthermore, the temporal evaluation of bone density in the ulna suggested that the trabecular volume decrease was a loss of bone density over time, while the decreased cortical bone area was a lack of new formation of cortical bone [88]. Bone strength in the femur is also decreased in terms of fracture moments, at around two-thirds the force required to fracture the T1D versus control specimens [88–90], and is associated with a 50% pentosidene increase, a marker for AGEs [88]. A recent human study of T1D would seem to parallel these findings, noting a trend to difference in radius trabecular volume ($P = 0.08$), and a significant difference in cortical thickness versus age-matched controls [91]. Therefore, it appears that bone structure is significantly affected in T1D by decreased

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