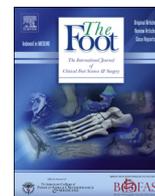




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Review

Hyperglycaemia is an under-appreciated but modifiable risk factor in managing people with type 1 diabetes and fragility fractures

Simon Lau^{a,*}, Melissa Lee^b^a Royal Melbourne Hospital, Victoria, Australia^b St Vincents Hospital, Victoria, Australia

A B S T R A C T

There are two major musculoskeletal effects of Type 1 diabetes mellitus (T1DM) — fragility fractures and impaired fracture union. Fractures in these patients are a significant and limb threatening injury. Traditionally, they have been treated with prolonged immobilisation and as rigid as possible internal fixation. Recently, hyperglycaemia has been recognised as the most significant modifiable risk factor in treating patients with T1DM and fractured limbs. This article reviews this association further and outlines the role of orthopaedic surgeons in minimising orthopaedic-related complications.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a lifelong autoimmune condition where destruction of pancreatic islet cells results in absolute insulin deficiency. T1DM is classically diagnosed in adolescence but complications and sequelae do not typically manifest until mid to late adulthood. Large cohort registry studies have consistently reported an increasing incidence of T1DM of 2–5% per year [1,2]. Further, advances in insulin treatment and technologies have enabled people with T1DM to live longer. Together, these pose new challenges to clinicians as the sequelae of long-duration T1DM and dysglycaemia develop.

The skeletal manifestations of T1DM are not as widely known as other systemic complications. There is also an emerging body of evidence to suggest that the effects of T1DM are more severe than in type 2 diabetes [3]. Firstly, it is well-known that prolonged hyperglycaemia and insulin deficiency is associated with decreased bone mineral density (BMD) and diabetic osteopathy [4]. This results in fragility fractures, which are both more common and occur earlier in T1DM. Secondly, T1DM is associated with slower fracture healing and significantly higher rates of non-union [5]. If surgery is performed, soft tissue and wound complications can be catastrophic. Glycaemic control, specifically hyperglycaemia, in this setting is the most significant modifiable risk factor that has been only recently identified. The purpose of this review is to therefore highlight the importance of achieving intensive glycaemic control in people with T1DM who sustain fractures.

2. Defining the problem of fragility fracture

There is a clear association between T1DM and decreased BMD [6].

Whilst the pathophysiology is not fully understood, it is likely multifactorial. Bone health can be highly variable, and a number of factors can contribute towards it. In T1DM, age of diagnosis, disease duration, glycaemic control, and the presence of microvascular complications have all been shown to affect bone mass [7]. BMD is typically reduced in people with diabetes with reductions of 0.5–1 standard deviations below those without diabetes [7]. In addition, those with microvascular complications have micro-architectural changes in bone morphology compared to people without microvascular complications [8,9]. Prolonged hyperglycaemia can also have a direct effect on bone cells and lead to the accumulation of advanced glycation end products (AGEs) within bone collagen [6].

Whilst fragility fractures in elderly patients with osteoporosis is well understood, it remains less clear in those with T1DM. The effect of hyperglycaemia and insulin deficiency are lifelong, and fragility fractures in people with T1DM can begin in childhood. The effect of reduced BMD in the growing skeleton is not well documented. In a population based cohort study of people with T1DM, the highest incidence of fracture in males was in those aged 10–20 years [10]. The bones in children with T1DM also tend to be smaller, which translates into higher risk of fracture [7]. Furthermore, in children, poor glycaemic control is an additional risk factor – with a 5% increased risk of fracture in males for each 1% of HbA1c rise [10]. As three-quarters of people with T1DM are diagnosed below the age of 18 years and therefore before peak bone mass is developed, skeletally immature children represent a challenge both acutely and into the future with a lifetime increased fracture risk.

* Corresponding author at: Level 7 East, Royal Melbourne Hospital, Grattan Street, Parkville 3050, Victoria, Australia.

E-mail addresses: drsimonchlau@gmail.com (S. Lau), Melissa.Lee@svha.org.au (M. Lee).

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3. Delayed fracture healing

Another known complication of T1DM is both impaired wound and impaired fracture healing. Prolonged hyperglycaemia leads to intravascular glycosylation of protein, and eventually the formation of AGEs. In turn, these AGEs attach to collagen, basement membranes, lipoproteins and inflammatory cell receptors and subsequently leads to cellular dysfunction. Hypoxia is the end result in the peripheral tissues, and is exacerbated by the higher viscosity of hyperglycaemic blood. In the setting of wound healing, collagen deposition is directly proportional to the wound oxygen perfusion. Thus in hyperglycaemic states, there is both reduced and less robust collagen deposition. Consequently, glycaemic control is a very significant but modifiable factor in limiting this pathophysiological cascade, and has been previously demonstrated in animal models [11], as well as in vivo in patients with HbA1c levels < 6.0% [12].

Patients with T1DM are at risk of both delayed and non-union after fracture, with reported union times of up to double that of those without diabetes [13]. Pathophysiologically, this process is driven by the effects of hyperglycaemia on osteoblasts and subsequently bone mineralisation and fracture union. Prolonged insulin deficiency result in insulin resistant osteoblasts, and therefore impaired glucose transporters. Hyperglycaemia and AGEs also directly impair osteoblast function [14]. Even if radiological union occurs, the callus produced tends to be smaller, and the mechanical strength of the bone is diminished compared to people without diabetes [15].

4. Current management strategies

Within the orthopaedic literature, there are some well-established principles for the management of T1DM fractures. Particular care must be given to examination of the affected limb. Vascularity can be assessed via a palpable pulse, capillary return and more formally with ankle-brachial indexes. Imaging can be arranged including Doppler ultrasounds and angiography. Neuropathy is a known risk factor for poor soft tissue and bone healing and must be established with monofilament sensory deficit testing.

Cast treatment of non-displaced fractures is possible – although has been an area of controversy [16,17]. In order to prevent malunion or the development of Charcot type arthropathies, non weight-bearing for a period of 2–3 times that of patients without diabetes has been advocated [18]. There remains no clear algorithm or guidelines to help determine fracture and patient characteristics to guide the need for surgical or non-surgical forms of care [5].

In displaced fractures, it is generally accepted that open reduction and rigid internal fixation followed by a protracted course of immobilisation and non weight-bearing is best. However, surgery is beset with problems, and it is widely acknowledged that these patients are prone to complications, wound issues and the need to return to theatre. Good diabetes control has been shown to improve complication rates when compared to patients with co-morbidities, although time to union is still higher than their non-diabetes counterparts [19]. A number of surgical techniques have been advocated to address the technical challenges of operating on patients with T1DM. From a soft tissue perspective, prompt reduction and temporary immobilisation is vital to allow a staged successful reconstruction. Additionally, the osteopaenic or osteoporotic nature of bone in a person with T1DM often necessitates the use of locking plate technology [5]. Finally, insufficient immobilisation after fracture – whether non operatively or surgically managed – risk the development of a neuropathic Charcot arthropathy, loss of fracture position and ultimately unsalvageable collapse. Surgical intervention, in particular, has been known to increase the risk of progression to Charcot arthropathy [20].

Open fractures in T1DM are potentially catastrophic to the fractured limb. White et al. studied 14 open ankle fractures in patients with diabetes, of which 9 (64%) had wound healing complications, and 5

(42%) required definitive amputation. Only 3 patients (21%) healed without complication [21]. Surgical management of these patients is often constrained by the extent of soft tissue damage on arrival and thus damage limitation may be a more appropriate mindset.

5. Can we predict who is at higher risk?

All patients with T1DM are at higher risk of non or delayed union and soft tissue complications for the reasons detailed above. Additional diabetes-specific factors such as poor glycaemic control, peripheral neuropathy, vasculopathy, poor compliance with insulin, and neuropathic or Charcot type joint deformity have all been identified as high risk [19,22]. Obesity and other microvascular complications such as nephropathy and retinopathy have also been postulated [23,24]. Recently, children with T1DM have been identified as particularly at risk of subsequently developing diabetic osteopathy – though the manifestations of this on long term bone formation and growth have not been identified yet [10].

6. Hyperglycaemia — glycaemic control and targets

Orthopaedic surgeons are often at the forefront of discussions with patients regarding smoking cessation as the effects of cigarette smoking on poor fracture union and bone healing are well known. In a similar way, surgeons should be also aware of the significance of glycaemic control in patients with T1DM and stress that glycaemic control is the best modifiable risk factor for improving bony and soft tissue outcomes. Surgeons should always try to refer as early as possible to Diabetes teams – particularly in patients with sub-optimal glycaemic control.

However, specific glycaemic targets have not been identified in the literature. In part, this is because the administration of diabetes treatments such as metformin and even exogenous insulin have been shown to directly delay bone union [25]. The degree to which the delay is secondary to pharmacodynamics or to hyperglycaemia itself is not clear.

Secondly, many of the perioperative glycaemic targets published relate to the acute perioperative period. This anaesthetic focus does not have the same implications as from the orthopaedic standpoint of the medium to long term musculoskeletal effects of hyperglycaemia. However, a number of orthopaedic papers have identified glycaemic control as an independent risk factor for peri-prosthetic joint infection in an elective arthroplasty setting. For instance, Cancienne found a HbA1c > 7.5% was significantly associated with risk of deep infection [26]. Similar studies in the setting of orthopaedic trauma have not been performed, although “close metabolic control” has been advocated [27].

The concept of intensive versus standard glycaemic control has been practised for a long time. The original Diabetes Control and Complications Trial found patients in the intensive control group (HbA1c levels were ~7%) had significantly lower rates of microvascular complications ie. retinopathy, neuropathy and nephropathy [28]. However, this was at the expense of increased hypoglycaemia. In the orthopaedic setting, this can be detrimental as hypoglycaemia can result in syncope, falls and further fractures. The effect of episodic hypoglycaemia on fracture repair and wound healing is not known.

To summarise, in the setting of T1DM and fracture, whether surgical or non-surgical management is undertaken, there are no clear guidelines to guide diabetes management. In these patients, glycaemic control is a major modifiable risk factor. Microvascular complications of T1DM are analogous with impaired bone union and wound healing, and numerous long-term trials demonstrate that strict or intensive glycaemic control aiming for a HbA1c of 7% help to reduce the microvascular [including bony] sequelae of T1DM. The NICE guidelines argue for a HbA1c target of 6.5% or lower in patients with T1DM [29], although there are no high level evidence to support this assertion in the setting of fracture and bony union. Ultimately, the best available evidence suggests that in those with T1DM and fracture, strict or

intensive glycaemic control should be the goal until fracture union occurs. This is particularly applicable in those in whom the risk of hypoglycaemia is minimal such as younger, otherwise healthy patients. The advent of newer diabetes-related technologies such as continuous glucose monitoring and closed-loop insulin pump therapies may be particularly useful to achieve this [30]. A caveat is in older patients, those with greater comorbidities or at high risk of falls – in whom a higher HbA1c target should be tolerated as the risk of hypoglycaemia likely outweighs the benefits.

7. Recommendations

- Recognise that fractures in T1DM are a significant and limb threatening injury that patients should be informed of from the first consult.
- Immobilise patients with T1DM for 2–3 times the usual period. Full weight-bearing should only be recommended once full union has been achieved.
- Aim for as rigid as possible internal fixation and pay particular attention to wound and soft tissue handling.
- Ask about glycaemic control and stress the importance of hyperglycaemia and the risk of complications when reviewing patients post-operatively or in the fracture clinic.
- Refer early and work collaboratively with Diabetes Team and Diabetes Nurse Educators to intensify glycaemic control.

8. Conclusion

Fracture in a person with T1DM has serious implications for their health and function. Whilst osteoporosis is a known contributor to fragility fracture, it does not impair the bone's ability to unite. The presence of T1DM combines the two; leading to both increased fragility and increased rates of fracture mal- or non-union. T1DM also affects all age groups, and in particular, may have implications in skeletally immature patients. Over a lifetime, glycaemic control is vital to the prevention of fragility fracture. In the acute setting after trauma, orthopaedic surgeons need to be aware that hyperglycaemia is the single most modifiable risk factor to poor fracture and wound healing. In the appropriate patient, intensive glycaemic control should be pursued. Early involvement of endocrinologists and diabetes nurse educators should be facilitated.

Conflicts of interest

The authors declare no conflicts of interest.

Previous presentations

Nil.

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