Diabetes and orthopaedic surgery: a review

Vishwajeet Kumar
Bhavik Y Patel
Andrew HN Robinson

Abstract

Diabetes mellitus (DM) is common, estimated to affect 425 million people worldwide in 2017. It is a condition that is continually growing in prevalence and is often associated with multiple co-morbidities. Its multi-system effects on the body mean that its management can pose a challenge, even to more experienced clinicians. In orthopaedic practice, diabetic patients are commonly encountered owing to their increased fracture risk and complications of the disease such as diabetic foot. An appropriate knowledge of diabetes, its pathophysiology, immunology and the pharmacology of medications used in its treatment is essential, as the consequences of mismanagement can be grave. Optimal treatment of diabetics can often require the involvement of a wider multidisciplinary team. Complications that can be encountered in the perioperative and postoperative periods include, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, surgical site infection and venous thromboembolism. This review outlines current concepts in the perioperative management of diabetes and its manifestations within orthopaedic surgery, with a focus on outcomes and complications. A review of the available literature reveals conflicting conclusions between studies, with no clear effect or consensus yet established for many issues. There is a need for a greater number of well-designed, high-quality, appropriately powered trials to establish the true effect of diabetes on outcomes in orthopaedic surgery.

Keywords diabetes mellitus; immunology; orthopaedic surgery; outcomes; pathophysiology; perioperative management

Background and history

Diabetes mellitus (DM) is a chronic, metabolic condition characterized by hyperglycaemia which is due to genetic and environmental factors. The name itself derives from the Greek (*dia,* through; *bainein,* to go) and the Latin word *mellītus* meaning honey-sweet. It is believed to have been first described in 1500 BC by the ancient Egyptians.[1] According to the International Diabetes Federation, diabetes affected 425 million people in 2017, with an expected rise in prevalence to affect 629 million people by 2045.[2] The morbidity, mortality, time lost from work and family burden is enormous. It is associated with a significant economic impact, with an estimated direct cost of £9.8 billion to the NHS in 2011.[3] The majority of this cost is associated with the treatment of diabetic complications, which are usually the sequalae of macrovascular and microvascular changes. Diabetic nephropathy, neuropathy, and retinopathy are the most common microvascular complications, whilst stroke and myocardial infarction are the main macrovascular complications. Moreover, immunological dysfunction occurs in patients with diabetes as a consequence of a combination of factors: the hyperglycaemic environment, leukocyte dysfunction, reduced interleukin release and impaired tissue perfusion due to microvascular changes.[4]

The cumulative effect of these complications can impair multiple systems and the spectrum of these complications, may require the involvement of multiple different medical specialties.

Due to its prevalence diabetes should be considered in any patient encountered in a clinic, an operating theatre or the emergency department and it must be detected and managed carefully, as disregarding it may put patients at risk of potentially life-threatening complications.

Diagnosed or undiagnosed diabetics may present to the orthopaedic service with various pathologies as a consequence of prolonged hyperglycaemia. Orthopaedic complications of diabetes typically affect the foot and ankle (foot ulcer, Charcot neuroarthropathy), but may involve the upper extremity (adhesive capsulitis) or the axial skeleton (diffuse idiopathic skeletal hyperostosis).[5]

People with diabetes mellitus, both type 1 and 2, have an increased risk of osteoporosis. Risk factors for osteoporosis include the duration of diabetes and how well controlled blood glucose levels are. Clearly, osteoporosis puts diabetics at an increased fracture risk. This effect has been demonstrated in several large scale studies of type 1 diabetics.[6–9] A similar trend has also been shown in type 2 diabetics.[10–12] This effect is especially true for hip fractures, which have been shown to be more common in diabetics by two meta-analyses.[13,14] Reduced bone density was hypothesized to be responsible for this observation. This seems to be true in the case of type 1 diabetics, where several studies have shown reduced bone mineral density.[14–16] The opposite effect is seen in type 2 diabetes where an increased bone density is often observed, even after adjusting for BMI.[10,14,16] Despite the higher bone mineral density, there is evidence to suggest reduced bone strength, which may go some way to explaining the increase risk of fracture.[17] This has been proposed to be due to inefficient bone mass redistribution in type 2 diabetics.[18]

Foot problems, especially infections, are the most common diabetes-related complication encountered in orthopaedic practice necessitating hospital admission. Between 50 and 70% of non-traumatic lower extremity amputations occur in patients with diabetes.[19] The global economic impact of diabetic foot problems and their sequelae is enormous.[20] In 2012 a report estimated that the NHS spends around £650 million (or £1 in every £150 the NHS spends) on foot ulcers or amputations in diabetics each year.[21] Besides the direct cost, there is also an indirect

Vishwajeet Kumar *FRCS (Tr &Orth) MCh (Orth) MRCS MS MBBS Consultant Orthopaedic Surgeon (Locum), Orthopaedic Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

Bhavik Y Patel *BSc (Hons) MBChB Core Surgical Trainee, Orthopaedic Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

Andrew HN Robinson *BSc FRCS (Tr&Orth) Consultant Orthopaedic Foot and Ankle Surgeon, Orthopaedic Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

monetary, psychological and social cost associated with morbidity, mortality and time lost from work. A multidisciplinary approach to the management of diabetic complications is vital, with orthopaedic intervention being an option for cases of ulceration, foot deformity, osteomyelitis and Charcot neuroarthropathy.

It is obvious that the diabetic patient should be carefully considered within orthopaedic practice, especially given a surgeon's role in managing several of the important diabetic complications. A basic understanding of the disease, its perioperative care and the effect of the condition on bone, soft tissue and thus postoperative complications is vital.

Pathophysiology and immunology

There are two major abnormalities that contribute to hyperglycaemia in people with diabetes mellitus.

In type 1 diabetes, there is a complete or near-complete loss of insulin synthesis as a result of an autoimmune response. There is initial insulitis, with T lymphocyte associated autoimmune-mediated destruction of the β cells in the pancreatic islets. The exact mechanism triggering this auto-immunity is yet to be determined, although it is thought to be due to a complex interplay between environmental and genetic factors.[22] The literature suggests that 85–90% of type 1 diabetes patients have humoral evidence of one or more autoantibodies. Anti-insulin antibodies are often the first to appear; glutamic acid decarboxylase (GAD65), tyrosine phosphatase-related islet antigen 2 (IA-2) and islet cell antigen (ICA) antibodies may also be seen.[23] There is positive association with human leucocyte antigen (HLA) DQA and DQB; HLA-DRB3 and HLA-DRB4 in type 1 diabetes.[24,25] Individuals with type 1 diabetes are more likely to have other autoimmune conditions such as Graves' disease, Hashimoto's thyroiditis, vitiligo, Addison's disease and pernicious anaemia.

Type 2 diabetes mellitus is more common and accounts for 90–95% of diabetics.[26] It is polygenetic, with a more complicated aetiology. It is characterized by hyperinsulinaemia and associated insulin resistance with a complex interplay between genetics and environmental factors such as diet and sedentary lifestyle. This leads to an imbalance in glucose homeostasis towards hyperglycemia. Traditionally, environmental factors were the main target for disease prevention, especially in the context of increasing prevalence and increasing consumption of carbohydrate-rich diets. Nevertheless, the genetics of type 2 diabetes have been gaining increasing attention, with over 60 loci having been identified as regions of interest. These are believed to contribute to a person's susceptibility to the condition.[27]

There is also increasing evidence to suggest an immunological basis for type 2 diabetes. Cross-sectional and prospective studies have demonstrated increased levels of acute phase proteins (e.g. C-reactive protein, fibrinogen, hapatoglobin and plasminogen activator inhibitor), sialic acid, cytokines and chemokines in affected individuals.[28] Furthermore, an elevation of interleukin-1β and interleukin-6 together carries an increased risk of developing type two diabetes versus interleukin-6 alone.[29]

Biochemically, there is an association between the skeletal system and diabetes. Bone cells release a hormone called osteocalcin, which helps in the regulation of blood sugar levels. Osteocalcin has been found to increase the secretion and sensitivity of insulin and reduces fat storage. Lower levels of osteocalcin have been found in people with a higher body mass index.

Perioperative considerations

A decision to operate on a patient with diabetes should be made carefully, as they have increased postoperative morbidity and mortality rates.[30,31] It should also be remembered that several complications of diabetes can be mistaken for surgical emergencies. Patients with diabetic ketoacidosis (DKA) may present with severe abdominal pain, which could be mistaken for an acute surgical abdomen. Diabetic autonomic neuropathy can manifest with gastrointestinal symptoms resulting in gastroenteropathy mimicking various surgical emergencies. Similarly, the rare diabetic pseudotabes syndrome, characterized by sharp neuropathic pain along thoracolumbar dermatomes, may be confused with visceral disorders.

Elective surgery in people with uncontrolled diabetes should be scheduled after glycaemic control has been achieved. Involvement of an appropriate specialist team with multidisciplinary input in the pre- and postoperative period is ideal for such patients. This will include specially trained nurses supported by diabetologists, and has been shown to reduce the length of stay of diabetic patients.[32]

Two major guidelines exist in the UK to aid clinical decision making.[33,34] The joint guidelines of the British Diabetes Societies for Inpatient Care and The Association of Anaesthetists of Great Britain & Ireland advocate:[33,34]

- before admission patients should be pre-assessed and referred to any relevant specialty, aims include optimization of diabetic control
- pre-admission should be avoided solely for the management of diabetes
- diabetic patients should be prioritized on an operating list to minimize the starvation time, ideally to one meal or less
- adjust the medications and avoid a variable rate insulin infusion (VRII) when possible
- if the patient is expected to miss more than one meal or their blood glucose rises above 12 on two occasions, start a VRII; the fluid of choice is 5% dextrose in 0.45% sodium chloride and either 0.15% potassium chloride (KCl) or 0.3% KCl
- early mobilization, resumption of normal diet and diabetes regime should be attempted as soon as possible
- patients should be encouraged to self-manage their diabetes as soon as possible after surgery.

The overall goal is to optimize metabolic control through close monitoring, adequate fluid management and the appropriate use of insulin. General anaesthetics require a period of fasting during which oral antidiabetic medications cannot be used. An appropriate understanding of the pharmacology of these agents is essential to ensure euglycaemia. Guidance from the Association of Anaesthetists of Great Britain & Ireland summarizes perioperative adjustment of insulin and oral hypoglycaemic agents for patients in whom a VRII can be avoided, that is, those who miss one meal or less.[34] Local policies and specialist advice should be sought when there is uncertainty or complexity in any given case.

Following surgery, the physiological stress response induced by the release of cytokines causes a metabolic response that alters glucose homeostasis. This is mediated by the release of the catabolic hormones such as: adrenaline (epinephrine), noradrenaline (norepinephrine), cortisol, glucagon, growth hormone and by the inhibition of insulin secretion.[34,35] This results in hyperglycaemia, osmotic diuresis and hypoinsulinaemia, which can lead to DKA or hyperosmolar hyperglycaemic state in diabetics or undiagnosed latent diabetics.[36] Some series suggests incidence of DKA to be as high as 25% in certain cohorts.[37] Furthermore, the persistent hyperglycaemia is also a risk factor for endothelial dysfunction, postoperative sepsis, impaired wound healing and cerebral ischaemia.[38,39] In addition to effects on glucose homeostasis, insulin also has an important anabolic actions which includes protein synthesis, essential for tissue recovery and repair.

Due to multiple variables affecting diabetes management and no two individuals being the same, treatment recommendations should be individualized and based on: diagnosis, usual regimen, state of glycaemic control and the nature of the surgical procedure. Postoperative nausea and vomiting is estimated to affect 30% of all surgical patients and orthopaedic surgery is no exception.[40] It compounds the volume depletion which may already be present due to osmotic diuresis induced by hyperglycaemia, thereby increasing the risk of acute kidney injury (AKI) and possibly cerebral ischaemic events.[41] Prescription of an 'as needed' antiemetic is strongly encouraged with early identification of refractory cases. Postoperative nausea and vomiting may also cause abnormalities in key electrolytes such as potassium and magnesium, with an arrhythmogenic risk. The electrolytes should be checked regularly with abnormalities identified and treated promptly, as a tachyarrhythmia in patients with underlying coronary artery disease can lead to myocardial ischaemia.

Outcomes

Hyperglycaemia has an adverse impact on the immune system, as a result of the activation of protein kinase C, which inhibits neutrophil function and phagocytosis.[42] This in combination with the microvascular effects of diabetes results in marked susceptibility to infective complications.[43] Two or more blood glucose readings greater than 11.1 mmol/litre increase the risk of surgical-site infection at 30 days (odds ratio: 2.7).[44] Better glycaemic control has been shown to reduce surgical site infection rates in general surgical patients.[45] Furthermore diabetic patients are also at increased risk of deeper infections such as periprosthetic joint infection (PJI), independent of being obese, which is also another risk factor for PJI.[46] The morbidity and mortality of PJI is well established.[47] The cost of a PJI is significant and is estimated to be between $43,586 and $347,789.[48]

Orthopaedic surgery carries a significant risk of venous thromboembolism when compared to most general surgery procedures.[49] The relationship between diabetes and venous thromboembolism risk in patients following orthopaedic surgery is unclear. A large cohort study in the USA found there to be lower rates of pulmonary embolism in diabetic patients after total hip and knee arthroplasty.[50] However, a meta-analysis of cohort studies in which patients had undergone total knee replacement, suggested that pre-existing diabetes was associated with an increased risk of deep-vein thrombosis (DVT).[51] A further study suggested that poor glycaemic control with readings above 11.1 mmol/litre is associated with a three times higher risk of pulmonary embolism, when compared to patients with blood sugars below 6.1 mmol/litre[52]

Some suggest inferior outcomes following orthopaedic surgery in diabetic patients. Schipper et al. reported an increased risk of myocardial infarction; urinary tract infection; blood transfusion; debridement in patients who had ankle arthrodesis or total ankle arthroplasty. There was also a comparably longer length of hospital stay.[53] Similarly, inferior outcomes were reported in diabetic patients in a meta-analysis of the outcome of elective primary total knee replacements, which identified increased risks of deep infection, deep vein thrombosis, periprosthetic fracture, aseptic loosening and a poorer Knee Society function score.[54] Other studies speculate that, obesity and multimorbidity are commonplace amongst diabetics and it is this that creates a causal relationship with endpoints such as length of stay, postoperative pain and patient-reported outcomes, rather than the diabetes.[55,56]

Historically, studies have reported that diabetes mellitus is associated with an increased risk of skeletal fractures, which could be attributed to altered bone mineral density as mentioned above .[57] Recently, it has been observed that individuals with diabetes mellitus have a higher incidence of both vertebral and non-vertebral fractures.[58] Jie Liu et al. performed a meta-analysis, which included 11 studies, to estimate the risk factor for limb fractures in type 2 diabetes mellitus. The sites of fracture in these studies included hip, pelvis, proximal humerus, distal forearm, ankle, knee, foot, wrist and vertebral. The results of their meta-analysis showed that individuals with type 2 diabetes mellitus had higher risk of limb fractures, and they observed that relationship is more pronounced in leg or ankle fracture.[59] Furthermore, to add to the growing evidence, Wang et al. concluded from their meta-analysis that patients with DM had greater risks of total, hip, upper arm and ankle fractures, with T1DM having a more harmful effect than T2DM.[60] Therefore, treatment of acute fractures caused by trauma, whether trivial or significant, in diabetics requires special consideration. It is important to be aware of the diagnosis of diabetes and document the presence or absence of neuropathy, vasculopathy and other potential diabetic complications.

Diabetes is a complex disease and therefore one must have a comprehensive and holistic approach, utilizing everything one can think of to improve lifestyle and motivate patients by focusing on what is important to them. Available evidence does show that when patients manage their own illness the outcomes are better. Therefore, we must engage, involve and empower patients in managing their condition, for example in allowing access to their own medical notes so that they can see their results and take control of their condition better. It is also important to have a care plan that is very individualized for each patient in partnership with them. Diabetic patients should be considered for, and offered, diabetes education workshops as part of perioperative optimization specially in elective procedures for achieving best possible outcome.

Summary

Patients with diabetes present a host of challenges and problems, and often as an acute orthopaedic problem. Therefore, recognition of the particular risks and complications is critical to achieving a satisfactory outcome in this ever-increasing group of patients. ◆

REFERENCES

1 Poretsky Leonid, ed. Principles of diabetes mellitus. 2nd ed. New York: Springer, 2009; 3. ISBN 978-0-387-09840-1.

2 International Diabetes Federation. IDF diabetes atlas. 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.

3 Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012; **29:** 855–62.

4 Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metab* 2012; **16**(suppl 1)**:** S27–36.

5 Uhl RL, Rosenbaum AJ, Dipreta JA, Desemone J, Mulligan M. Diabetes mellitus: musculoskeletal manifestations and perioperative considerations for the orthopaedic surgeon. *J Am Acad Orthop Surg* 2014; **22:** 183–92.

6 Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care* 2006; **29:** 1573–8.

7 Weber DR, Haynes K, Leonard MB, Willi SM, Denburg MR. Type 1 diabetes is associated with an increased risk of fracture across the life span: a population-based cohort study using the Health Improvement Network (THIN). *Diabetes Care* 2015; **38:** 1913–20.

8 Zhukouskaya VV, Eller-vainicher C, Vadzianava VV, et al. Prevalence of morphometric vertebral fractures in patients with type 1 diabetes. *Diabetes Care* 2013; **36:** 1635–40.

9 Chen HF, Ho CA, Li CY. Increased risks of hip fracture in diabetic patients of Taiwan: a population-based study. *Diabetes Care* 2008; **31:** 75–80.

10 Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: the women's health initiative observational study. *J Clin Endocrinol Metab* 2006; **91:** 3404–10.

11 Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. *J Bone Miner Res* 2009; **24:** 702–9.

12 Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 2001; **86:** 32–8.

13 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* 2007; **166:** 495–505.

14 Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. *Osteoporos Int* 2007; **18:** 427–44.

15 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* 2006; **29:** 306–11.

16 Rakic V, Davis WA, Chubb SA, Islam FM, Prince RL, Davis TM. Bone mineral density and its determinants in diabetes: the Fremantle Diabetes Study. *Diabetologia* 2006; **49:** 863–71.

17 Petit MA, Paudel ML, Taylor BC, et al. Bone mass and strength in older men with type 2 diabetes: the Osteoporotic Fractures in Men Study. *J Bone Miner Res* 2010; **25:** 285–91.

18 Burghardt AJ, Issever AS, Schwartz AV, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010; **95:** 5045–55.

19 Boulton AJ, Vileikyte L, Ragnarson-tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005; **366:** 1719–24.

20 Raghav A, Khan ZA, Labala RK, Ahmad J, Noor S, Mishra BK. Financial burden of diabetic foot ulcers to world: a progressive topic to discuss always. *Ther Adv Endocrinol Metab* 2018; **9:** 29–31.

21 National Institute for Health and Care Excellence. Diabetic foot problems: prevention and management (update). [NG19]. London: National Institute for Health and Care Excellence, 2016.

22 Katsarou A, Gudbjörnsdottir S, Rawshani A, et al. Type 1 diabetes mellitus. *Nat Rev Dis Primers* 2017; **3:** 17016.

23 Narendran P, Estella E, Fourlanos S. Immunology of type 1 diabetes. *QJM* 2005; **98:** 547–56.

24 Wang H, He R. HLA-DQA and DQB alleles contribute to susceptibility to insulin-dependent diabetes mellitus. *Chin Med Sci J* 1993; **8:** 231–4.

25 Zeliszewski D, Tiercy JM, Boitard C, et al. Extensive study of DRB, DQA, and DQB gene polymorphism in 23 DR2-positive, insulin-dependent diabetes mellitus patients. *Hum Immunol* 1992; **33:** 140–7.

26 Cheng D. Prevalence, predisposition and prevention of type II diabetes. *Nutr Metab* 2005; **2:** 29.

27 Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* 2012; **44:** 981–90.

28 Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011; **11:** 98–107.

29 Spranger J, Kroke A, Möhlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003; **52:** 812–7.

30 Tsai MS, Wang YC, Kao YH, Jeng LB, Kao CH. Preexisting diabetes and risks of morbidity and mortality after gastrectomy for gastric cancer: a nationwide database study. *Medicine (Baltim)* 2015; **94:** e1467.

31 Kubal C, Srinivasan AK, Grayson AD, Fabri BM, Chalmers JA. Effect of risk-adjusted diabetes on mortality and morbidity after coronary artery bypass surgery. *Ann Thorac Surg* 2005; **79:** 1570–6.

32 Flanagan D, Moore E, Baker S, Wright D, Lynch P. Diabetes care in hospital–the impact of a dedicated inpatient care team. *Diabet Med* 2008; **25:** 147–51.

33 Dhatariya K, Levy N, Flanagan D, et al. Management of adults with diabetes undergoing surgery and elective procedures: improving standards. Joint British Diabetes Societies for Inpatient Care Group, March 2016.

34 Association of Anaesthetists of Great Britain and Ireland. Perioperative management of the surgical patient with diabetes 2015. *Anaesthesia* 2015; **70:** 1427–40.

35 Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373:** 1798–807.

36 Haldar R, Khandelwal A, Gupta D, Srivastava S, Singh PK. Acute post-operative diabetic ketoacidosis: atypical harbinger unmasking latent diabetes mellitus. *Indian J Anaesth* 2016; **60:** 763–5.

37 Aminian A, Kashyap SR, Burguera B, et al. Incidence and clinical features of diabetic ketoacidosis after bariatric and metabolic surgery. *Diabetes Care* 2016; **39:** e50–3.

38 Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. *Int J Vasc Med* 2012; **2012:** 918267.

39 Zhang Z, Yan J, Shi H. Hyperglycemia as a risk factor of ischemic stroke. *J Drug Metab Toxicol* 2013; **4**.

40 Pierre S, Whelan R. Nausea and vomiting after surgery. *Cont Educ Anaesth Crit Care Pain* 2013; **13:** 28–32.

41 Rodriguez GJ, Cordina SM, Vazquez G, et al. The hydration influence on the risk of stroke (THIRST) study. *Neurocritical Care* 2009; **10:** 187–94.

42 Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci* 2016; **351:** 201–11.

43 Martin ET, Kaye KS, Knott C, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2016; **37:** 88–99.

44 Richards JE, Kauffmann RM, Zuckerman SL, Obremskey WT, May AK. Relationship of hyperglycemia and surgical-site infection in orthopaedic surgery. *J Bone Joint Surg Am* 2012; **94:** 1181–6.

45 Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; **34:** 256–61.

46 Jämsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. *J Bone Joint Surg Am* 2012; **94**: e101.

47 Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one-year mortality. *J Bone Joint Surg Am* 2013; **95:** 2177–84.

48 Hernández-vaquero D, Fernández-fairen M, Torres A, et al. Treatment of periprosthetic infections: an economic analysis. *ScientificWorldJournal* 2013; **2013:** 821650.

49 Calfon M, Seddighzadeh A, Piazza G, Goldhaber SZ. Deep vein thrombosis in orthopedic surgery. *Clin Appl Thromb Hemost* 2009; **15:** 512–6.

50 Memtsoudis SG, Besculides MC, Gaber L, Liu S, González della valle A. Risk factors for pulmonary embolism after hip and knee arthroplasty: a population-based study. *Int Orthop* 2009; **33:** 1739–45.

51 Yang G, Meng F, Liu Y, Kong L, Shen Y. Diabetes mellitus and risk of deep vein thrombosis after total knee replacement: a meta-analysis of cohort studies. *Int J Clin Exp Med* 2015; **8:** 9086–92.

52 Mraovic B, Hipszer BR, Epstein RH, Pequignot EC, Parvizi J, Joseph JI. Preadmission hyperglycemia is an independent risk factor for in-hospital symptomatic pulmonary embolism after major orthopedic surgery. *J Arthroplast* 2010; **25:** 64–70.

53 Schipper ON, Jiang JJ, Chen L, Koh J, Toolan BC. Effect of diabetes mellitus on perioperative complications and hospital outcomes after ankle arthrodesis and total ankle arthroplasty. *Foot Ankle Int* 2015; **36:** 258–67.

54 Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. *Bone Joint Lett J* 2014; **96-B:** 1637–43.

55 Lenguerrand E, Beswick AD, Whitehouse MR, Wylde V, Blom AW. Outcomes following hip and knee replacement in diabetic versus nondiabetic patients and well versus poorly controlled diabetic patients: a prospective cohort study. *Acta Orthop* 2018; **89:** 399–405.

56 Lovecchio F, Beal M, Kwasny M, Manning D. Do patients with insulin-dependent and noninsulin-dependent diabetes have different risks for complications after arthroplasty? *Clin Orthop Relat Res* 2014; **472:** 3570–5.

57 Heath 3rd H, Melton 3rd LJ, Chu CP. Diabetes mellitus and risk of skeletal fracture. *N Engl J Med* 1980; **303:** 567–70.

58 Kilpadi KL, Eldabaje R, Schmitz JE, et al. Type 2 diabetes is associated with vertebral fractures in a sample of clinic- and hospital-based Latinos. *J Immigr Minority Health* 2014; **16:** 440–9.

59 Liu J, Cao L, Qian YW, et al. The association between risk of limb fracture and type 2 diabetes mellitus. *Oncotarget* 2018 Jan 5; **9:** 31302–10. https://doi.org/10.18632/oncotarget.23937. eCollection 2018 Jul 27.

60 Wang H, Ba Y, Xing Q, Du JL. Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis. *BMJ Open* 2019 Jan 3; **9**: e024067. https://doi.org/10.1136/bmjopen-2018-024067.