Predictive value of common serum glycaemic markers on periprosthetic joint infection following Total Joint Arthroplasty: A review of the literature

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ABSTRACT

It is well established that diabetes mellitus and osteoarthritis commonly exist together and among various treatment modalities for osteoarthritis, Total Joint Arthroplasty (TJA) has been effective. Prosthetic Joint Infection (PJI) is a serious complication of TJA with high costs and morbidity associated with it. The aim of this study is to provide background information and relevance of diabetes on PJI, and to conduct a review on existing literature, to find out if common serum glycaemic markers in diabetes could be used as predictors for PJI after TJA. These markers include measuring pre-operative glucose levels with glycated haemoglobin (HbA1c) or capillary blood glucose, peri-operative or post-operative blood glucose levels. We have found that existing literature studying these markers as predictors of PJI after TJA has been largely contentious. Despite not being used widely in clinical practice, serum fructosamine has been shown to be more reliable and accurate than the above-mentioned markers. Future studies should be carried out to confirm and better understand this association.

1. Introduction

Total Joint Arthroplasty (TJA) is an established treatment modality in the management of severe refractory Osteoarthritis (OA) of the hip and knee. Current practices yield good results and allow patients to regain a high degree of mobility and function.¹ Since both Diabetes Mellitus (DM) and OA share similar risk factors such as obesity, they commonly co-exist in the same patient.^{2,3} The World Health Organization (WHO) predicts that the prevalence of DM around the world will increase by 114% by 2030.⁴ In Singapore alone, 1 in 4 Singaporeans above the age of 65 will be diabetic by 2030, an increase from 1 in 8 today.⁵ This increased prevalence of DM and OA will lead to a corresponding increase in the number of arthroplasty procedures performed in diabetic patients.

Despite the success of TJA, surgeons should be wary of prosthetic joint infections (PJI) as a potential complication. In addition to being a common indication for revision arthroplasty,^{6,7} the costs borne by both patients and hospitals are high.⁸ Hence, it is important to minimize the risk of PJI in preventing unnecessary costs and morbidity. The effect of DM on PJI risk is well studied with differing results in the literature.^{9–13} There is also recent interest in identifying glycaemic markers as a predictor of PJI.

Given this background, the aim of this article is to summarize the

existing literature on common glycaemic markers such as pre-operative glycated haemoglobin (HbA1c) and capillary blood glucose readings as predictors of PJI in diabetic patients undergoing TJA. This will prompt surgeons to think and re-look into management strategies for diabetic patients.

2. Methodology

We performed a search on PubMed, Embase and Cochrane Library using the search terms “diabetes” or “HbA1c” or “capillary blood glucose” and “arthroplasty” and “prosthetic joint infection” or “surgical site wounds”. Only articles in English were included. We conducted our search in a stepwise fashion where results were initially screened based on the title, next the abstract, and subsequently the paper. Results were reviewed and excluded if they were unrelated to our research question, if they had a small sample size or used other glycaemic markers that were not from serum such as urine glucose. In addition, to be included, studies were required to discuss associations between PJI and the various markers for glycaemic control.

2.1. Pathophysiology of diabetes

The effect of hyperglycaemia on infection risk of various surgical

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procedures is well reported.^{14–17} Although the exact mechanism remains poorly defined, several hypotheses exist in the literature including impaired wound healing¹⁸ and immune system dysfunction.¹⁹ Normal wound healing involves a balance between angiogenesis, apoptosis and maturation of new vessels at the wound site through a series of complex mechanisms. In diabetic patients, this balance is deranged and there is a decrease in angiogenesis at wound sites. This is due to a decrease in pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) being the main one among many others, as well as an increase in pigment-epithelium derived factor (PEDF) which are anti-angiogenic factors. In addition, in patients who are in a hyperglycaemic state, endothelial cells exposed to elevated levels of blood glucose for an extended period of time eventually became dysfunctional and are more susceptible to apoptosis.¹⁸ Diabetes also affects the immune system through various pathways. It causes a decrease in production and activation of the complement system, inflammatory cytokines, polymorphonuclear and mononuclear lymphocytes, and antibodies.¹⁹ Hence, a combination of poor wound healing and an impaired immune system could theoretically predispose patients to PJI.

2.2. Diabetes and prosthetic joint infections

Specifically for arthroplasty procedures, several studies identified DM as a risk factor for PJI.^{9–11,20} Kunutsor et al. reported in a meta-analysis on 66 observational studies consisting of 210,087 participants undergoing TJA that diabetes was a significant risk factor for PJI (RR, 1.74; 95% CI = 1.45–2.09).²¹ This finding was likewise reported in another meta-analysis done by Kong et al. on 24 studies showing that DM was a significant risk factor for PJI (OR, 1.58; 95% CI = 1.37–1.81).²²

On the contrary, in a retrospective study carried out by Kremers et al. consisting of 20,171 Total Hip Arthroplasties (THA) and Total Knee Arthroplasties (TKA) patients from the Mayo Clinic registry, DM was found not to be a significant risk factor (RR, 1.23; 95% CI = 0.87–1.74) for PJI after adjusting for variables such as age, gender, body-mass index (BMI), gender, type of surgery (THA vs TKA), American Society of Anesthesiologists (ASA) score and operative time.²³ These confounders including obesity,²⁴ gender^{25,26} and operative time,²⁷ among many others, have been reported to be independent risk factors for PJI in itself. Hence, it is postulated that in studies showing that DM is a significant risk factor for PJI after THA or TKA, this association could possibly be contributed by other confounders instead.

2.3. HbA1c as a predictor

Since the abovementioned pathophysiology behind DM affecting our immune system and wound healing occurs over an extended period of time, traditional means of quantifying diabetic control with capillary blood glucose readings may be inadequate and prone to bias. HbA1c is a reflection of the average plasma glucose in the past 8–12 weeks.²⁸ Unlike capillary blood glucose level which only provides a momentary reading, HbA1c is thought to be more accurate in assessing recent glycaemic control as it is dependent on the lifespan of the red blood cell before it is metabolized by the body and is less susceptible to transient fluctuations in diet or insulin changes.²⁸ Recently, there has been changes in clinical practice guidelines in various countries such as introducing HbA1c as a screening diagnostic tool for DM.^{29,30} Hence, with a strong emphasis placed on HbA1c in the diagnosis and management of DM, as well as the fact that good diabetic control is important in reducing infection risk, it follows that a deranged HbA1c reading could be a surrogate marker for infection risk.

Studies attempting to elucidate a pre-operative HbA1c value predictive of PJI risk have been largely contentious. A recent systematic review and meta-analysis carried out by Shohat et al., in 2018 consisting of 10 studies showed that elevated levels of HbA1c were

associated with a higher risk of infection after TJA (pooled OR = 1.49, 95% CI = 0.94–2.37; $p = 0.09$), although there were significant heterogeneity between studies ($I^2 = 81.32\%$; $p < 0.0001$). However, on further sub-group analysis with a HbA1c of 7%, this association was no longer noticed ($p = 0.50$).³¹ In a systematic review carried out by Lopez, L.F et al. consisting of 13 studies, 5 larger studies having 1,513 to 55,408 participants found that high levels of HbA1c levels (above HbA1c $\geq 7\%$) did not result in an increased rate of PJI. On the contrary, the smaller studies consisting of 30 to 462 participants demonstrated an increased rate of PJI with higher levels of HbA1c.³² In a separate systematic review done by K.E. Rollins et al., high HbA1c of 7% prior to surgery was also not related to an increased risk of PJI.³³ However, it is important to note that the various papers included in these systematic reviews contained data which were highly variable and difficult to analyse. This variability stemmed from the definitions of adequate long term glycaemic control where arbitrary values of HbA1c are used as cut-offs and whether they are analysed as a continuous variable. In addition, the variability in demographics and variables collected from patient data also made it difficult to be consistent in analysis too. Currently, the American Diabetes Association recommends a HbA1c threshold of 7.0% prior to surgery.³⁴ However, if tight glycaemic control is sought prior to surgery, and the value of 7.0% is strictly followed, patients with a higher HbA1c may end up having their surgery delayed.³⁵ In terms of the upper limit of HbA1c which is recommended as a threshold level, many studies were unable to recommend an absolute number. Some studies advise an upper limit of 8.0–9.0%, which is more realistic for patient achievability.^{36–38} Till today, there remains uncertainty whether this conundrum is due to the inadequacy for a single instrument to predict for a polyphenotypic disease or ethnicity and demographic differences leading to a variable cut-off among different patient populations.

2.4. Other glycaemic markers as a predictor

Currently, it is not well understood which crucial stage in the management of the patient does hyperglycaemia predispose to PJI. Even less understood is the marker of choice (for instance, capillary blood glucose and HbA1c) to guide management and to optimize the patient before surgery. Important stages for optimizing glycaemic levels could include the pre-operative,³⁹ post-operative⁴⁰ or even the peri-operative stage.⁴¹

A study carried out by Richards et al. reported that stress-induced hyperglycaemia itself, regardless of whether the patient has been previously diagnosed with DM is also a risk factor for PJI.⁴² This led to a recent interest in studying peri-operative and post-operative glycaemic control.

A retrospective study carried out by Chrastil et al. on 13,272 patients found that high pre-operative hyperglycaemia (≥ 194 mg/dL), which was defined as the maximum pre-operative glucose measured within 7 days of surgery, is a significant risk factor of PJI (HR = 1.44; 95% CI = 1.10–1.89; $p = 0.008$).⁴³ In the retrospective study carried out by Kremers et al., when adjusted for age and gender, peri-operative hyperglycaemia (> 180 mg/dL) did show an association with PJI (OR 1.59; 95% CI = 1.07–2.35). However, this association was not seen on further adjusting for BMI, type of surgery, ASA score, operative time and diabetes diagnosis.²³

Apart from pre- and peri-operative blood glucose, post-operative blood glucose has also been shown to be associated with PJI after TJA. A retrospective study carried out by Kheir, M. M et al. showed that the rate of PJI was significantly associated with, and increases linearly with blood glucose levels from 115 mg/dL ($p = 0.028$) and the optimal glucose level to reduce PJI would be 137 mg/dL, where post-operative glucose was defined as the fasting glucose on the first post-operative day.⁴⁰ In addition, Shohat, N et al. showed that high post-operative blood glucose level variability is associated with increased rates of SSI and PJI risks where adjusted analysis for every 10% point increase in

the coefficient of variation the risks of periprosthetic joint infection and surgical site infection increased by 20% (OR = 1.20, 95% CI = 1.02 to 1.41; $p = 0.03$) and 14% (OR = 1.14, 95% CI = 1.00 to 1.31; $p = 0.06$), respectively. In this study, post-operative glucose levels were measured twice daily with a bedside point-of-care capillary glucose test, at least 5 min apart.⁴⁴ Hence, apart from the absolute post-operative glucose levels, variability in the levels post-operatively is also thought to be a risk factor for PJI.

2.5. Novel markers

Recently, serum fructosamine, a marker of glycated proteins in the blood has also shown to be associated with PJI after TJA. A study by Burekovic et al. reported a higher rate of infection amongst diabetic patients who had higher serum fructosamine levels.⁴⁵ Specifically for TJA, Shohat et al., in 2017 reported that patients with a fructosamine level of $\geq 292 \mu\text{mol/L}$ had a significantly higher risk of PJI (OR = 6.2, 95% CI = 1.6 to 24.0; $p = 0.009$). That same study reported that a HbA1c of 7.0% did not show a correlation with an increased risk of PJI too.⁴⁶ In a separate prospective multi-institutional cohort study carried out by Shohat et al., a fructosamine level of $293 \mu\text{mol/L}$ was found to be a statistically significant cut-off value for TJA associated with complications. In that study, patients with a serum fructosamine level of $> 293 \mu\text{mol/L}$ were 11.2 times more likely to develop PJI post-operatively ($p = 0.001$).⁴⁷

3. Discussion

The value of biochemical indices (both HbA1c and blood glucose monitoring) as predictive factors remains elusive. Current pre-operative practices and recommendations such as the use of surgical antibiotic prophylaxis, antiseptic cleaning of the surgical site prior to surgery and draping techniques are effective techniques in lowering the rates of PJI.^{48–50} Since hyperglycaemia at different operative stages can affect different phases of wound healing, relying on a single index may be oversimplifying this clinical conundrum. The HbA1c cut-off value precluding surgery is often quoted to be the 'optimal' value of 7.0% despite mixed conclusions in the literature. We caution against adopting an arbitrary cut-off in clinical practice. Paradoxically, given the low prevalence of PJI with modern aseptic techniques, a low threshold cut-off value will disqualify patients unnecessarily leading to poorer patient care.

There is increasing evidence of serum fructosamine being a good predictor of post-operative PJI. However, it has not seen widespread use in clinical practice. Serum fructosamine is a marker of glycated proteins (majority albumin) and has a half-life of about 21 days.⁵¹ As such, it reflects pre-operative blood glucose levels on a smaller interval. Various studies have also reflected how these shorter term glucose changes affect the body's physiological defences against infections,^{52,53} though further prospective studies should be done in elucidating and solidifying this association.

4. Conclusion

Given that effective modern aseptic practices are in place, more research needs to be done in addressing the role of glycaemic control and better-defined cut-offs, since it may ironically result in unnecessary harm to our patients by setting an unrealistic goal for patients and preventing timely surgery. Serum fructosamine has recently shown to be a novel marker of interest for predicting post-operative PJI, though future studies should look into examining this association.

Declaration of competing interest

None.

References

- Jones CA, Voaklander DC, Johnston DW, Suarez-Almazor ME. Health related quality of life outcomes after total hip and knee arthroplasties in a community based population. *J Rheumatol*. 2000;27:1745–1752.
- Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;17:961–969. <https://doi.org/10.2337/diacare.17.9.961>.
- Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. *Casp J Intern Med*. 2011;2:205–212.
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27:1047–1053. <https://doi.org/10.2337/diacare.27.5.1047>.
- Zsin Woon T, Zainal K. Successful ageing: progressive governance and collaborative communities. Civ Serv Coll Singapore; 2018 accessed <https://www.csc.gov.sg/articles/successful-ageing-progressive-governance-and-collaborative-communities>, Accessed date: 16 July 2019.
- Sharkey PF, Lichstein PM, Shen C, Tokarski AT, Parvizi J. Why are total knee arthroplasties failing today—has anything changed after 10 Years? *J Arthroplasty*. 2014;29:1774–1778. <https://doi.org/10.1016/j.arth.2013.07.024>.
- Sadoghi P, Liebensteiner M, Agreiter M, Leithner A, Böhler N, Labek G. Revision surgery after total joint arthroplasty: a complication-based analysis using worldwide arthroplasty registers. *J Arthroplasty*. 2013;28:1329–1332. <https://doi.org/10.1016/j.arth.2013.01.012>.
- Bozic KJ. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. *J Bone Jt Surg*. 2005;87:1746. <https://doi.org/10.2106/JBJS.D.02937>.
- Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *J Hosp Infect*. 2015;89:82–89. <https://doi.org/10.1016/j.jhin.2014.10.008>.
- Lee QJ, Mak WP, Wong YC. Risk factors for periprosthetic joint infection in total knee arthroplasty. *J Orthop Surg*. 2015;23:282–286. <https://doi.org/10.1177/230949901502300303>.
- 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. *Bone Joint Lett J*. 2014;96-B:1637–1643. <https://doi.org/10.1302/0301-620X.96B12.34378>.
- Teo BJX, Chong H-C, Yeo W, Tan AHC. The impact of diabetes on patient outcomes after total knee arthroplasty in an asian population. *J Arthroplasty*. 2018;33:3186–3189. <https://doi.org/10.1016/j.arth.2018.06.021>.
- Almustafa MA, Ewen AM, Deakin AH, Picard F, Clarke JV, Mahmood FF. Risk factors for surgical site infection following lower limb arthroplasty: a retrospective cohort analysis of 3932 lower limb arthroplasty procedures in a high volume Arthroplasty unit. *J Arthroplasty*. 2018;33:1861–1867. <https://doi.org/10.1016/j.arth.2018.01.037>.
- Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol*. 2001;22:607–612. <https://doi.org/10.1086/501830>.
- Jämsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection. *J Bone Jt Surg Am*. 2012;94:1–9. <https://doi.org/10.2106/JBJS.J.01935> e101.
- Dryden M, Baguneid M, Eckmann C, et al. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. *Clin Microbiol Infect*. 2015;21:S27–S32. <https://doi.org/10.1016/j.cmi.2015.03.024>.
- Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care*. 1999;22:1408–1414. <https://doi.org/10.2337/diacare.22.9.1408>.
- Okonkwo U, DiPietro L. Diabetes and wound angiogenesis. *Int J Mol Sci*. 2017;18:1419. <https://doi.org/10.3390/ijms18071419>.
- Alves C, Casqueiro J, Casqueiro J. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metab*. 2012;16:27. <https://doi.org/10.4103/2230-8210.94253>.
- Wu C, Qu X, Liu F, Li H, Mao Y, Zhu Z. Risk factors for periprosthetic joint infection after total hip arthroplasty and total knee arthroplasty in Chinese patients. *PloS One*. 2014;9:e95300. <https://doi.org/10.1371/journal.pone.0095300>.
- Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Patient-related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *PloS One*. 2016;11:e0150866. <https://doi.org/10.1371/journal.pone.0150866>.
- Kong L, Cao J, Zhang Y, Ding W, Shen Y. Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis. *Int Wound J*. 2017;14:529–536. <https://doi.org/10.1111/iwj.12640>.
- Maradit Kremers H, Lewallen LW, Mabry TM, Berry DJ, Berbari EF, Osmon DR. Diabetes mellitus, hyperglycemia, hemoglobin A1C and the risk of prosthetic joint infections in total hip and knee arthroplasty. *J Arthroplasty*. 2015;30:439–443. <https://doi.org/10.1016/j.arth.2014.10.009>.
- Dowsey MM, Choong PFM. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. *Clin Orthop Relat Res*. 2008;466:153–158. <https://doi.org/10.1007/s11999-007-0016-3>.
- Robinson J, Shin JI, Dowdell JE, Moucha CS, Chen DD. Impact of gender on 30-day complications after primary total joint arthroplasty. *J Arthroplasty*. 2017;32:2370–2374. <https://doi.org/10.1016/j.arth.2017.03.001>.
- Basques BA, Bell JA, Sershon RA, Della Valle CJ. The influence of patient gender on

- morbidity following total hip or total knee arthroplasty. *J Arthroplasty*. 2018;33:345–349. <https://doi.org/10.1016/j.arth.2017.09.014>.
27. Teo BJX, Yeo W, Chong H-C, Tan AHC. Surgical site infection after primary total knee arthroplasty is associated with a longer duration of surgery. *J Orthop Surg*. 2018;26. <https://doi.org/10.1177/2309499018785647> 2309499018785647.
 28. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia*. 2007;50:2239–2244. <https://doi.org/10.1007/s00125-007-0803-0>.
 29. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42:S13–S28. <https://doi.org/10.2337/dc19-S002>.
 30. Chua R. *USE OF HAEMOGLOBIN A1C (“HbA1c”) AS A SCREENING TEST FOR DIABETES MELLITUS – REGULATORY REGIME*. Minist Heal Singapore; 2019. <https://www.moh.gov.sg/docs/librariesprovider5/default-document-library/circular-on-hba1c-test-for-dm-docxcba8dbdf8496453b86e0ed5b8b454b51.pdf>, Accessed date: 16 July 2019.
 31. Shohat N, Muhsen K, Gilat R, Rondon AJ, Chen AF, Parvizi J. Inadequate glycemic control is associated with increased surgical site infection in total joint arthroplasty: a systematic review and meta-analysis. *J Arthroplasty*. 2018;33:2312–2321. <https://doi.org/10.1016/j.arth.2018.02.020> e3.
 32. Lopez LF, Reaven PD, Harman SM. Review: the relationship of hemoglobin A1c to postoperative surgical risk with an emphasis on joint replacement surgery. *J Diabet Complicat*. 2017;31:1710–1718. <https://doi.org/10.1016/j.jdiacomp.2017.08.016>.
 33. Rollins KE, Varadhan KK, Dhataria K, Lobo DN. Systematic review of the impact of HbA1c on outcomes following surgery in patients with diabetes mellitus. *Clin Nutr*. 2016;35:308–316. <https://doi.org/10.1016/j.clnu.2015.03.007>.
 34. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41:S55–S64. <https://doi.org/10.2337/dc18-S006>.
 35. Giori NJ, Ellerbe LS, Bowe T, Gupta S, Harris AHS. Many diabetic total joint arthroplasty candidates are unable to achieve a preoperative hemoglobin A1c goal of 7% or less. *J Bone Jt Surg*. 2014;96:500–504. <https://doi.org/10.2106/JBJS.L.01631>.
 36. Dhataria K, Levy N, Kilvert A, et al. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes *. *Diabet Med*. 2012;29:420–433. <https://doi.org/10.1111/j.1464-5491.2012.03582.x>.
 37. Cizmic Z, Feng JE, Huang R, et al. Hip and knee section, prevention, host related: proceedings of international consensus on orthopedic infections. *J Arthroplasty*. 2019;34:S255–S270. <https://doi.org/10.1016/j.arth.2018.09.010>.
 38. Underwood P, Askari R, Hurwitz S, Chamarthi B, Garg R. Preoperative A1C and clinical outcomes in patients with diabetes undergoing major noncardiac surgical procedures. *Diabetes Care*. 2014;37:611–616. <https://doi.org/10.2337/dc13-1929>.
 39. Godshaw BM, Ojard CA, Adams TM, Chimento GF, Mohammed A, Waddell BS. Preoperative glycemic control predicts perioperative serum glucose levels in patients undergoing total joint arthroplasty. *J Arthroplasty*. 2018;33:S76–S80. <https://doi.org/10.1016/j.arth.2018.02.071>.
 40. Kheir MM, Tan TL, Kheir M, Maltenfort MG, Chen AF. Postoperative blood glucose levels predict infection after total joint arthroplasty. *J Bone Jt Surg*. 2018;100:1423–1431. <https://doi.org/10.2106/JBJS.17.01316>.
 41. Alamanda VK, Springer BD. Perioperative and modifiable risk factors for periprosthetic joint infections (PJI) and recommended guidelines. *Curr Rev Musculoskelet Med*. 2018;11:325–331. <https://doi.org/10.1007/s12178-018-9494-z>.
 42. Richards JE, Kauffmann RM, Obremskey WT, May AK. Stress-induced hyperglycemia as a risk factor for surgical-site infection in nondiabetic orthopedic trauma patients admitted to the intensive care unit. *J Orthop Trauma*. 2013;27:16–21. <https://doi.org/10.1097/BOT.0b013e31825d60e5>.
 43. Chrastil J, Anderson MB, Stevens V, Anand R, Peters CL, Pelt CE. Is hemoglobin A1c or perioperative hyperglycemia predictive of periprosthetic joint infection or death following primary total joint arthroplasty? *J Arthroplasty*. 2015;30:1197–1202. <https://doi.org/10.1016/j.arth.2015.01.040>.
 44. Shohat N, Restrepo C, Allierezaie A, Tarabichi M, Goel R, Parvizi J. Increased postoperative glucose variability is associated with adverse outcomes following total joint arthroplasty. *J Bone Jt Surg*. 2018;100:1110–1117. <https://doi.org/10.2106/JBJS.17.00798>.
 45. Burekovic A, DizdarevicBostandzic A, Godinjak A. Poorly regulated blood glucose in diabetic patients-predictor of acute infections. *Med Arch*. 2014;68:163. <https://doi.org/10.5455/medarch.2014.68.163-166>.
 46. Shohat N, Tarabichi M, Tischler EH, Jabbour S, Parvizi J. Serum fructosamine: a simple and inexpensive test for assessing preoperative glycemic control. *J Bone Joint Surg Am*. 2017;99:1900–1907. <https://doi.org/10.2106/JBJS.17.00075>.
 47. Shohat N, Tarabichi M, Tan TL, et al. John Insall Award: fructosamine is a better glycaemic marker compared with glycated haemoglobin (HbA1C) in predicting adverse outcomes following total knee arthroplasty. *Bone Joint Lett J*. 2019;101-B:3–9. <https://doi.org/10.1302/0301-620X.101B7.BJJ-2018-1418.R1>.
 48. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhawe A, Mont MA. Periprosthetic joint infection. *Lancet*. 2016;387:386–394. [https://doi.org/10.1016/S0140-6736\(14\)61798-0](https://doi.org/10.1016/S0140-6736(14)61798-0).
 49. Fletcher N. Prevention of perioperative infection. *J Bone Jt Surg*. 2007;89:1605. <https://doi.org/10.2106/JBJS.F.00901>.
 50. Siddiqi A, Forte SA, Docter S, Bryant D, Sheth NP, Chen AF. Perioperative antibiotic prophylaxis in total joint arthroplasty. *J Bone Jt Surg*. 2019;101:828–842. <https://doi.org/10.2106/JBJS.18.00990>.
 51. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. *Clin Chim Acta*. 1983;127:87–95. [https://doi.org/10.1016/0009-8981\(83\)90078-5](https://doi.org/10.1016/0009-8981(83)90078-5).
 52. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans. *Circulation*. 2002;106:2067–2072. <https://doi.org/10.1161/01.CIR.0000034509.14906.AE>.
 53. Turina M, Miller FN, Tucker CF, Polk HC. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. *Ann Surg*. 2006;243:845–853. <https://doi.org/10.1097/01.sla.0000220041.68156.67>.