Editorial

Fructosamine: a promising new risk stratification tool?

Afshin A. Anoushiravani, James E. Feng, Ran Schwarzkopf

NYU Langone Health, Department of Orthopaedic Surgery, NYU Langone Orthopedic Hospital, New York, NY, USA

Correspondence to: Ran Schwarzkopf, MD, MSc. NYU Langone Health, Department of Orthopaedic Surgery, NYU Langone Orthopedic Hospital, 301 E. 17th St., New York, NY 10003, USA. Email: schwarzk@gmail.com.

Comment on: Shohat N, Tarabichi M, Tischler EH, *et al*. Serum Fructosamine: A Simple and Inexpensive Test for Assessing Preoperative Glycemic Control. J Bone Joint Surg Am 2017;99:1900-7.

Received: 27 February 2018; Accepted: 12 March 2018; Published: 04 April 2018.

doi: 10.21037/amj.2018.03.18

View this article at: http://dx.doi.org/10.21037/amj.2018.03.18

Diabetes mellitus is one of the most common chronic conditions worldwide, affecting an estimated 422 million individuals (1). Disrupted insulin production and resistance to insulin leads to aberrant carbohydrate metabolism. Left untreated, chronically elevated blood sugars damages capillary walls and causes severe end-organ damage. Poor glycemic control is particularly concerning amongst total joint arthroplasty (TJA) candidates as it predisposes patients to suboptimal outcomes in the acute postoperative phase, while also conferring an elevated lifelong risk for revision surgery (*Table 1*). In an effort to ensure the best outcomes, it is essential that clinicians efficiently and reproducibly assess the TJA candidate's glycemic status prior to surgery.

Current glycemic monitoring measures

Currently, glycemic control is primarily evaluated using two strategies: plasma glucose and glycated hemoglobin (HbA1c) levels (*Table 2*). Although both tests are readily available and cost effective, their prognostic capabilities in TJA candidates have been limited (3). Plasma glucose is highly sensitive to pre-testing condition variabilities, such as food ingestion, diurnal changes, acute stress, and common medications (e.g., corticosteroids, beta-blockers, diuretics, fibrates, cyclosporine, and sulfamethoxazole) (4). HbA1c has also been well recognized to perform poorly in specific patient populations including the elderly, non-Hispanic blacks, individuals with iron deficiency anemia, malnutrition, and patients with increased red blood cell (RBC) turnover (e.g., major blood loss and hemolytic anemia). As a result of these inconsistencies, the American Diabetes Association (ADA) has acknowledged that in patients with unreliable HbA1c and plasma glucose levels, alternative measures, namely glycosylated albumin (GA) and serum fructosamine (SF), should be obtained.

Albumin is the most abundant extracellular plasma protein, accounting for 60–70% of total serum protein. When combined with glucose, a non-enzymatic reversible reaction occurs (Maillard reaction), yielding GA and water. A further transformation of GA (Amadori rearrangement) forms fructosamine, a relatively stable ketoamine linkage between an albumin and glucose (5,6). Hence, because albumin is the most common serum protein, fructosamine is primarily a measure of GA which increases in states of elevated serum glucose concentrations. Compared to hemoglobin, whose life span in RBCs is approximately 90–120 days, albumin and its pre-glycated variants has a much lower half-life ranging from 14–21 days. HbA1c therefore provides a longer-term perspective on glycemic control, whereas GA and SF provide information on the last 2 weeks. Additionally, the rate of non-enzymatic glycation of albumin is approximately 9- to 10-fold greater, suggesting that glycated albumin and its derivatives may more accurately portray glycemic fluctuations than the current long-term and acute indices, HbA1c and plasma glucose, respectively.

Serum fructosamine: is it a simple and inexpensive test for assessing preoperative glycemic control?

Although GA and SF have been demonstrated to accurately and reproducibly detect fluctuations in serum glucose levels, neither have been extensively evaluated and correlated with clinical outcomes within an orthopaedic population. Shohat

Table 1 Prevalence of complications associated with diabetes mellitus as reported by Marchant *et al.* (2)

Complication	Risk with diabetes mellitus
Stroke	3.42 (95% CI: 1.87–6.25; P<0.001)
Urinary tract infection	1.97 (95% CI: 1.61–2.42; P<0.001)
Ileus	2.47 (95% CI: 1.67–3.64; P<0.001)
Postoperative hemorrhage	1.99 (95% CI: 1.38–2.87; P<0.001)
Transfusion	1.19 (95% CI: 1.04–1.36; P=0.011)
Wound infection	2.28 (95% CI: 1.36–3.81; P=0.002)
Death	3.23 (95% CI: 1.87–5.57; P<0.001)

Table 2 Current diagnostic criteria for diabetes mellitus

Method	Laboratory values
Glycosylated hemoglobin (HbA1c)	≥6.5%
Fasting plasma glucose (FPG)	≥126 mg/dL
2-hour plasma glucose	≥200 mg/dL
Random plasma glucose	≥200 mg/dL ×4 times
Serum fructosamine (SF)	287.5 mmol/L

and colleagues (7) are the first to examine the clinical utility of SF as a predictor for adverse outcomes following elective TJA. The investigators included a total of 829 TJA patients from September 2012 to July 2013. Blood samples were preoperatively obtained from all patients 2 to 4 weeks prior to surgery and assessed for HbA1c levels and SF. Fasting plasma glucose (FPG) was also assessed immediately preoperatively and on postoperative day 1. Overall, 119 (14.4%) TJA recipients had a history of diabetes and 308 (37.2%) had HbA1c levels in the pre-diabetic range (5.7–6.4%). Of the 51 patients that had elevated fructosamine levels (≥292 mmol/L), 20 patients (39.2%) had elevated fructosamine levels without an HbA1c ≥7%. Analyses of postoperative outcomes among the cohort demonstrated a six-fold higher risk for deep infection and a three-fold increased risk for hospital readmission and reoperation when fructosamine levels were ≥292 mmol/L. An analysis within the same population comparing patient cohorts with HbA1c levels ≥7% versus <7% failed to correlate with deep infection (P=0.14), hospital readmission (P=1.0), or reoperation (P=0.7).

This retrospective analysis of prospectively collected data is the first large scale study investigating the clinical role of SF and its correlation with commonly measured quality metrics (e.g., infection, hospital readmission, and reoperation rates). The study is well designed and the investigators demonstrate that preoperative elevated levels of fructosamine ≥292 mmol/L are associated with suboptimal clinical outcomes. Although there is a paucity of literature examining SF thresholds and hospital outcomes, the authors derived this cutoff from the poor glycemic control cutoff of HbA1c ≥7% (as described by the American Diabetes Association). This HbA1c cutoff equated to the 94th percentile of patients, which translated to a SF value of 292 mmol/L. Moreover, the study utilized the Elixhauser Comorbidity Index (ECI) (8) to report comorbidity profiles among the TJA patients. The ECI varies from other preoperative risk stratification instruments [e.g., American Society of Anesthesiologists (ASA) (9) and Charleston Comorbidity Index (CCI) (10)] in that it is a validated prognostic indices using 30 binary variables specifically designed to assess a patients risk for in-hospital death. The combination of a relatively large matched study population, standardization of blood draw technique (e.g., patient instructions and intervals), and a substantiated SF threshold suggest that preoperative SF evaluation may be a more sensitive and specific method of preoperatively risk stratifying poor glycemic control TJA with at risk for suboptimal outcomes. In addition to the postoperative TJA advantages associated with preoperative glycemic assessment with SF, the test is clinically pertinent, easy to administer and costs less than $20 USD per study.

The current study has several limitations which may limit the clinical effectiveness of SF within the TJA population. It is well-recognized that SF levels are very sensitive to fluctuations related to metabolic or nutritional disorders resulting in serum protein deficiency (11). Unfortunately, the current study did not assess and normalize for variations in preoperative albumin levels, allowing poor nutritional status to potentially confound the results (12). Aside from the fluctuations in albumin caused by nutritional deficiency, metabolic syndromes, and hepatic and renal disease, the fructosamine threshold used may have been a more conservative estimate than its HbA1c equivalent of 7%. When applying the accepted HbA1c/SF conversion equation [HbA1c = 0.017 (SF) + 1.61] (13), an SF of 292 mmol/L is equivalent to an HbA1c of 6.57%. Conversely, an HbA1c of 7% should be equal to a SF of 317 mmol/L. Interestingly, the study's receiver operator curve (ROC) demonstrated an optimal cutoff of 293 mmol/L for their patient cohort. Although seemingly small, this difference in

HbA1c and SF equivalence demonstrates the strengths and limitations of these glycemic monitoring tests. Furthermore, it is possible that SFs may allude to a more holistic perspective of the patient's metabolic status, combining the effects of suboptimal glycemic control and poor nutritional status, making it a potentially valuable prognostic tool for TJA outcomes. In addition, as mentioned by the authors there is currently no literature to suggest that optimization of SF levels will result in superior clinical outcomes. Lastly, the study may have benefited from a comparative analysis of patients with elevated SF and serum glucose on day of surgery or postoperatively, which several studies have reported to be both predictive for adverse events and cost effective (14,15). Nevertheless, other studies have also suggested that serum fructosamine may be a more effective method of monitoring diabetic control in non-surgical patients (16). Despite these limitations, SF offers patients and providers an alternative to FGP and HbA1c potentially providing TJA candidates with a superior method of evaluating glycemic control.

Summary

In order to better appreciate the predictive capabilities of SF and adverse postoperative outcomes associated with poor glycemic control in TJA patients. Future large scale randomized control trials are needed to better delineate the advantages and disadvantages associated with the preoperative SF values. In response, the American Academy of Hip and Knee Surgeons (AAHKS) has recently sponsored a multi-center study to elucidate the clinical effectiveness associated with SF amongst patients undergoing TJA.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Zhantao Deng, PhD (Department of Orthopedics, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China).

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.03.18). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. WHO. Diabetes. WHO 2017.
2. Marchant MH Jr, Viens NA, Cook C, et al. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am 2009;91:1621-9.
3. Lippi G, Mattiuzzi C, Targher G. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:2030; author reply 2031.
4. Lippi G, Targher G. Glycated hemoglobin (HbA1c): old dogmas, a new perspective? Clin Chem Lab Med 2010;48:609-14.
5. Danese E, Montagnana M, Nouvenne A, et al. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. J Diabetes Sci Technol 2015;9:169-76.
6. Anguizola J, Matsuda R, Barnaby OS, et al. Review: Glycation of human serum albumin. Clin Chim Acta 2013;425:64-76.
7. Shohat N, Tarabichi M, Tischler EH, et al. Serum Fructosamine: A Simple and Inexpensive Test for Assessing Preoperative Glycemic Control. J Bone Joint Surg Am 2017;99:1900-7.
8. van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 2009;47:626-33.
9. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). StatPearls Publishing, 2017.

10. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
11. Greene KA, Wilde AH, Stulberg BN. Preoperative nutritional status of total joint patients. Relationship to postoperative wound complications. J Arthroplasty 1991;6:321-5.
12. Cross MB, Yi PH, Thomas CF, et al. Evaluation of malnutrition in orthopaedic surgery. J Am Acad Orthop Surg 2014;22:193-9.
13. Cohen RM, Holmes YR, Chenier TC, et al. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care 2003;26:163-7.
14. Hwang JS, Kim SJ, Bamne AB, et al. Do glycemic markers predict occurrence of complications after total knee arthroplasty in patients with diabetes? Clin Orthop Relat Res 2015;473:1726-31.
15. Stryker LS, Abdel MP, Morrey ME, et al. Elevated postoperative blood glucose and preoperative hemoglobin A1C are associated with increased wound complications following total joint arthroplasty. J Bone Joint Surg Am 2013;95:808-14, S1-2.
16. Austin GE, Wheaton R, Nanes MS, et al. Usefulness of fructosamine for monitoring outpatients with diabetes. Am J Med Sci 1999;318:316-23.

doi: 10.21037/amj.2018.03.18
Cite this article as: Anoushiravani AA, Feng JE, Schwarzkopf R. Fructosmaine: a promising new risk stratification tool? AME Med J 2018;3:53.