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Orthopedic & Muscular System: Current research

Review Article

Glycemic Markers in Operative Orthopaedics-Is Fructosamine Better than HbA1c

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ABSTRACT

An accurate glycemic control is dependent on an ideal glycemic marker to identify the patient at risk for complications after orthopaedic surgery. Recent evidences suggest that it is not the chronically elevated glucose levels that account for a higher postoperative risk of complications, rather the levels in the immediate peri-operative period. The purpose of this literature review is to look into the latest advances in glycemic markers, given the significance of diabetes in operative orthopaedics. Various indices in current practise includes-the traditional ones being plasma blood glucose (Fasting, Post prandial, Random sample), and Glycosylated Hemoglobin (HbA1c), and the novel markers Serum Fructosamine (SF), Glycated Albumin (GA) and 1,5-Anhydroglucitol (1,5-AG). Multi-centric studies and systematic reviews have shown inconsistent association between the conventional HbA1c cut off and Peri-Prosthetic Joint Infection (PJI). Serum fructosamine seems to be a more promising marker for pre-operative glycemic optimisation in orthopaedics since it reflects glycemic control over 2-3 weeks, and assays are rapid, inexpensive, and and values are not affected by the limitations of HbA1c.

Keywords: Peri-prosthetic joint infection; Arthroplasty; Diabetes; Glycemic markers; Serum fructosamine; HbA1c; 1,5-Anhydroglucitol; Glycated albumin

INTRODUCTION

World Health Organisation (WHO) describes Diabetes Mellitus (DM) as a 'metabolic disorder with heterogenous aetiologies which is characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both' [1]. Diabetes mellitus have become one of the most important public health challenge for all nations and the disease burden is projected to increase globally [2].

Diabetes is a common co-morbidity in orthopaedics. The disease increases the risk of osteoporosis and fragility fractures, either inherently or due to the effect of anti-diabetic therapy on bone metabolism [3]. Compared to other surgical streams, a larger part of orthopaedic surgeries use implants in trauma, arthroplasty, arthroscopy, spine or deformity corrective surgery. Even though diabetes mellitus is associated with many intra- and post-operative complications, post-operative infection is always a nightmare to the surgeon especially where the surgery includes an implant, either metallic or bio-absorbable. Individual studies have reported higher rates of infection, wound complications, deep vein thrombosis, poorer functional outcomes and higher mortality in patients with diabetes undergoing major joint replacement compared with patients without diabetes [4-18]. Those with poor glycemic control appear to be at further increased risk. Various meta-analysis also substantiates the fact that in patients undergoing Total Joint Arthroplasty (TJA) diabetes was a significant risk factor for peri-prosthetic joint infection [19,20].

Hyperglycaemia in a diabetic patient undergoing surgery may be categorised as pre-, peri- and post-operative. Peri-operative hyperglycaemia has been associated with postoperative infections following surgery, increased mortality in emergency surgeries, and longer hospital stay following joint replacement [21]. Surgery itself causes metabolic stress and catabolic hormone secretion that induces transient hyperglycaemia. Starvation in the pre-op period adds to this metabolic stress. Post-operatively there is a period of insulin resistance causing a period of

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Received date: June 9, 2020; **Accepted date:** June 17, 2020; **Published date:** June 25, 2020

Citation: Govindan NO (2020) Glycemic Markers in Operative Orthopaedics-Is Fructosamine Better than HbA1c. Orthop Muscular Syst 9:279. doi:10.35248/2161-0533.2020.9.279.

functional insulin insufficiency. Diabetic patients are unable to respond to this increased demand for insulin [22]. A recent study found that early management of diabetes starting nearly 2 weeks before surgery resulted in improved intra-operative and post-operative glycemic control and a shorter length of hospital stay [23]. Even in the absence of diabetes, transient hyperglycaemia in the peri-operative period has been shown to be an important risk factor for post-operative infection in orthopaedic surgery [24].

Unfortunately, both the absolute numbers of joint replacement surgery as well as the prevalence of diabetes among patients undergoing total joint replacement are on the rise [25]. An accurate glycemic control is dependent on an ideal glycemic marker to identify patients at risk for complications after orthopaedic surgery. The purpose of this literature review is to look into the recent advances about the glycemic markers, given the significance of DM in operative orthopaedics. Better knowledge about the glycemic markers helps in better optimisation of the surgical patient. Various indices in current practise includes-the traditional ones being plasma blood glucose (Fasting, Post prandial, Random sample), and Glycosylated Hemoglobin (HbA1c), and the newer markers Serum Fructosamine (SF), Glycated Albumin (GA) and 1,5-Anhydroglucitol (1,5-AG).

We aim to go through the pros and cons of each glycemic markers based on the recent available literature, and identify whether HbA1c or SF is a better marker for pre-operative glycemic control.

PLASMA GLUCOSE

Plasma glucose offers a direct measure through a readily available assay with fasting levels of glucose ≥ 140 mg/dL and random values ≥ 180 mg/dL used as the thresholds for hyperglycaemia in the inpatient setting [26]. An International Consensus Meeting held in 2013 to identify the best practices for prevention of PJI recommends a glucose level <200 mg/dl for peri-operative glycemic control [27].

The efficacy of fasting or random plasma glucose levels in predicting the risk of postoperative complications remains inconclusive. This is because plasma glucose gives a snapshot of a control that is highly variable, causing an exceptionally high rate of false negatives and low test sensitivity [28]. Besides, plasma glucose may be elevated with increased stress and metabolic demand typically encountered during an operative procedure, leading to a high rate of false positive results and low test specificity [28].

Additionally, plasma glucose is also altered by a number of factors including recent food ingestion, sample storage, high within-subject biological variability, acute stress and diurnal variations, common drugs which influence glucose metabolism like diuretics, beta-blockers, corticosteroids, thyroid hormone etc. [29], making it an unsatisfactory marker for glycemic control.

GLYCOSYLATED HEMOGLOBIN (HbA1c)

Glycosylated hemoglobin is formed through the non-enzymatic attachment of glucose to haemoglobin in circulating erythrocytes and is a reflection of the average plasma glucose in the past 8 weeks to 12 weeks [30]. HbA1c is thought to be a more accurate measure of glycemic control as it is dependent on the lifespan of the red blood cells and is less susceptible to transient fluctuations in diet or insulin changes.

HbA1c is considered the 'reference standard' for monitoring glycemic control and has proved to be important not just in the management of diabetic patients [31] but also as a predictor of diabetic micro-vascular and macro-vascular complications; and interventions that reduce HbA1c correspondingly reduce the risk of these complications [32,33]. Currently, the American Diabetes Association recommends an HbA1c threshold of 7.0% for non-pregnant adults with diabetes prior to surgery [34]. Unfortunately, in a real life setting, not only are the diabetic patients unable to achieve a preoperative cut off of <7%, the mean duration for reaching adequate glycemic control takes many months.

Besides, glycemic control based on HbA1c levels has not been consistently associated with adverse outcomes post-surgery. A retrospective review of 4241 Total Knee Arthroplasty (TKAs) or Total Hip Arthroplasty (THAs) performed at a single centre found that patient HbA1c levels were not reliable predictors of the risk of infection after total joint arthroplasty [35]. Furthermore, the conventional cut-off HbA1c level of less than or equal to 7 was reported to have poor predictive value for the development of postoperative wound complications and prosthetic joint infection [36].

Table 1: Common conditions causing inaccuracies of HbA1c (Adapted and modified from Gallagher et al. [37].

HbA1c recording high	HbA1c recording low	HbA1c with variable values
• Iron and vitamin B12 deficiency	• Administration of iron and vitamin B12	• Fetal Hemoglobin
• Chronic renal failure	• Administration of erythropoietin	• Methemoglobin
• Alcoholism	• Reticulocytosis	• Hemoglobinopathies
• Splenectomy	• Vitamin C, E administration	• Aspirin
• Hyperbilirubinemia	• Splenomegaly	
• Opiates	• Rheumatoid arthritis	
	• Hypertriglyceridemia	
	• Drugs - Antiretrovirals, ribavirin, dapsone	

Certain individual studies have identified that patients undergoing surgery with HbA1c ≥ 8 and/or fasting blood glucose ≥ 200 mg/dL were associated with superficial surgical site infection [38]. Multi-centric studies and systematic reviews, attempting to elucidate a pre-operative HbA1c value predictive

of Periprosthetic Joint Infection (PJI) risk, have shown inconsistent association between the conventional HbA1c cut off and PJI [39,40].

Furthermore, HbA1c levels are influenced by a variety of genetic, haematological and other factors making interpretation difficult in such scenarios. Certain well-recognised inaccuracies in measurement of HbA1c have been listed in Table 1.

SERUM FRUCTOSAMINE

Fructosamine is the collective term for plasma protein ketoamines, formed by spontaneous non-enzymatic glycation of serum proteins [41]. Fructosamine is a generic term that refers to not just glycated albumin in serum, but other circulating proteins such as glycated lipoproteins and glycated globulins as well [42]. Because the turnover of human serum albumin is much shorter (half-life ~14 days), fructosamine is a measure of glycemia control in the preceding 2-3 week period [43]. Plasma fructosamine levels ≥ 270 µmol/L is indicative of hyperglycemia and is estimated to correspond with HbA1c ≥ 6.5% [44,45].

Fructosamine captured the attention of Orthopaedics with a recent study that suggested a strong association between elevated fructosamine levels and adverse outcomes following Total Joint Arthroplasty (TJA) in both known diabetics and unknown diabetics who seemed to be adequately controlled based on HbA1c levels [46]. The same group went on to conduct a prospective multi-centric study [47] involving 1119 patients to identify that fructosamine is a valid and an excellent predictor of complications following Total Knee Arthroplasty (TKA). This marker better reflected the glycemic control, had greater predictive power for adverse events, and responded quicker to treatment compared with HbA1c. Patients with fructosamine levels >293 µmol/l had a higher risk for Periprosthetic Joint Infection (PJI), re-admission, and re-operation compared with those with fructosamine below this threshold, and even compared with patients with an elevated HbA1c, who did not show any significant association with the aforementioned complications [47].

Fructosamine is, however, a negative acute phase reactant [48] and is not suggested for use as glycemic biomarker in acutely ill patients. There is an ongoing debate about the need to correct fructosamine values for protein or albumin concentration, but in circumstances where HbA1c is not valid, albumin corrected fructosamine may be a useful glycemic biomarker in acute illness. Unlike HbA1c, fructosamine remains reliable in patients undergoing hemodialysis and renal impairment [49].

GLYCATED ALBUMIN

Glycosylated Albumin or Glycated Albumin (GA) is formed through specific non-enzymatic glycation of albumin [50]. Similar to fructosamine, GA is elevated in the setting of hyperglycaemia and reflects intermediate-term glycemic control over the preceding 2-3 weeks [51,52]. Both fructosamine and GA levels increase in states of abnormally high glucose concentrations, and is used for assessing glucose control over a short to intermediate time frame. GA is a more accurate glycemic indicator than HbA1c in patients with diabetes with chronic kidney disease [53] and is thought to be reliable in patients with anaemia [54].

GA has a tendency to be overestimated in conditions resulting in an extended half-life of albumin, in conditions of low concentration. However, this effect is somewhat mitigated as the level is measured as the proportion of the serum GA to the total albumin (GA/albumin) [55].

1,5-ANHYDROGLUCITOL

1,5-Anhydroglucitol (1,5-AG) is a naturally occurring dietary polyol that is not metabolised in our body. During euglycemia, serum 1,5-AG concentrations are maintained at a constant steady state due to renal tubular reabsorption of all of the serum 1,5-AG [56]. When plasma glucose levels rises to >180 mg/dL, glucose competes with 1,5-AG for reabsorption in the renal tubules, resulting in increased 1,5-AG urinary excretion. Thus, circulating levels of 1,5-AG are inverse to the plasma glucose levels. This marker is FDA approved for use in intermediate-term monitoring of glycemic control in people with diabetes in the United States.

1,5-AG reflects postprandial and day-to-day glucose control over the last one week [57,58] and, hence, offers a shorter- term measure of glycemic control. 1,5-AG is inversely associated with HbA1c and fasting glucose in persons with diagnosed diabetes, and the strongest correlations are observed at the highest glucose concentrations [59]. 1,5-AG can also be used to better differentiate patients with excessive glycemic fluctuations in the presence of near-normal HbA1c values [28,60]. The marker may be of use in elective surgery to detect minor hyperglycaemic variations over a shorter timeframe that happens due to withdrawal oral hypoglycaemic agents.

Comparative properties of the traditional and novel glycemic markers have been listed in Table 2.

	Plasma Glucose	HbA1c	SF	GA	1,5-AG
Span of glycemic control	Instant	8-12 weeks	2-3 weeks	2-3 weeks	1 week
Assay method	Spectrophotometry	Enzymatic	Spectrophotometry	Enzymatic	Colorimetric Enzymatic
Preferred Sample	Serum	Whole blood	Serum	Plasma	Serum

Non-diabetic Reference Range	• Fasting 65 mg/dl- 99 mg/dl • Non fasting 65 mg/dl-139 mg/dl	<5.7% of total Hemoglobin	205 µmol/L-285 µmol/L	11%-15%	12 mcg/mL-40 mcg/mL
Advantages	• Cheap • Snap shot value	• Less susceptible to transient fluctuation in diet, insulin changes • Predictor of long term diabetic complications • Can be used in cirrhosis and Nephrotic syndrome	• Reflects pre-operative glycemic control • Better than HbA1c in anaemia, autologous blood donation and HIV.	• Not affected by serum albumin levels (GA is given as proportion of serum GA to total albumin) • Not affected by RBC life span or variant Hb • Better than HbA1c in kidney disease and chronic anaemia.	• Reflects post prandial glycemic excursion better than HbA1c.
Limitations	• Low sensitivity and specificity	• Does not ref lect short term glycemic changes • Uncertain association with PJI	• Values must be adjusted if serum albumin concentration is abnormal	• Alterations in albumin metabolism	• Applicable only in overt hyperglycaemia (Blood glucose level above renal threshold of 180 mg/dl)
Factors influencing measurement	• Recent food ingestion • Sample storage • Biological variabilities • Acute stress • Diurnal variation • Drugs	• Erythropoietic changes • Altered Hemoglobin • Glycation determinants • Erythrocyte destruction • Assay methodology	• Nephrotic syndrome • Liver diseases • Protein losing enteropathy • Acutely ill patients • increased glycated immunoglobulin or bilirubin	• Smoking • Cirrhosis • Thyroid disease • Hypertriglyceridemia • Hyperuricemia	• Diet • Nutritional status • Renal impairment

DISCUSSION

As far as elective surgery is concerned, in the developing countries, patients often come in the advanced stage of the disease and surgeons may not get time for adequate glycemic control prior to surgery. The existing practice in most of the institutions is to check the plasma glucose levels and HbA1c, and plan surgery accordingly. But HbA1c provides an estimate of average blood glucose levels over the preceding 3 months. Hence, it is unlikely to adequately reflect the fluctuations in glycemia in the days to weeks preceding surgery. This may explain the mixed results obtained in studies that have attempted to correlate HbA1c with adverse surgical outcomes [61-64].

HbA1c is well established as a prognostic marker for long-term diabetes related morbidity in the general diabetic population and provides a standard for the medical management decisions in patient with diabetes. But it is uncertain whether HbA1c is the correct marker for glycemic optimisation of surgical candidates. Multiple literatures including systematic reviews and meta-analysis pertaining to orthopaedics, especially joint replacement surgeries, have failed to identify an exact correlation between HbA1c and post-operative complications. Also, a certain study identified that the mean duration for reaching glycemic control based on HbA1c took nearly 4-5 months [65], which potentially is too long a duration for planned elective surgery.

Recent evidences suggest that it is not the chronically elevated glucose levels that account for a higher postoperative risk of complications in orthopaedics, rather the levels in the immediate peri-operative period [66-72]. Since it is the shorter term glucose changes which affect the body's physiological defences against infections [73,74], it is unlikely that the blood sugar levels during the previous three months of surgery will have an effect on outcome following surgery. It may even be misleading, as a patient could have excellent glycemic control for the preceding 3 months but have very deranged glucose levels in the final few weeks prior to surgery, yet their HbA1c values would be normal [75].

Many alternative glycemic markers have emerged in recent times for shorter and sharper glycemic controls. These novel markers provide certain explicit benefits compared to HbA1c when measured in the preoperative setting. Fructosamine and glycated albumin measures hyperglycemia over the preceding 2-3 weeks compared to three months for glycated haemoglobin represented by HbA1c. Since the glycemic control over a shorter period is being detected, they are better than HbA1c in determining spikes and variations from the mean [42,76]. GA and fructosamine seems useful not only as an alternative index of glycemic control in conditions where HbA1c is unreliable, but

also for identifying impaired control of blood glucose before any noticeable changes in HbA1c may occur, as well as for monitoring diabetics with fluctuating glycemic control [77]. For an HbA1c value of 7%, fructosamine levels corresponds to approximately 312 µmol/L [59] and glycated albumin values are in the range of 16%-22% [77,78].

I,5-AG, on the other hand, reflects the occurrence of glycosuria over the past 1-2 weeks and has an inverse relation with the blood glucose levels. It reflects post prandial glycemic fluctuations better than HbA1c [79] but its clinical use may be limited to those with overt hyperglycaemia where the blood glucose levels exceed the renal threshold. Though these tests have started to become popular in developed countries, they are not popular in the third world regions and there are no definitive guidelines for their use.

Amongst the novel markers, serum fructosamine has been noted by the orthopaedic fraternity due to the large multi centric study indicating a valid association with post-surgical complications; while the other two, GA and 1,5-GA, are yet to find their place in orthopaedic trials. Existing literature states that fructosamine assay costs lesser [28] and this makes it a prospective alternative to HbA1c in developing countries. However, the author, upon independent enquiry, found that the test is not routinely done in his community and different laboratories are quoting variable, higher price compared to HbA1c. This might be due to the unfamiliarity with the newer markers, and given that spectrophotometry is the common assay method for fructosamine, the test may be made available at a much cheaper rate in future.

CONCLUSION

Recent hyperglycaemia seems to be the most important factor for preventing post-operative complications. For any marker to be acceptable in peri-operative hyperglycaemia, it not only must reflect accurate glycemic control but also be easily available, affordable and unaffected by other co-morbidities. Considering that in the developing countries, where patients often come for surgery in advanced stages of the disease and diabetic control based on HbA1c takes long time, it is imperative to rely on a marker reflecting short term glycemic control. The newer glycemic markers include 1,5-AG, GA and SF with span of glycemic control ranging from 1week to 2-3 weeks. There is good correlation between SF and HbA1c values, as well as between SF levels and post-operative complications in orthopaedics. Since the SF assays are rapid, inexpensive, and values are not affected by the limitations of HbA1c, serum fructosamine seems to be a more promising marker for pre-operative glycemic optimisation in orthopaedics.

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