Glycated Hb levels and its effect on outcomes in Cardiac Surgery

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Abstract

There remains a significant paucity of information evaluating the effect of glycated HbA1c levels and its theorized effect on mortality and morbidity rates following cardiac surgery. Diabetes is a very common comorbidity in patients undergoing open heart surgery as there is shift in patient characteristics and being higher risk. Currently, the evidences are controversial and there is no clear consensus that increased HbA1c levels is associated with an increased perioperative mortality rate. However, reported literature are more commonly able to demonstrate elevated HbA1c levels to be associated with increased rates of wound infection, cardiovascular events and renal failure; thus, higher morbidities postoperatively. This literature review aims to examine the evidence synthesis behind each of morbidities and mortalities associated with open heart surgery and the impact of high HbA1c on the reported outcomes.

Introduction:

HbA1c levels refer to the levels of glycated hemoglobin present in the blood. These levels are used to represent the average plasma glucose of the person over the previous 8 to 12 weeks [1]. It is also commonly used to determine whether someone is suffering from diabetes or not. More recently, there has been a substantial amount of interest in using it as a diagnostic test for diabetes, alongside using it as a screening test for those at a great risk of developing diabetes[2].

It is believed that HbA1c levels are viewed as a risk factor for postoperative complications of cardiac surgery and these procedures can result in increased glycated hemoglobin levels, which are associated with increased morbidity and mortality rates. Despite this, some papers state that the increased HbA1c levels cannot be directly attributed as the causes of increased mortality and morbidity [3]. A recent and large meta-analysis reported that a higher HbA1c concentrations are frequently linked with the presence of other metabolic disorders, such as hypertension, dyslipidaemia and obesity, which are in fact the real problems causing an increased risk of poor clinical outcomes. [3]

These beliefs, however, can be viewed as controversial as some other studies showed that diabetes and raised HbA1c levels were independently associated with a higher risk of adverse outcomes [4]. The whole process behind surgical procedures can place a great deal of physical stress on patients and thus impaired glucose metabolisms therefore worsen diabetes status. Those suffering with diabetes and chronic hyperglycaemia, determined by their HbA1c levels, may be at particular risk at suffering from perioperative morbidity from diabetes-related complications such as wound infections and renal dysfunction [5-7].

Literature Search:

A comprehensive literature search was done on PubMed, SCOPUS, Embase, Cochrane database, google scholar and Ovid to identify the articles that discussed the HbA1c, glycated haemoglobin and its implications on perioperative cardiac surgery outcomes. Key words used were 'HbA1c' 'Glycated haemoglobin' 'Cardiac

Surgery' 'Haemoglobin A' 'HbA1c and outcomes' 'Diabetes' 'Diabetic correlation'. The search terms were used as key words and in combination as MeSH terms to maximize the output from literature findings. A staged literature search was done, whereby a separate literature search was performed for each section within this article and all the relevant studies were identified and summarized separately. If a paper is reporting on many aspects of the practice of HbA1C, then the results have been shared between different parts of this review. The relevant articles are cited and referenced within each section separately. No limits were placed on publication time or language of the article.

Pathophysiology of HbA1c

Proteins are frequently glycated during various enzymatic reactions when the conditions are physiologically favourable. However, in the case of hemoglobin A, the glycation occurs by the nonenzymatic reaction between the condensation of glucose and the N-terminal end of the β-chain of hemoglobin A, commonly lysine, forming a Schiff base aldimine[7]. The Schiff base may then undergo a rearrangement, converting into a stable Amadori product, otherwise known as HbA1c[8]. The formation of glycated hemoglobin is a routine part of the physiologic function cycle. It was found that as the average plasma glucose increases, so does the rate of this glycation reaction and the total quantity of HbA1c produced in the plasma[9]. The longer hyperglycaemia occurs in blood, the more glucose binds to hemoglobin in the red blood cells. This results in increased rates of production of glycated hemoglobin. Once a hemoglobin molecule is glycated, it remains that way and its Amadori arrangement is viewed as "nearly irreversible" according to a study from Higgins and Bunn [10]. As a result, this specific characteristic of the hemoglobin is utilized as a biomarker, estimating a humans average blood glucose levels over the previous 2 to 3 months[9].

The glycation of hemoglobin results in the formation of advanced glycation end products (AGEs). Alongside their formation is the accompanied release of free radicals and oxidants as side products from the Amadori rearrangement. These result in oxidative damage to cells and the extracellular matrix of the body tissue [11]. It is found that additionally, the accumulation of these free radicals alters erythrocyte membrane properties leading to erythrocyte aggregation, increased blood viscosity and impaired blood flow [12]. This can result in shear stress, due to thicker abrasive blood consistency which affects the vascular endothelium can result in a number of inflammatory and atherogenic events should the levels become excessive [13]. Following a consultation from the World Health Organization (WHO), it was concluded that HbA1c can be used as a viable diagnostic test for diabetes. This was as long as "stringent quality assurance tests are in place" and assays are kept consistent and standardised to their stated criteria, which are aligned to their internationally set reference values [14]. It is also important that there are no conditions present which interfere with the accuracy of its measurement. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes, according to guidelines set by the World Health Organization [14]. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests [14]. According to the American Diabetes Association (ADA) Guidelines 2020, the value of HbA1c should be kept below 7% in all non-pregnant adult diabetics (53 mmol/mol) [15]. Values greater than 7% indicate an increased chance of progression to diabetic complications, especially microvascular ones. The HbA1c levels appear to be closely related to the blood glucose levels and are resultantly affected by any forms of glycaemic control. An initially raised HbA1c levels has been found to progressively decrease in the weeks following the introduction of insulin and dietary therapy; with a tendency for these values to level out after approximately seven weeks of therapy[16].

HbA1c and mortality rates

As the incidence of Diabetes Mellitus (DM) increases, the proportion of people with DM undergoing cardiac surgery has also increased[17]. There exists a large body of evidence which has looked at the association between patient HbA1c levels and mortality following cardiac surgery. The evidence on the effect of HbA1c levels on mortality is contradictory with some studies reporting that increased HbA1c levels are associated with increased mortality[18–25]. But by in large, most studies seem to show that increased HbA1c is not predictive of increased mortality as solo indicator [26–40]. The findings from all these studies are summarised in Table 1 and Table 2.

The study with the largest patient cohort looked at outcomes in 6,313 patients with type 2 DM who underwent CABG surgery between 2003 and 2013[18]. The study found that HbA1c was associated with an increased risk of death in patients with HbA1c level between 9.1-10.0% (Hazard ratio (HR) 1.26; 95% CI 1.04-1.53), and this risk was even greater in patients with HbA1c >10.0% (HR 1.33; 95% CI 1.05-1.69). Other studies similarly showed that elevated HbA1c was associated with increased mortality [19–25]. One study showed that 30-day mortality was significantly higher in patients with HbA1c greater than 6.5% compared to those with Hb1ac <6.5% (4.22% vs 3.07%; P= 0.0035), however following multivariable adjustment this association was lost and there was no significant difference in the mortality rates [26].

All these studies, overall, demonstrates that increased HbA1c increases mortality in cardiac surgery patients and all of them, with the exception of one, had large sample sizes meaning they were all by in large sufficiently statistically powered to make their findings significant. However, all the aforementioned studies were retrospective in nature meaning they were liable to biases inherent in the study design and the studies do not demonstrate causality.

The largest cohort study demonstrating that there is no relationship between HbA1c levels and mortality looked at outcomes in 6,393 patients undergoing cardiac surgery [27]. The study found that HbA1c was not a significant predictor of post-operative mortality (P= 0.88). Further studies similarly showed that there was no significant difference in mortality following cardiac surgery according to HbA1c levels, regardless of the HbA1c cut-off levels utilised[28–32,34–40].

Overall the evidence showing that there is no significant difference between higher HbA1c levels in the incidence of mortality outweighs evidence showing that elevated HbA1c is associated with increased mortality, suggesting that HbA1c alone may not be predictive of mortality following cardiac surgery.

HbA1c and wound infection

A chronic state of impaired glucose metabolism has long been demonstrated to affect components of the immune system, thereby meaning HbA1c may impact the rate of post-operative infections. Post-operative wound infection affects patient morbidity and length of stay in hospital following cardiac surgery and hence it is important to analyse the relationship between HbA1c levels and infection rate. Some studies that have been carried out have shown that HbA1c level has no effect on the rate of wound infection [28,30,32,39,41]. By contrast, far more studies have demonstrated that elevated HbA1c levels are associated with increased rate of wound infection[20,21,23,26,29,34–37,40,42]. The main outcomes from these studies are summarised in Table 3 and Table 4.

Biskupski *et al* [39] analysed outcomes in 350 patients who were stratified into three groups according to HbA1c levels: <7.0%, 7.0-8.0%, and >8.0%. The study found that there was no significant difference in the incidence of wound infection for the group with HbA1c <7.0% when compared to those with HbA1c 7.0-8.0% and to those with HbA1c >8.0% (1.53% vs 3.40%, P= 0.57 and 1.53% vs 5.97%, P= 0.13 respectively). These findings were replicated in two further studies which showed that HbA1c level had no effect on the incidence of wound infection. In a study where the primary outcome analysed was the incidence of wound infections, it was found that there was no statistically significant difference in the rate of all subset of wound infection in patients with HbA1c <7.0% and in those with HbA1c >7.0% (P=0.431 and P=0.744 for sternal and non-sternal infections respectively) [42].

By contrast, Gatti *et al* [41] specifically looked at whether HbA1c was a risk factor for sternal wound infection following CABG surgery in 2,130 patients and found that the mean baseline HbA1c level was significantly higher in patients who had sternal wound infection (54±17mmol/mol vs 45±13mmol/mol; P< 0.0001). Logistic regression showed that HbA1c level was an independent risk factor for sternal wound infection (OR 1.04; 95% CI 1.02-1.05;P< 0.0001) with an HbA1c level greater than 8.6% being associated with the highest risk of sternal wound infection (OR 5.01; 95% CI 2.47-10.15). Similar results were shown in a range of other studies which all showed that pre-operative elevated HbA1c was associated with increased incidence of both sternal and non-sternal wound infection.

Overall the evidence suggests that elevated HbA1c level is associated with an increased incidence of wound infection in cardiac surgery patients but it is unclear if there is a specific level of HbA1c associated with this increased incidence which could serve as a target for pre-operative glycaemic control as studies used a range of HbA1c cut-offs in their analyses. Yet, further work is required to determine the exact cut-off level and association of HbA1C level and non-sternal wound infections.

Cardiovascular events with poorly controlled HbA1c

Several studies have analysed the relationship between HbA1c levels and the incidence of cardiovascular events such as peri-operative myocardial infarction (MI), atrial fibrillation (AF), and low cardiac output syndrome. The overwhelming body of evidence has demonstrated that HbA1c level alone cannot be used as a predictor for cardiovascular events[29-33]. By contrast, only one study showed a relationship between HbA1c and cardiovascular event which suggested that elevated pre-operative HbA1c may be protective for developing AF[43]. The main outcomes of these studies are summarised in Table 5.

The largest cohort study which demonstrated that there was no relationship between HbA1c level and cardiovascular events analysed outcomes in 1,461 patients undergoing CABG with or without valvular surgery [35]. The study found that there was no difference in the incidence of cardiovascular events in patients with HbA1c <6.5% and >6.5%: AF (26.3% vs 26.6%;P= 0.90), acute MI (0.5% vs 0; P= 0.333) and cardiac tamponade (0 vs 0.2%; P= 0.313). Other studies similarly showed that there was no significant difference in the incidence of cardiovascular events between patients with raised HbA1c levels and those with normal levels[38, 40, 44, 45].

Kinoshita *et al* [43] carried out a retrospective analysis of 912 patients who underwent isolated CABG. They found that median HbA1c was significantly lower in patients who developed AF post-operatively when compared to patients who did not ((5.8%, 95 % CI, 5.4-6.3) vs 6.1%, 95% CI, 5.5-7.2); P= 0.01). Additionally, results also showed that the incidence of post-operative AF showed a stepwise trend where the incidence decreased as HbA1c level decreased: 28.3% incidence for patients with HbA1c [?]5.6%, 17.4% for HbA1c 5.7-6.7% and 12.5% for HbA1c 6.8-11.4% (P= 0.01). These findings suggest that high HbA1c levels may be associated with a lower risk of post-operative AF but this is a single retrospective study carried out on Japanese patients thereby limiting the generality of findings and cannot be used as a sole evidence to support this clinical outcome in general population.

HbA1c and Cerebrovascular accident

Cerebrovascular accident (CVA) is a severe complication following CABG surgery. CVA indicates whether a patient had a stroke (acute neurologic deficit lasting more than 24 hours) or a transient ischemic attack (TIA) (deficit resolving within 24 hours). The meta-analysis by Zheng et al. assessed the effect of HbA1c levels and CVA among diabetic patients (n=4356) undergoing CABG surgery [44]. Their analysis, which included five studies [20,28,45–47] indicated that HbA1c levels were directly correlated with the risk of stroke after CABG surgery (OR 2.07, 95% CI 1.29–3.32, p = 0.003), with very low heterogeneity (I^2 = 0%; p = 0.42). Only one retrospective study significantly indicated a possible role for HbA1c in predicting stroke outcomes[20]. This retrospective study had a comparatively large sample size (n=3089), hence sufficient power to solely elucidate an association between HbA1c levels and stroke. The study indicated that patients with HbA1c values of 7.6% or more have adjusted odds of CVA 2.23 (1.06-4.70) times higher than patients with values below that threshold. The overall incidence of stroke for all patient was very low (1.7%). Other studies were either contradictory [45,46] or inconclusive[28,47] due to small sample sizes and inherent low incidence of stroke.

However, a larger and more recent meta-analysis (n=5,381) conducted by Wang et al. showed that there was no significant difference in stroke incidence between diabetic patients with lower preoperative HbA1c levels and those with higher preoperative HbA1c levels after CABG and PCI (OR 1.49, 95% CI 0.94-2.37, p = 0.37, andI^2 = 8%) [48]. Higher HbA1c levels were defined as preoperative HbA1c [?] 6.5% or 7% and lower HbA1c levels as preoperative HbA1c < 6.5%% or 7%.

Interestingly, Biskupski et al [39] noted that TIAs were more common in patients with HbA1c < 7%, while

strokes were significantly more common in patients with decompensated diabetes (HbA1c < 7% vs HbA1c > 8%, $p = 0.04$). Current research indicates a potential association between the baseline risk of TIA events and exposure to hypoglycaemia[49,50].

HbA1c and renal failure

A recent prospective study reported that acute renal failure is one of the most common complications in the post-CABG in diabetic patients[50]. Compared with diabetic patients with HbA1c [?] 7%, those with HbA1c > 7% had more incidence of renal failure (10% vs. 0%) [47]. Additionally, the results of recent meta-analysis, involving nine studies (n = 5,858), suggested that a higher preoperative HbA1c level was associated with a high risk of renal failure after cardiac surgery (OR = 1.63, 95% CI 1.13-2.33, $p = 0.47$, and $I^2 = 0\%$)[48]. Furthermore, by using receiver operating characteristic value thresholds, Halkos et al. showed that renal failure occurred more commonly in patients with elevated HbA1c (threshold 6.7, odds ratio 2.1) [20]. It is worth noting that the 6.7 threshold derived is the below the 7% glycaemic target of the American Diabetes Association [15].

HbA1c and prolonged hospital stay

There are differences between studies in their definition of a prolonged hospital stay (from [?]3 to 14 days) [51–53], which sheds interesting light on the association between HbA1c and length of hospital stay (LOS).

In a retrospective study (n=570), extended LOS was defined as > 3 days[12]. They found that HbA1c was an independent predictor of hospital stay regardless of blood sugar levels ($p = 0.001$). Moreover, Medhi et al. found similar LOS results in 135 patients who underwent coronary artery bypass surgery; HbA1c [?]7% was found to be strong predictor of LOS [?] 6 days ($p = 0.025$)[52]. However, interestingly, when defining prolonged LOS as [?] 14 days, LOS was not affected by preoperative HbA1c levels (with a cut-off of HbA1c = 7% for optimal and suboptimal levels;$p = 0.367$) [53].

It is noted that diabetic patient's undergoing CABG, HbA1c levels significantly correlated with postoperative length of stay (LOS). Patients with suboptimal medium-term glycaemic control (HbA1c > 7%, n=38) had longer LOS than patients with optimal medium-term glycaemic control (HbA1c [?] 7%, n=57) (mean postoperative LOS 6 days vs. 7.5 days; postoperative LOS mean rank: 32 days vs 46 days; p = 0.008) [47].

The meta-analysis of five studies (n = 3,002) conducted by Wang et al. reported a higher preoperative HbA1c level resulted in a 1.08-day mean increase in hospital stay after cardiac surgery (WMD = 1.08, 95% CI 0.46-1.71) [48].

On the other hand, intensive care stay was not affected by the level of HbA1c as several studies reported no significant difference in ICU days between patients with lower preoperative HbA1c levels and those with higher HbA1c levels after cardiac surgery [45,46,54,55].

Summary

Despite conflicting clinical evidence on higher HbA1c as prognostic marker of poor outcomes post-cardiac surgery, there is universal consensus of possible underlying mechanism of association. Therefore, future research to further elucidate any possible clinical association is warranted. Such research has the potential to improve perioperative cardiac surgery clinical practice guidelines.

HbA1c have significant role in inducing dyslipidaemia, hyperhomocysteinemia, hypertension and increasing C-reactive protein, oxidative stress, and blood viscosity [56]. Cardiac surgery, stress, and anaesthesia can exacerbate oxidative stress and increase blood viscosity, thereby perpetuating the effect of high HbA1c in patients with diabetes and likelihood of devolvement of cardiovascular event [57]. Increased blood viscosity of diabetic patients, leading to blood clots, which can precipitate acute MI [58]. Moreover, high HbA1c can cause vascular endothelial cell damage, due to blood flow shear stress, with increased cellular proliferation [59–62], which can cause MI and stroke after coronary artery stenting [63]. Chronic hyperglycaemia-induced dysmetabolism, weakens chemokine chemotaxis and decreases immune function in patients with diabetes[64]. This increases likelihood of wound infection post-cardiac surgery and increases collateral tissue damage upon

infection. For these reasons, high preoperative HbA1c levels may be predictive of a prolonged postoperative hospital stay.

Future Directions

In this review we have discussed both retrospective and prospective studies that have looked at HbA1c as predictor of various postoperative adverse outcomes. However, the majority of these studies had small sample sizes, thus from onset limited ability to draw statistically meaningful conclusions about adverse outcomes of inherently low event rates in any cohort; reduced statistical power and possible type II statistical error. Moreover, studies have used different cut-off values of preoperative HbA1c levels, such as 6.5%, 7%, 7.5%, and 8%. Further research should be directed at determining a preoperative cut-off of 'suboptimal glycaemic control' for pre-operative optimisation clinical guidelines of the surgical patient.

A recent retrospective study by Kim et al. of 703 patients with diabetes mellitus who underwent off-pump coronary artery bypass surgery(OPCAB) provides strongest evidence to date of prognostic role of HbA1c [25]. The use of composite of postoperative morbidity and mortality (CMM) endpoints (permanent stroke, prolonged ventilation, deep sternal wound infection, renal failure, reoperation, and 30-day mortality) attenuates the prospect of a misleading statistical conclusion by combining adverse events of low incidence. Kim et al. found that incidence of CMM endpoints was greater in patients with HbA1c [?]7.0% (21% vs 15%, $P = .041$). Moreover, receiver operator-characteristic curve analysis revealed HbA1c 7.85% as the optimal threshold for CMM endpoints (area under the curve; 0.556, 95% CI, 0.501-0.611, $P = .048$). This study has provided rationale for future prospective studies with sufficient power to examine whether postponing cardiac surgery in patients with high preoperative HbA1c levels would improve postoperative outcomes.

Moreover, Kim et al. indicated that high preoperative HbA1c ([?]7.0%) level alone, and not the variables related to perioperative glycemic control, was independently associated with adverse outcome in diabetic patients undergoing OPCAB, although high HbA1c levels contributed to greater perioperative glycemic variability[25]. However, a randomised controlled trial conducted by Blaha et al. suggested that it is cardiac surgery patients with previously undiagnosed diabetes who have the worst prognosis[65]. Comparable conclusion was suggested in non-cardiac studies [66,67]. Recent studies have shown that perioperative intravenous insulin infusion is more frequently administered in known diabetics due to more frequent monitoring of their capillary glucose concentrations [25,68]. However, despite more frequently administered insulin in the high HbA1c group, adverse outcomes remained more prevalent in this group compared to normal HbA1c group, thereby further attenuating prognostic role of HbA1c. Nevertheless, optimisation of pre-operative HbA1c concentrations with a combined intravenous and subcutaneous insulin glucose has been shown to reduce surgical mortality and morbidity in diabetic patients undergoing cardiac surgery[69].

Future research should be directed at the determining the optimal level of perioperative glycaemic management and the crucial perioperative period to maintain this HbA1c level. Although there are current ongoing outcome studies currently in this area (e.g. the Optimising Cardiac Surgery outcomes in People with diabetes (OCTOPUS) trial – protocol number HTA16/25/12), there remain few data on the outcomes and effects of intervention on those not known to have diabetes[70].

Conclusion:

The cohorts of patients undergoing cardiac surgery are shifting to be a higher risk than a decade ago with more diabetes and other comorbidities; therefore, poorly controlled diabetes and deranged pre-operative HbA1c can have detrimental effect on outcomes post cardiac surgery and significantly affecting morbidity. Optimum peri-operative diabetes control can help in minimizing complications post-operatively.

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