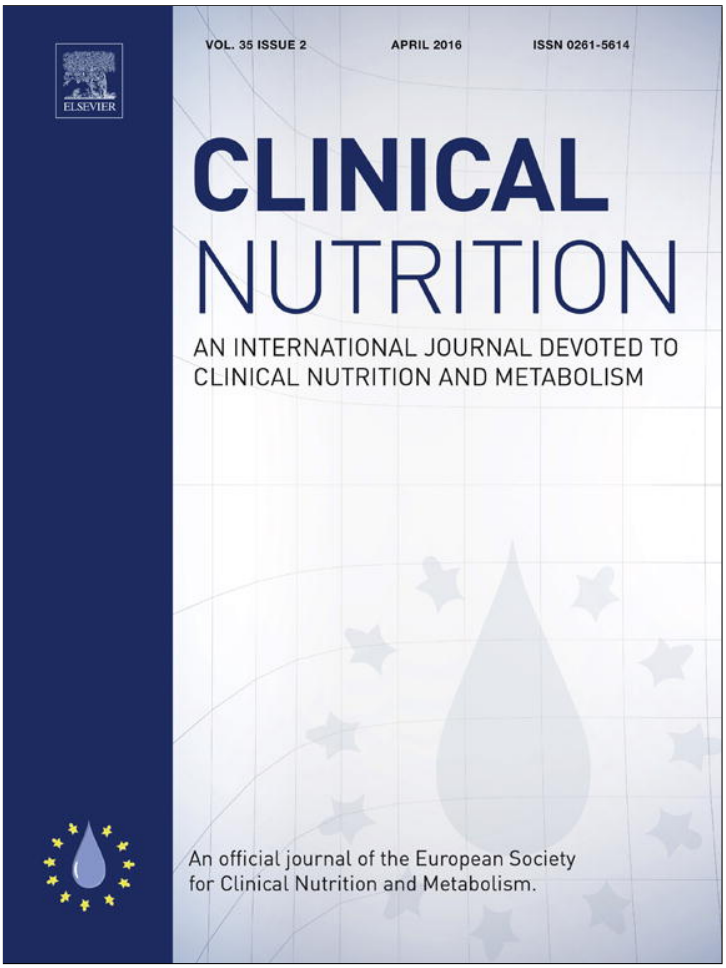

Clinical Nutrition 35 (2016) 308–316

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Systematic review of the impact of HbA1c on outcomes following surgery in patients with diabetes mellitus

Katie E. Rollins [a], Krishna K. Varadhan [a], Ketan Dhatariya [b], Dileep N. Lobo [a, *]

[a] Division of Gastrointestinal Surgery, Nottingham Digestive Diseases Centre National Institute for Health Research Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, UK
[b] Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich NR4 7UY, UK

ARTICLE INFO

Article history:
Received 8 December 2014
Accepted 9 March 2015

Keywords:
Diabetes mellitus
HbA1c
Surgery
Outcome
Complications

SUMMARY

Background & aims: Diabetes is a significant risk factor for surgical complications and also increases the prevalence of comorbidities, thereby increasing surgical risk. The aim of this systematic review was to establish the relationship between long-term preoperative glycemic control as measured by HbA1c and postoperative complications.
Methods: A systematic search was conducted to source articles published between 1980 and 2014 pertinent to the review. Full-text articles were included if they met the pre-determined criteria as determined by two reviewers. Studies reporting the impact of preoperative HbA1c levels on postoperative outcomes in all disciplines of surgery were included.
Results: Twenty studies, including a total of 19,514 patients with diabetes mellitus from a range of surgical specialties, were suitable for inclusion. Preoperative glycemic control did not have a bearing on 30-day mortality. There were no significant differences in the incidence of stroke, venous thromboembolic disease, hospital readmission and ITU length of stay based on glycemic control. The majority of studies suggested no link between preoperative HbA1c levels and acute kidney injury or need for postoperative dialysis, dysrhythmia, infection not related to the surgical site and total hospital length of stay. The literature was highly variable with regards to myocardial events, surgical site infection and reoperation rates.
Conclusions: Elevated preoperative HbA1c was not definitively associated with increased postoperative morbidity or mortality in patients with diabetes mellitus. The studies included in this review were relatively heterogeneous, predominantly retrospective, and often contained small patient numbers, suggesting that good quality evidence is necessary.

1. Introduction

The incidence of diabetes mellitus is increasing rapidly in the UK, having gone from 1.4 million new cases in 1996 [1] to 3.1 million in 2013 [2], likely linked to an aging population with a rising prevalence of obesity. Diabetes is a significant risk factor for complications following many forms of surgery [3]. It increases the incidence of infection [4–6], as well as general morbidity and mortality [7,8]. Diabetes is associated with other comorbidities which increase the risk of surgical intervention, particularly cardiovascular adverse events [9]. Perioperative short-term glycemic control is associated with poor surgical outcomes both in patients with [10] and without diabetes [11], underpinning the role of stress hyperglycemia in this relationship.

Glycated hemoglobin (HbA1c) has been used as a measure of diabetic control, reflecting long-term glucose concentrations over the preceding months [12,13], and tight control is associated with reduced incidence [14,15] and slower progression [16] of diabetes-related complications, myocardial infarction, and stroke. The American Diabetes Association (ADA) released guidelines recommending that "target HbA1c for people with diabetes should be <7%" (53 mmol/mol) [17], and furthermore that surgery should not be undertaken if at all possible if the HbA1c exceeds 7% (53 mmol/mol) [18]. Despite this, HbA1c measurement is currently not a standard part of the preoperative workup of the surgical patient, nor is it specifically recommended in the UK National Institute for Clinical Excellence (NICE) preoperative care guideline [19].

* Corresponding author. Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH, UK. Tel.: +44 115 8231149; fax: +44 115 8231160.
E-mail address: dileep.lobo@nottingham.ac.uk (D.N. Lobo).

http://dx.doi.org/10.1016/j.clnu.2015.03.007
0261-5614/

One area in which there has been significant interest in the association between HbA1c and postoperative outcome is cardiac surgery. The incidence of diabetes in this cohort is recognized to be elevated due to the association between diabetes and cardiac disease, and the complication rates in these patients are established to be high. In this field, elevated preoperative HbA1c is associated with increased morbidity and mortality rates [20,21], as well as infectious [22] and renal [23] complications.

Thus, whilst there are reasonably convincing data to show that perioperative high glucose concentrations are associated with harm, what is not well established is whether such a relationship exists for HbA1c and surgical outcomes. The aim of this review was to clarify the relationship between preoperative HbA1c and postoperative complications.

2. Methods

2.1. Search strategy

A search of PubMed, MEDLINE, Google™ Scholar and the Cochrane Library databases was conducted to identify studies evaluating the association between preoperative HbA1c levels and postoperative surgical outcomes published between 1966 and September 2014. Electronic search terms employed were 'HbA1c AND 'surgery', 'glyc(a)emic control AND surgery' and (('glycosylated h(a)emoglobin a1c' OR 'glycated h(a)emoglobin a1c' 'glyc(a)emic control' OR 'HbA1c')) AND surgery. The search was limited to adult patients with diabetes and English language publications, with all cases of gestational or post-transplant diabetes excluded. We also searched the references of all studies that met the inclusion criteria for further suitable articles. We excluded any studies which examined the association of HbA1c and postoperative outcome in patients who did not have diabetes.

2.2. Selection of articles

Following exclusion of citations based on title and abstract, full text articles were screened for inclusion. Studies were selected if they included patients with diabetes who had HbA1c levels measured within three months before surgical intervention and if the study reported at least one postoperative outcome. Studies were excluded if they analyzed results based on HbA1c without distinguishing between patients with and without diabetes, duplicated data from another study included or did not include any relevant clinical outcome measures (postoperative morbidity and mortality, hospital length of stay, readmission and reoperation rates). Studies reporting the outcomes of a population who were not all managed surgically were also excluded.

2.3. Data extraction

One reviewer extracted the data and the results were checked by a second. Data collated included authors' names, year of publication, type of surgery, study design, and inclusion criteria. With regards to patient data, the number of patients, type of diabetes, treatment method for diabetes, mean HbA1c level, number of patients with stated HbA1c levels, mortality rates, length of stay, and a range of complications (acute kidney injury, acute coronary syndrome, arrhythmia, stroke, surgical site infection, other infections, venous thromboembolism, reoperation and readmission to hospital) were also collected. Mortality was defined either as short-term (either in-hospital or at 30-days postoperatively) or long-term (three years or more).

Publications were screened for data on overlapping patient populations and if identified, the study which included the greatest number of patients reporting the largest or most clinically relevant complications were included. Three studies were excluded due to overlapping results [22,24,25]. Since June 2011 the unit of measurement of HbA1c has changed from % to mmol/mol. With this in mind, an HbA1c of 6.0% corresponds to 42 mmol/mol, 7.0% to 53 mmol/mol, and 8.0% to 64 mmol/mol [26].

2.4. Protocol registration

We registered the protocol for this review with the PROSPERO database (www.crd.york.ac.uk/prospero) – registration no. CRD42014013110.

2.5. Assessment of quality and risk of bias

The quality of evidence was assessed and graded using GRADEpro software for each outcome (http://ims.cochrane.org/revman/other-resources/gradepro/download) as recommended by the Cochrane Collaboration. The judgments of quality of specific outcomes were based on 5 main areas: study design and execution limitations, inconsistency, indirectness, imprecision of results, and publication bias across all studies. The overall quality of evidence for each outcome is the combination of assessments in all domains and is graded as very low, low, moderate, or high to make a recommendation for intervention.

3. Results

From 2935 studies, 89 articles were identified as potentially relevant (Fig. 1) and 2846 deemed unsuitable. Following manuscript review, 20 studies were considered eligible for inclusion [20,27–45].

3.1. Demographics

The 20 studies included a total of 19,514 patients with diabetes (Table 1); 9590 male and 6392 female. Gender was not detailed in 3532 patients. Only a small number included the type of diabetes [28,33,37,42], including 26 patients with type 1 and 257 with type 2 diabetes. Publication year was between 1992 and 2014. There was significant variability in HbA1c cut-off, however, the most frequently employed measure was the ADA [18] guideline of <7% (53 mmol/mol) representing good control.

Overall, seven studies (3921 patients) were based on cardiac surgery [20,31,35–37,40,44], six (8667 patients) on orthopedics [27,28,30,32,33,39], two (939 patients) on 'major non-cardiac' surgery [29,43], two (123 patients) on vascular [41,42], one (2872 patients) on renal transplant with pre-existing diabetes [34], one (32 patients) on urology [45], and one (2960 patients) on 'major surgical procedures' [38].

3.2. Postoperative complications

3.2.1. Mortality

Eight studies reported the effect of preoperative HbA1c level on short-term mortality [20,29,31,34,36–38,42] and one paper reported long-term mortality [41] (Table 2). There is good evidence based upon all studies (9538 patients) that HbA1c has no impact upon mortality.

In cardiac surgery, four studies (3214 patients) reported no change in mortality (Table 2). The four general studies (6324 patients) also found no significant difference in 30-day mortality rates.

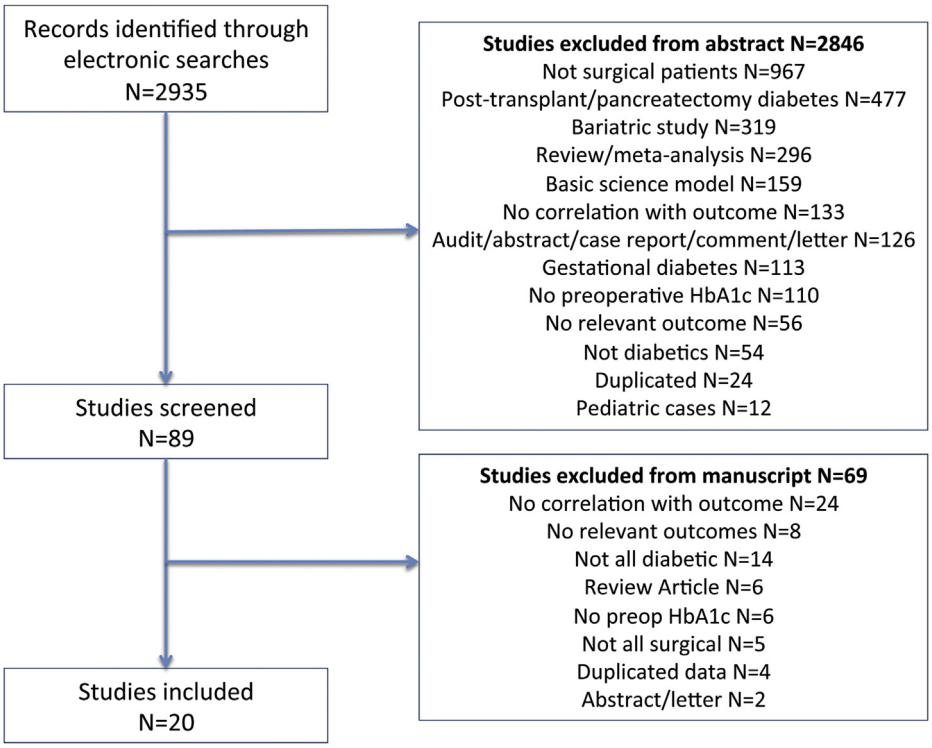

Fig. 1. PRISMA diagram showing identification of relevant studies from initial search.

One study reported long-term mortality [41], which found no significant difference by level of glycemic control at 3 and 5 years postoperatively.

3.2.2. Acute kidney injury (AKI)

Eight studies (4113 patients) examined the impact of HbA1c upon the incidence of AKI [20,29,31,35–37,40,42]. Seven studies (2873 patients) demonstrated no difference, whereas one study did (1240 patients) [20] (Table 3).

In cardiac surgery, five studies found no difference in the incidence of either AKI or requirement for dialysis by HbA1c [31,35–37,40]. In contrast, Halkos et al. [20] found a significantly higher rate of AKI if HbA1c $\geq$ 7% (53 mmol/mol). In general surgery, two studies (492 patients) [29,42] demonstrated no significant difference in the rate of AKI.

3.2.3. Acute coronary syndrome (ACS)

Five studies (10,694 patients) examined the impact of HbA1c on postoperative ACS [20,30,31,36,42]. These gave a wide variety of results; two studies [30,31] (8676 patients) suggested a cardioprotective effect conveyed by elevated HbA1c, one [36] showing increased events in this group (735 patients) and two [20,42] demonstrating no difference (1283 patients).

In 7567 orthopedic patients [30], there was a higher incidence of ACS in those with an HbA1c <7%. In cardiac surgery a lower preoperative HbA1c was associated with increased ACS incidence [31]. The counter result was reported in a similar cohort [36], with a significantly greater incidence of ACS in poorly controlled patients. One further cardiac study [20] found no significant difference by HbA1c level. In a study of vascular surgical patients [42], again there was no significant difference by HbA1c level.

3.2.4. Dysrhythmia

Five studies (2799 cardiovascular surgical patients) documented the relationship between preoperative HbA1c and postoperative dysrhythmia [20,31,35,40,42]. All but one demonstrated no significant difference [31,35,40] in cardiac surgery cohorts and [42] in a vascular surgery cohort. Counter to this was the study by Halkos et al. [20] who found a significantly higher rate of atrial fibrillation in those well controlled preoperatively.

3.2.5. Stroke

Six studies (3621 cardiac surgery patients) explored the relationship between HbA1c and stroke [20,31,35–37,40], all of which showed no difference, providing good consistency in results.

3.2.6. Surgical site infection (SSI)

Most studies examined the impact of HbA1c on SSI: sixteen studies including 13,153 patients. When all studies were taken together, five (1704 patients) provided evidence of a significant increase in SSI by elevated HbA1c versus ten studies (3561 patients) which suggested no relationship. Two studies did not quote statistical significance. Within orthopedic surgery, six studies (8667 patients) included data on SSI [27,28,30,32,33,39]. Overall, three studies [27,28,33] (432 patients) showed a significantly increased rate by elevated HbA1c, one paper [30] (7567 patients) showed a trend, however two studies [32,39] (668 patients) demonstrated no link. Within cardiac surgery, seven studies (3921 patients) compared SSI rates by HbA1c [20,31,35–37,40,44], although the definition of SSI was highly inconsistent. Despite this, 5 studies [31,35–37,40] (2381 patients) showed no significant difference, one [20] showed a significant increase in poor control (1240 patients) and one [44] did not include data on significance (300 patients). Amongst the general studies, one paper [45] (32 patients) demonstrated a significant increase in SSI rate by HbA1c, versus two studies [42,43] demonstrating no difference (533 patients).

3.2.7. Non-surgical site infection

There are six remaining studies (2941 patients) which examined infection unrelated to the surgical site [20,31,37,39,40,42]. Overall,

Table 1
Patient demographics for 19,514 patients with diabetes included in the systematic review.

Author	Pro/ Retro	N (Male: Female)	Age (years)	Management of diabetes			Level of glycaemic control		
				Diet	Tablet	Insulin	Good (<6.5%)	Moderate (6.5–7.5%)	Poor (>7.5%)
					Orthopedic				
Hikata [27] (2014)	Retro	36 (19:17)	64.3[a]	0	n/a	4 (11.1%)	19 < 7.0%, 17 > 7.0%		
Jupiter [28] (2014)	Retro	322 (97:225)	60.2[a] ± 10.39	0	322 (100%)		99	105	118
Adams [30] (2013)	Retro	7567 (3237: 4330)	68#	n/a	n/a	n/a	5042 < 7.0%, 2525 > 7.0%		
Iorio [32] (2012)	Retro	350	n/a	278 (79.4%)		72 (20.6%)	191 < 7.0%, 85 > 7.0%		
Myers [33] (2012)	Retro	74 (31:43)	57.3[a] ± 10.4	41 (55%)		33 (45%)	30 < 7.0%, 44 > 7.0%		
Lamloum [39] (2009)	Retro	318 (175:143)	58#	n/a	n/a	n/a	80 < 7.0%, 238 > 7.0%		
					Cardiac				
Strahan [31] (2013)	Retro	1109	n/a	179 (16.1%)	718 (64.7%)	212 (19.1%)	265 < 7.0%, 447 > 7.0%		
Tsuruta [35] (2011)	Retro	306 (242:64)	n/a	72 (23.5%)	142 (46.7%)	89 (29.1%)	115	96	95
Knapik [36] (2011)	Retro	735 (487:248)	64.9 ± 8.1 <7.0, 64.4 ± 7.7 >7.0	104 (14.1%)	290 (39.5%)	341 (46.4%)	453 < 7.0%, 282 > 7.0%		
Sato [37] (2010)	Pro	130 (91:39)	68 < 6.5, 66 > 6.5	97 (74.6%)		33 (25.4%)	61 < 6.5%, 69 > 6.5%		
Matsuura [40] (2009)	Retro	101 (80:21)	n/a	46 (45.5%)	33 (32.7%)	22 (21.8%)	47 < 6.5%, 54 > 6.5%		
Halkos [20] (2008)	Retro	1240	n/a	182 (14.7%)	676 (54.5%)	372 (30.0%)	516 < 7.0%, 724 > 7.0%		
Latham [44] (2001)	Pro	300	n/a	n/a	n/a	n/a	174 < 8.0%, 126 > 8.0%		
					General				
Underwood [29] (2014)	Retro	449 (220:229)	59.1[a] ± 14.1	n/a	n/a	n/a	109 < 6.5%, 202 6.5–8%, 91 8–10%, 47 > 10%		
Molnar [34] (2011)	Retro	2872 (1839:1033)	53[a] ± 11	n/a	n/a	n/a	1752 < 7.0%, 1120 > 7.0%		
Acott [38] (2009)	Retro	2960 (2960:0)	63.7[a]	n/a	n/a	n/a	895 < 6.0%, 799 6–7%, 1266 > 7.0%		
Jones [41] (2008)	Pro	80 (80:0)	68.5[a] ± 7.2	n/a	n/a	n/a	43 < 8.0%, 37 > 8.0%		
O'Sullivan [42] (2006)	Pro	43	72[a]	n/a	n/a	n/a	21 < 7.0%, 22 > 7.0%		
Dronge [43] (2006)	Retro	490	71.3#	0	289 (59.0%)	201 (41.0%)	197 < 7.0%, 293 > 7.0%		
Bishop [45] (1992)	Pro	32 (32:0)	n/a	n/a	n/a	n/a	19 < 11.5%, 13 > 11.5%		

[a] Mean #Median. Pro – prospective study. Retro – retrospective study. In terms of measures of glycemic control as HbA1c; 6.5% (48 mmol/mol), 7.0% (53 mmol/mol); 7.5% (59 mmol/mol); 8.0% (64 mmol/mol), 10.0% (86 mmol/mol), 11.5% (102 mmol/mol).

four studies suggested no link, one suggested a significantly increased incidence in those with poorly controlled diabetes and one study suggested a link with urinary tract infection alone [39]. In cardiac surgery, three studies [20,31,40] (2450 patients) reported no significant difference in the rate of general infection by HbA1c level versus one study [37] (130 patients) showing a significant increase by poor control. In the orthopedic literature, one study suggested a significant difference in urinary tract infection rates but no other forms of infection [39] (318 patients) and one other study suggested no difference (43 patients) [42].

3.2.8. Venous thromboembolism

One study [30] found that rates of both deep venous thrombosis (DVT) and pulmonary embolism (PE) within 90 days of surgery were not significantly different by HbA1c.

3.2.9. Reoperation

Four studies looked at reoperation rates, interestingly two studies (10,046 patients) showed higher reoperation rates in those with lower HbA1c levels [30,31] and two showed no relationship (407 patients) [35,40].

3.2.10. Readmission

Only one study [30] examined the impact of preoperative HbA1c level on hospital readmission, finding no significant difference by one year postoperatively following knee replacement.

3.2.11. ITU and hospital length of stay (LOS)

Two studies explored the relationship between HbA1c level and ITU stay, both following cardiac surgery, and both finding no significant link [36,37]. Five studies explored the impact of HbA1c level on total LOS, with the majority demonstrating no significant difference [20,36,37,40]. However, Underwood et al. [29] found those with an HbA1c of 6.5%–8% (48 mmol/mol – 64 mmol/mol) had a significantly shorter LOS than those <6.5% or >8%, however this did not form a linear relationship.

Table 2
Postoperative outcome by HbA1c level in 19,514 patients included in the systematic review.

Author	Number of Patients	Mortality	Morbidity	ITU stay (days)	Re-operation	Re-admission	Length of stay (days)
			Orthopedic				
Hikata [27] (2014)	36	0	n/a	n/a	n/a	n/a	n/a
Jupiter [28] (2014)	322	n/a	n/a	n/a	n/a	n/a	n/a
Adams [30] (2013)	7567	n/a	n/a	n/a	88 (1.7%) <7.0% 31 (1.2%) ≥7.0%	1571(31.2%) <7.0% 755 (29.9%) ≥7.0%	n/a
Iorio [32] (2012)	350	n/a	n/a	n/a	n/a	n/a	n/a
Myers [33] (2012)	74	n/a	13 < 7.0% 20 > 7.0%	n/a	n/a	n/a	n/a
Lamloum [39] (2009)	318	0	14 < 7.0% 76 > 7.0%	n/a	n/a	n/a	n/a
			Cardiac				
Strahan [31] (2013)	1109	2 (0.75%) <7.0% 2 (0.5%) ≥7.0%	n/a	n/a	11 (4.2%)<7.0% 11 (2.5%)≥7.0%	n/a	n/a
Tsuruta [35] (2011)	306	0	n/a	n/a	2 (1.7%) <6.5% 1 (1.0%) 6.5–7.5% 0 (0%) >7.5%	n/a	n/a
Knapik [36] (2011)	735	7 (1.6%) ≤7.0% 8 (2.8%) >7.0%	32 ≤ 7.0% 27 > 7.0%	1.6[a] ≤ 7.0% 1.7[a] > 7.0%	n/a	n/a	7.4[a] ≤ 7.0% 7.7[a] > 7.0%
Sato [37] (2010)	130	2 (3.3%) <6.5% 4 (5.8%) >6.5%	7 (11.5%) < 6.5% 12 (17.4%) > 6.5%	21 h <6.5% 25 h >6.5%	n/a	n/a	8 < 6.5% 11 > 6.5%
Matsuura [40] (2009)	101	0	n/a	n/a	0(0%) <6.5% 1(1.9%) >6.5%	n/a	22.1[a] < 6.5% 21.7[a] > 6.5
Halkos [20] (2008)	1240	3 (0.6%) <7.0% 10 (1.4%) ≥7.0%	n/a	n/a	n/a	n/a	6.5[a] < 7.0% 7.0[a] ≥ 7.0%
Latham [44] (2001)	300	n/a	n/a	n/a	n/a	n/a	n/a
			General				
Underwood [29] (2014)	449	9 (8%) <6.5% 6 (3%) >6.5–8% 3 (3%) >8–10% 1 (2%) >10%	n/a	n/a	n/a	n/a	8.3 < 6.5% 5.3 6.5–8% * 7.9 8–10% 6.8 > 10%
Molnar [34] (2011)	2872	201 (10%) <7.0% 130 (11%) >7.0%	n/a	n/a	n/a	n/a	n/a
Acott [38] (2009)	2960	35 (3.9%) <6.0% 39 (4.9) 6–6.9% 49 (3.7%) 7.0–7.9%	246 < 6.0% 228 6–7% 306 > 7.0%	n/a	n/a	n/a	n/a
Jones [41] (2008)	80	3 years 16 (37.2%) ≤8.0% 13 (64.8%) >8.0% 5 years 24 (55.8%) ≤8.0% 25 (65.7%) >8.0%	n/a	n/a	n/a	n/a	n/a
O'Sullivan [42] (2006)	43	1 < 7.0% 0 > 7.0%	n/a	n/a	n/a	n/a	n/a
Dronge [43] (2006)	490	n/a	n/a	n/a	n/a	n/a	n/a
Bishop [45] (1992)	32	n/a	n/a	n/a	n/a	n/a	n/a

[a] Mean #Median. All columns given as number of patients (%). All mortality quoted is 30-day unless specifically stated. In terms of measures of glycemic control as HbA1c; 6.5% (48 mmol/mol), 7.0% (53 mmol/mol); 7.5% (59 mmol/mol); 8.0% (64 mmol/mol), 10.0% (86 mmol/mol), 11.5% (102 mmol/mol). * indicates statistically significant result.

Assessment of quality and risk of bias

The quality of the individual studies, assessment of bias and strength of evidence are summarised in Table 4.

4. Discussion

This systematic review has shown no definite relationship between preoperative HbA1c and postoperative outcomes in patients with diabetes. Overall data quality was variable and generally poor, making comparisons between papers difficult. In addition, definitions of good long-term glycemic control varied considerably, making data synthesis difficult. Preoperative HbA1c level did not have a bearing on 30-day or long term mortality in any study [41]. There was no significant difference in the incidence of stroke, VTE, hospital readmission, and ITU length of stay. The majority of studies suggested no link between HbA1c and AKI, dysrhythmia, infection unrelated to the surgical site, and total hospital LOS. The literature was highly variable regarding ACS, SSI and reoperation rates. The variability surrounding myocardial events may be due to evidence that patients with diabetes experience extra vigilance from medical and nursing staff with regards to adverse events, with increased patient contact may come earlier detection and treatment of complications [46].

4.1. Strengths and limitations

Many of the included studies are retrospective observational studies, often with small patient numbers, limiting the quality of the conclusions of this review. There were several other limitations due to the nature of the studies included. There were high levels of

Table 3
Postoperative complications by preoperative HbA1c level.

Author	Number of Patients	AKI	ACS	Dysrhythmia	CVA	SSI	Other infection	VTE
				Orthopedic				
Hikata [27] (2014)	36	n/a	n/a	n/a	n/a	0 (0%) <7.0% 6 (35.3%) ≥7.0%*	n/a	n/a
Jupiter [28] (2014)	322	n/a	n/a	n/a	n/a	14 (14%) <6.5% 25 (21%) 6.5–7% 54(28%) >7–7.5%	n/a	n/a
Adams [30] (2013)	7567	n/a	101(2.0%) <7.0 36 (1.4%) ≥7.0	n/a	n/a	58 (1.2%) <7.0% 13 (0.5%) ≥7.0%	n/a	DVT 29(0.6%) <7.0% 12 (0.5%) ≥7.0% PE 30 (0.6%) <7.0% 10 (0.4%) ≥7.0%
Iorio [32] (2012)	350	n/a	n/a	n/a	n/a	5 (2.69%) <7.0% 5 (5.88%) >7.0%	n/a	n/a
Myers [33] (2012)	74	n/a	n/a	n/a	n/a	2 (6.7%) <7.0%* 12 (27.3%) >7.0%	n/a	n/a
Lamloum [39] (2009)	318	n/a	n/a	n/a	n/a	10(12.5%) <7.0% 33(13.9%) >7.0%	6 (5%) <7.0%* 55 (17.6%) >7.0%	n/a
				Cardiac				
Strahan [31] (2013)	1109	4 (1.5%) <7.0% 8 (1.8%) ≥7.0%	4 (1.5%) <7.0% 1 (0.2%) ≥7.0%	63(23.8%) <7.0% 94 (21.1%) ≥7.0%	3 (1.1%) <7.0% 2 (0.5%) ≥7.0%	5 (1.9%) <7.0% 8 (1.8%) ≥7.0%	14 (5.3%) <7.0% 21 (4.7%) ≥7.0%	n/a
Tsuruta [35] (2011)	306	2 (1.7%) <6.5% 1 (1.0%) 6.5–7.5% 2 (2.1%) > 7.5%	0	12 (10.4%) <6.5% 9 (9.4%) 6.5–7.5% 16 (16.8%) >7.5%	0 (0%) <6.5% 0 (0%) 6.5–7.5% 2 (2.1%) >7.5%	0 (0%) <6.5% 0 (0%) 6.5–7.5% 2 (2.1%) >7.5%	n/a	n/a
Knapik [36] (2011)	735	3 (0.7%) ≤7.0% 4 (1.4%) >7.0%	6 (1.3%) ≤7.0% 12(4.3%) >7.0%*	n/a	6 (1.3%) ≤7.0% 9 (3.2%) >7.0%	2 (0.4%) ≤7.0% 4 (1.4%) >7.0%	n/a	n/a
Sato [37] (2010)	130	1 (1.6%) <6.5% 3 (4.3%) >6.5%	n/a	n/a	2 (3.3%) <6.5% 1 (1.6%) >6.5%	5 (8.2%) <6.5% 10(11.6%) >6.5%	8 (13.1%) <6.5% 19 (27.5%) >6.5%	n/a
Matsuura [40] (2009)	101	3 (6.4%) <6.5% 0 (0%) >6.5%	n/a	14 (29.7%) <6.5% 12 (22.2%) >6.5%	0 (0%) <6.5% 1 (1.9%) >6.5%	3 (2.1%) <6.5% 6 (1.9%) >6.5%	3 (6.4%) <6.5% 1 (1.9%) >6.5%	n/a
Halkos [20] (2008)	1240	14 (2.7%) <7.0% 38 (5.3%) ≥7.0%*	1 (0.2%) <7.0% 4 (0.6%) ≥7.0%	108 (20.9%) <7.0% 109 (15.1%) ≥7.0%*	9 (1.7%) <7.0% 21 (2.9%) ≥7.0%	3 (0.6%) <7.0% 19 (2.6%) ≥7.0%*	9 (1.7%) <7.0% 25 (3.5%) ≥7.0%	n/a
Latham [44] (2001)	300	n/a	n/a	n/a	n/a	7 (4%) <8.0% 10 (8%) >8.0%	n/a	n/a
				General				
Underwood [29] (2014)	449	1 (0.9%) <6.5% 0 (0%) >6.5%	n/a	n/a	n/a	n/a	n/a	n/a
Molnar [34] (2011)	2872	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Acott [38] (2009)	2960	83	90	267	84	480	203	13
Jones [41] (2008)	80	n/a	n/a	n/a	n/a	n/a	n/a	n/a
O'Sullivan [42] (2006)	43	0 (0%) <7.0% 1 (4.5%) >7.0%	0 < 7.0% 1 > 7.0%	0 (0%) <7.0% 1 (4.5%) >7.0%	0	1 (4.8%) <7.0% 5 (22.7%) >7.0%	0 (0%) <7.0% 2 (4.5%) >7.0%	n/a
Dronge [43] (2006)	490	n/a	n/a	n/a	n/a	24 (12%) <7.0% 59 (20%) >7.0%*	n/a	n/a
Bishop [45] (1992)	32	n/a	n/a	n/a	n/a	1 (5%) <11.5% 4 (31%) >11.5%*	n/a	n/a

AKI – acute kidney injury. ACS – acute coronary syndrome. CVA – stroke. SSI – surgical site infection. VTE – venous thromboembolism/pulmonary embolism. All columns given as number of patients(%). * indicates statistically significant result. In terms of measures of glycemic control as HbA1c; 6.5% (48 mmol/mol), 7.0% (53 mmol/mol); 7.5% (59 mmol/mol); 8.0% (64 mmol/mol), 10.0% (86 mmol/mol), 11.5% (102 mmol/mol).
In terms of measures of glycemic control as HbA1c; 6.5% (48 mmol/mol), 7.0% (53 mmol/mol); 7.5% (59 mmol/mol); 8.0% (64 mmol/mol), 10.0% (86 mmol/mol), 11.5% (102 mmol/mol).

inconsistency in HbA1c cut-off levels, with many studies using the ADA cut-off of 7% (53 mmol/mol) [18] as the borderline for good control, however the lack of consistency between the studies makes these difficult to interpret. Furthermore, the populations were described as above or below a threshold, however a more meaningful description of the group may have been to provide a mean HbA1c for the group to better delineate long-term control. A large number of the studies employ similar cutoffs around 6.5 (48 mmol/mol) to 8% (64 mmol/mol), however the oldest study [45] used a cutoff of 11.5% (102 mmol/mol), which although it provided a statistically higher rate of SSI, was greatly different from the other studies. Several studies broke down HbA1c levels into multiple groups [28,29,38], resulting in small patient numbers per group, particularly in the high HbA1c groups. There were three studies which included patients from multiple surgical specialities, resulting in a heterogeneous patient population. Underwood et al. [29] described a cohort of 'major non-cardiac surgical procedures', including patients who had undergone general (including gastrointestinal, endocrine, thoracic or oncologic), or vascular surgical procedures. Acott et al. [38] examined patients who had undergone "major surgical procedures" which included general, cardiothoracic, vascular, orthopedic, otolaryngologic, and urological surgery. Finally, Dronge et al. [43] examined patients who had undergone "noncardiac surgery", again which included urological, gastrointestinal, vascular, orthopedic, general, thoracic, neurosurgical, and otolaryngological procedures.

Table 4
Quality assessment using GRADE approach.

Quality assessment							Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Postoperative complications (assessed with: numbers reported in studies)								
17	Observational studies	Serious. Differing HbA1c cutoff levels were used in each study and definitions of each of the complications were inconsistent between studies	Serious. Differing HbA1c cutoff levels were used in each study and definitions of each of the complications were inconsistent between studies	Serious. Multiple confounders affecting the directness of the relationship between HbA1c and postoperative complications	Serious. Small population size and small event rate for each individual complication	Reporting bias. Multiple database studies, predominantly retrospective	⊕OOO Very low	Critical
Mortality (assessed with: numbers reported in studies)								
9	Observational studies	No serious risk of bias	Serious. Differing HbA1c cutoff values for individual studies making this a highly heterogeneous group	No serious indirectness	Serious. Small population size and small event rate for each individual complication	None	⊕OOO Very low	Important
ITU and Hospital Length of Stay (assessed with: numbers reported in studies)								
5	Observational studies	No serious risk of bias	Serious. Differing HbA1c cutoff values for individual studies making this a highly heterogeneous group	No serious indirectness	Serious. Small population size and small event rate for each individual complication	None	⊕OOO Very low	Important
Reoperation (assessed with: numbers reported in studies)								
4	Observational studies	Serious. Small population size and small event rate for each individual complication	Serious. Differing indications and time frames for reoperation used between different papers	Serious. Time of reoperation disparate between papers making this relationship unclear	Serious. Small population size and small event rate for each individual complication	None	⊕OOO Very low	Not important
Readmission to Hospital (assessed with: numbers reported in studies)								
1	Observational studies	Serious. Single retrospective database study only	No serious inconsistency	No serious indirectness	Serious. Single retrospective database study only	Reporting bias. Single retrospective database study only	⊕OOO Very low	Not important

Several studies grouped their statistical analysis between outcome as composite measures, for example Strahan et al. [31] looked at composite minor (return to theatre, postoperative MI, arrhythmias, renal failure, infection and pulmonary) and major (dialysis, multiorgan failure, stroke, death) complications. Whilst the numerical incidence of the individual complications is stated, the statistical significance of these is not which hampers interpretation. The authors commented that this technique was used as due to small numbers of each individual complication, grouping them together was felt to be a more statistically valid method. Similarly, Sato et al. [37] only quoted significance if $p < 0.05$ however if the value exceeded this, the figure was not detailed. The inclusion criteria included the measurement of HbA1c level in the three months prior to the date of surgery, however four studies [30,33,35,37] did not include information on the time that HbA1c was measured other than stating that it was "preoperative" and one study included HbA1c measured within 6 months of surgery [43]. Although it was decided to include these studies, they may give a less accurate representation of the relationship with postoperative complications.

Some limitations were introduced into the review by the paper selection employed. A wide range of surgical specialties contributed to the review, with predominantly cardiac and orthopedic studies. There was some variability in the definition of surgical site infection (SSI); some studies used mediastinitis, some deep sternal wound infection, and some superficial infections. In addition, several studies included infection as a composite rather than individual outcome. A large number of studies were database studies which only consider patient contact with secondary care providers. Many of the perioperative complications included could be managed in the primary care setting and by the study design, these complications would not be detected, thus suggesting their rates may be underestimated. Some complications may have been investigated by other medical specialities at re-presentation to hospital, e.g. VTE, raising the possibility again of under-reporting. The studies included in this systematic review did not include data on any validated risk scoring tool such as the Charleston Comorbidity Index. As such, it is likely there may be an element of confounding bias which cannot be adjusted for as part of this review.

5. Conclusions

This review has highlighted the lack of good quality prospective observational studies in the area of preoperative HbA1c level as a predictive factor of postoperative morbidity and mortality. Given the American Diabetes Association guidelines suggestion that surgery should not be undertaken if at all possible in a patient with an HbA1c >7% (53 mmol/mol) [18], it is not clear upon what evidence this recommendation has been based specifically in surgical patients. This cutoff has been adopted from the established threshold for good glycemic control from large cohort studies [47], however its relevance to the surgical population in this study appears unclear. The UK Joint British Diabetes Society guidelines [3] took a more pragmatic approach towards what level of HbA1c was considered safe. An HbA1c of 8.5% (69 mmol/mol) was chosen because there was a paucity of data to show that intensive lowering was beneficial in this cohort. Also, it was felt that an HbA1c goal of 69 mmol/mol was more likely to be safely achievable than a lower target given that may patients may be put at increased risk of developing severe hypoglycemia. This is in line with the retrospective data analysis by Underwood et al. [29], who found that an HbA1c of >8% (64 mmol/mol) was associated with increasing risk of harm. There is little evidence to show that more aggressive glucose lowering is associated with better outcomes. Indeed, if patients with long-standing diabetes are asked to achieve this target it may be associated with increased mortality [48]. Before this guideline is adopted in a more widespread manner, better quality evidence should be sought to clarify what effect, if any, HbA1c has upon postoperative outcome as this systematic review has suggested that this relationship is not as clear cut as may be expected when considering the impact that the general presence or absence of diabetes mellitus has upon postoperative outcomes.

Funding

KER was funded by a Research Fellowship awarded by the European Society for Clinical Nutrition and Metabolism (ESPEN). The funders had no role in the design, execution and writing up of the study.

Author contributions

Study design: KER, KKV, KD, DNL.
Literature search and data retrieval: KER, KKV, DNL.
Data interpretation: KER, KKV, KD, DNL.
Writing of manuscript: KER, KKV, KD, DNL.
Critical revision: KER, KKV, KD, DNL.
Final approval: KER, KKV, KD, DNL.
Overall supervision: DNL.

Conflict of interests

The authors have no direct conflicts of interest to declare. DNL has received unrestricted research funding and speaker's honoraria from Fresenius Kabi, BBraun and Baxter Healthcare for unrelated work.

References

[1] Diabetes U.K. Diabetes in the UK 2012. Key statistics on diabetes. London: Diabetes UK; 2012. Available at: http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf [Accessed 10.10.14].
[2] International Diabetes Federation. IDF diabetes Atlas. 6th ed. Brussels: International Diabetes Federation; 2013 Available at: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf [Accessed 09.10.14].
[3] Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, et al. NHS diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med 2012;29:420–33.
[4] Wukich DK, Lowery NJ, McMillen RL, Frykberg RG. Postoperative infection rates in foot and ankle surgery: a comparison of patients with and without diabetes mellitus. J Bone Jt Surg Am 2010;92:287–95.
[5] King Jr JT, Goulet JL, Perkal MF, Rosenthal RA. Gycemic control and infection in patients with diabetes undergoing noncardiac surgery. Ann Surg 2011;253:158–65.
[6] Ata A, Valerian BT, Lee EC, Bestle SL, Elmendorf SL, Stain SC. The effect of diabetes mellitus on surgical site infections after colorectal and noncolorectal general surgical operations. Am Surg 2010;76:697–702.
[7] Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418–23.
[8] Lobo SM, Rezende E, Knibel MF, Silva NB, Paramo JA, Nacul FE, et al. Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. Anesth Analg 2011;112:877–83.
[9] Puskas JD, Winston AD, Wright CE, Gott JP, Brown 3rd WM, Craver JM, et al. Stroke after coronary artery operation: incidence, correlates, outcome, and cost. Ann Thorac Surg 2000;69:1053–6.
[10] Ouattara A, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology 2005;103:687–94.
[11] Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, Koch CG. Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. Anesthesiology 2010;112:860–71.
[12] Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Position statement executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2011;34:1419–23.

[13] Bazerbachi F, Nazarian S, Alraiyes AH, Alraies MC. Q: Is hemoglobin A1c an accurate measure of glycemic control in all diabetic patients? Cleve Clin J Med 2014;81:146–9.

[14] The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977–86.

[15] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65. Erratum in: *Lancet* 1998; 352: 1558.

[16] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.

[17] KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(2 Suppl 2). S12–S154.

[18] Standards of medical care in diabetes. Diabetes Care 2013;36(Suppl 1): S11–66.

[19] National Institute for Clinical Excellence. Preoperative tests. The use of routine preoperative tests for elective surgery. Clinical guideline 3. London: National Institute for Clinical Excellence; 2003. Available at: https://www.nice.org.uk/guidance/cg3/resources/guidance-preoperative-tests-pdf [Accessed 10.10.14].

[20] Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg 2008;136:631–40.

[21] Engoren M, Schwann TA, Arslanian-Engoren C, Maile M, Habib RH. U-shape association between hemoglobin A1c and late mortality in patients with heart failure after cardiac surgery. Am J Cardiol 2013;111:1209–13.

[22] Halkos ME, Thourani VH, Lattouf OM, Kilgo P, Guyton RA, Puskas JD. Preoperative hemoglobin A1c predicts sternal wound infection after coronary artery bypass surgery with bilateral versus single internal thoracic artery grafts. Innov (Phila) 2008;3:131–8.

[23] Gumus F, Polat A, Sinikoglu SN, Yektas A, Erkalp K, Alagol A. Use of a lower cut-off value for HbA1c to predict postoperative renal complication risk in patients undergoing coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2013;27:1167–73.

[24] Halkos ME, Lattouf OM, Puskas JD, Kilgo P, Cooper WA, Morris CD, et al. Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. Ann Thorac Surg 2008;86: 1431–7.

[25] Humphers JM, Shibuya N, Fluhman BL, Jupiter D. The impact of glycosylated hemoglobin and diabetes mellitus on wound-healing complications and infection after foot and ankle surgery. J Am Podiatr Med Assoc 2014;104: 320–9.

[26] John WG. Haemoglobin A1c towards global standardization. Diabet Med 2010;27:733–4.

[27] Hikata T, Iwanami A, Hosogane N, Watanabe K, Ishii K, Nakamura M, et al. High preoperative hemoglobin A1c is a risk factor for surgical site infection after posterior thoracic and lumbar spinal instrumentation surgery. J Orthop Sci 2014;19:223–8.

[28] Jupiter DC, Humphers JM, Shibuya N. Trends in postoperative infection rates and their relationship to glycosylated hemoglobin levels in diabetic patients undergoing foot and ankle surgery. J Foot Ankle Surg 2014;53:307–11.

[29] 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;37:611–6.

[30] Adams AL, Paxton EW, Wang JQ, Johnson ES, Bayliss EA, Ferrara A, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. J Bone Jt Surg Am 2013;95:481–7.

[31] Strahan S, Harvey RM, Campbell-Lloyd A, Beller E, Mundy J, Shah P. Diabetic control and coronary artery bypass: effect on short-term outcomes. Asian Cardiovasc Thorac Ann 2013;21:281–7.

[32] Iorio R, Williams KM, Marcantonio AJ, Specht LM, Tilzey JF, Healy WL. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. J Arthroplasty 2012;27:726–9. e1.

[33] Myers TG, Lowery NJ, Frykberg RG, Wukich DK. Ankle and hindfoot fusions: comparison of outcomes in patients with and without diabetes. Foot Ankle Int 2012;33:20–8.

[34] Molnar MZ, Huang E, Hoshino J, Krishnan M, Nissenson AR, Kovesdy CP, et al. Association of pretransplant glycemic control with posttransplant outcomes in diabetic kidney transplant recipients. Diabetes Care 2011;34:2536–41.

[35] Tsuruta R, Miyauchi K, Yamamoto T, Dohi S, Tambara K, Dohi T, et al. Effect of preoperative hemoglobin A1c levels on long-term outcomes for diabetic patients after off-pump coronary artery bypass grafting. J Cardiol 2011;57:181–6.

[36] Knapik P, Ciesla D, Filipiak K, Knapik M, Zembala M. Prevalence and clinical significance of elevated preoperative glycosylated hemoglobin in diabetic patients scheduled for coronary artery surgery. Eur J Cardiothorac Surg 2011;39:484–9.

[37] Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schricker T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. J Clin Endocrinol Metab 2010;95: 4338–44.

[38] Acott AA, Theus SA, Kim LT. Long-term glucose control and risk of perioperative complications. Am J Surg 2009;198:596–9.

[39] Lamloum SM, Mobasher LA, Karar AH, Basiony L, Abdallah TH, Al-Saleh AI, et al. Relationship between postoperative infectious complications and glycemic control for diabetic patients in an orthopedic hospital in Kuwait. Med Princ Pract 2009;18:447–52.

[40] Matsuura K, Imamaki M, Ishida A, Shimura H, Niitsuma Y, Miyazaki M. Off-pump coronary artery bypass grafting for poorly controlled diabetic patients. Ann Thorac Cardiovasc Surg 2009;15:18–22.

[41] Jones RN, Marshall WP. Does the proximity of an amputation, length of time between foot ulcer development and amputation, or glycemic control at the time of amputation affect the mortality rate of people with diabetes who undergo an amputation? Adv Skin Wound Care 2008;21:118–23.

[42] O'Sullivan CJ, Hynes N, Mahendran B, Andrews EJ, Avalos G, Tawfik S, et al. Haemoglobin A1c (HbA1c) in non-diabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of adverse outcome? Eur J Vasc Endovasc Surg 2006;32:188–97.

[43] Dronge AS, Perkal MF, Kancir S, Concato J, Aslan M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. Arch Surg 2006;141:375–80. discussion 380.

[44] Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas Jr CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. Infect Control Hosp Epidemiol 2001;22:607–12.

[45] Bishop JR, Moul JW, Sihelnik SA, Peppas DS, Gormley TS, McLeod DG. Use of glycosylated hemoglobin to identify diabetics at high risk for penile periprosthetic infections. J Urol 1992;147:386–8.

[46] Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg 2013;257:8–14.

[47] Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol 2009;53:298–304.

[48] Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545–59.