Arch Gynecol Obstet (2016) 294:161–164
DOI 10.1007/s00404-015-3983-8

GYNECOLOGIC ONCOLOGY

Preoperative HBA1c and risk of postoperative complications in patients with gynaecological cancer

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Received: 29 August 2015 / Accepted: 7 December 2015 / Published online: 16 December 2015

Abstract
Background HBA1c is used as an indicator for the long-term control of the glycaemic state and outcome predictors in diabetic patients. Diabetic patients have an increased risk of post-operative complications especially those related to infection. The aim of our study is to ascertain the relationship between HBA1c levels and post-operative recovery within the subspecialty of gynaecological oncology.
Method Prospective cohort study during the period 1 August 2012 through 31 August 2014. Preoperative measurement of HBA1c on all gynaecological oncology patients that underwent major surgery. Patient variables collected and analysed were BMI (kg/m^2), length of stay (LOS in days), cancer stage (stage 1 through stage 4), infective complications, non-infective complications and readmission to hospital.
Results A total of 300 patients were included in our study, 34 of them were known to be diabetic while 266 were presumed to be non-diabetic. Of the presumed non-diabetic cohort, 17.3 % (46/266) had impaired glucose tolerance or diabetes. Mean BMI was significantly increased in the pre-existing diabetic group (32.8 vs. 29.3 kg/m^2, $p = 0.016$). Infective complications were almost double the rate amongst the known diabetic women than those presumed to be non-diabetic (32.4 vs. 18.0 %, $p = 0.048$). Rate of re-admission to hospital due to complications was 20.6 % in the diabetic group and 4.1 % within the presumed non-diabetic group ($p < 0.001$). Infective complications occurred in 16.9 % of women with HBA1c <42 mmol/mol, 22.7 % of those with HBA1c of 42–47 mmol/mol, 43.5 % of patients with HBA1c 48–64 mmol/mol and 37.5 % of patients with HBA1c >64 mmol/mol. Non-infective complications were also more frequent in women with elevated HBA1c (11.1, 22.7, 26.1 and 12.5 % in those women with HBA1c <42, 42–47, 48–64 and >64 mmol/mol, respectively). Re-admission to hospital within 30 days for a complication of surgery occurred in 4.4 % of women with HBA1c <42 mmol/mol, 4.5 % of women with HBA1c measured at 42–47 mmol/-mol, 30.8 % of those with HBA1c 48–64 mmol/mol and 25 % of women with HBA1c >64 mmol/mol.
Conclusion Preoperative measurement of HBA1c may identify patients (both diabetic and non-diabetic women) at higher risk of postoperative complications and could be used as a trigger for modification of the perioperative management of such patients.

Keywords HBA1c · Diabetes mellitus · Gynaecological malignancies · Infection · Hospital stay · Non-infective complications

Introduction

HBA1c is the stable glucose adduct in the N-terminal group of the β-chain of HBA0 and is an indicator of blood glucose control during the previous 3–4 months [1]. HBA1c is used as an indicator for the long-term control of the glycaemic state and outcome predictors in diabetic patients. The International Federation of Clinical Chemistry (IFCC) units had been adopted by the UK in 2011 to allow easier comparisons between UK and European results. According to the World Health Organisation

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(WHO) diagnostic guidelines, patients with HBA1c <42 mmol/mol are considered to be non-diabetic, those with levels between 42 and 47 mmol/mol are deemed to have impaired glucose regulation and values >48 mmol/mol have type 2 diabetes mellitus.

Diabetic patients have an increased risk of post-operative complications especially those related to infection. Moreover, the correlation between endometrial cancer and high BMI is well established. A 5 kg/m^2 increase in BMI equates to an increased relative risk of endometrial cancer of 1.59 ($p < 0.0001$) [2, 3]. Approximately 50 % of endometrial cancer in the UK is attributed to obesity [4].

In February 2015, a large series from UK has shown that there are significant patient and surgical factors related to the considerable morbidity in gynaecological oncology patients [5]. For example, previous abdominal surgery, metabolic/endocrine disorders, surgical complexity and final diagnosis were associated with intraoperative complications. In the same study, age, commorbidities, diabetes mellitus, surgical approach, duration of surgery and final diagnosis were associated with postoperative complications. Recent published data show how an elevated HBA1c carries a relative risk of 3.4 for surgical site infection in another branch of surgical practice. These authors concluded that ability to predict surgical site infection may help with risk stratification and may help with prevention strategies [6]. Our study aimed to ascertain the relationship between HBA1c levels and post-operative recovery within the subspecialty of gynaecological oncology. The data obtained were to be used to propose potential improvements to service for women as well as to guide future research.

Methods

This was a prospective cohort during the time period 1 August 2012 through 31 August 2014. The study population comprised collecting consecutive data on all gynaecological oncology patients that underwent major surgery at University Hospital South Manchester (UHSM). All patients had an HBA1c pre-operatively at the preoperative assessment clinic.

Patient variables collected and analysed were BMI (kg/m^2), length of stay (LOS in days), cancer stage (stage 1 through stage 4), infective complications, non-infective complications and readmission to hospital. Results were broken down using the IFCC range of HBA1c results, which was then further subdivided into known diabetic patients and those whose diabetic status is not known. The infective complications that were analysed included UTI, wound infection, major full thickness wound infection, chest infection and pyrexia treated with antibiotics. The non-infective complications analysed included hyponatraemia, haematuria, ileus, lymphocyst, prolonged drains, renal failure, DVT, anaesthetic problems and other complications due to pre-existing co-morbidities.

Two-tailed Student's t test for normally distributed data and Chi squared for 2×2 contingency tables were performed.

Results

A total of 300 patients were included in our study, 34 of them were known to be diabetic while 266 were presumed to be non-diabetic. Of the presumed non-diabetic cohort, 17.3 % (46/266) had impaired glucose tolerance or diabetes. Mean BMI was significantly increased in the pre-existing diabetic group (32.8 vs. 29.3 kg/m^2, $p = 0.016$). Cancer stage at time of surgery, length of peri-operative hospital stay and non-infective complications did not significantly differ between the groups.

Infective complications were almost double the rate amongst the known diabetic women than those presumed to be non-diabetic (32.4 vs. 18.0 %, $p = 0.048$). Rate of re-admission to hospital due to complications was 20.6 % in the diabetic group and 4.1 % within the presumed non-diabetic group ($p < 0.001$) (see Table 1).

Analysis of the study population based on HBA1c values alone showed no difference in mean length of hospital stay and mean stage of cancer across the groups of patients. There was a significantly elevated BMI in the HBA1c = 42–47 mmol/mol group and HBA1c = 48–64 mmol/mol group compared to the normal HBA1c group (BMI 32.0, 34.0 and 28.7 kg/m^2, respectively).

Infective complications occurred in 16.9 % of women with HBA1c <42 mmol/mol, 22.7 % of those with HBA1c of 42–47 mmol/mol, 43.5 % of patients with HBA1c 48–64 mmol/mol and 37.5 % of patients with HBA1c >64 mmol/mol. Non-infective complications were also more frequent in women with elevated HBA1c (11.1, 22.7, 26.1 and 12.5 % in those women with HBA1c <42, 42–47, 48–64 and >64 mmol/mol, respectively) (see Table 2). As shown in Table 3, logistic regression analysis results show that infective complications, when all patients are grouped together, are significantly increased as HBA1c rises. This is irrespective of their diabetic status. The OR of 1.033 implies that for every one unit rise in HBA1c (i.e. 1 mmol/mol) there is a 3 % rise in postoperative infective complications.

Re-admission to hospital within 30 days for a complication of surgery occurred in 4.4 % of women with HBA1c <42 mmol/mol, 4.5 % of women with HBA1c measured at 42–47 mmol/mol, 30.8 % of those with HBA1c 48–64 mmol/mol and 25 % of women with HBA1c >64 mmol/mol.

Table 1 Broken down by DM status and HBA1c

	HBA1c (mmol/mol)				Total (%)
	<42	42–47	48–64	>64	p value compared to corresponding non diabetic total
Pre-existing diabetic (%)	5/34 (14.7)	4/34 (11.8)	18/34 (52.9)	7/34 (20.6)	34 (100)
Mean BMI (kg/m^2)	33	31	33.4	32.2	32.8 ($p = 0.016$)*
Mean length of stay (days)	6.8	5.5	7.5	5.4	6.8 ($p = 0.78$)
Infective complications	1/5 (20.0)	1/4 (25.0)	8/18 (44.4)	1/7 (28.6)	11/34 (32.4) ($p = 0.048$)*
Non-infective complications	1/4 (25.0)	2/3 (66.7)	4/18 (22.2)	1/7 (14.3)	8/34 (23.5) ($p = 0.089$)
Re-admission	1/4 (25.0)	1/3 (33.3)	3/18 (16.7)	2/7 (28.6)	7/34 (20.6) ($p < 0.001$)*
Presumed non-diabetic (%)	220/226 (82.7)	40/226 (15.0)	5/226 (1.9)	1/226 (0.4)	266 (100)
Mean BMI (kg/m^2)	28.6	32.1	36	47	29.3
Mean length of stay (days)	6.0	9.2	6.4	8.0	6.5
Infective complications (%)	36/220 (16.4)	8/40 (20.0)	1/5 (20.0)	1/1 (100)	48/266 (18.0)
Non-infective complications (%)	25/220 (11.4)	7/40 (17.5)	2/5 (40.0)	0	34/266 (12.8)
Re-admission (%)	9/220 (4.1)	1/40 (2.5)	1/5 (20.0)	0	11/266 (4.1)

Table 2 Broken down by HBA1c status alone (p value compared to HBA1c <42 mmol/mol cohort)

	HBA1c (mmol/mol)			
	<42 ($n = 225$)	42–47 ($n = 44$)	48–64 ($n = 23$)	>64 ($n = 8$)
Mean BMI (kg/m^2)	28.7	32.0 ($p = 0.002$)*	34.0 ($p = 0.008$)*	34.7 ($p = 0.09$)
Mean length of stay (days)	6.0	8.9 ($p = 0.30$)	7.3 ($p = 0.33$)	5.8 ($p = 0.89$)
Infective complications (%)	38/225 (16.9)	10/44 (22.7) ($p = 0.35$)	10/23 (43.5) ($p = 0.002$)*	3/8 (37.5) ($p = 0.13$)
Non-infective complications (%)	25/225 (11.1)	10/44 (22.7) ($p = 0.04$)*	6/23 (26.1) ($p = 0.04$)*	1/8 (12.5) ($p = 0.90$)
Re-admission (%)	10/225 (4.4)	2/44 (4.5) ($p = 0.98$)	4/13 (30.8) ($p = 0.01$)*	2/8 (25) ($p = 0.01$)*

* Statistically significant ($p < 0.05$)

Table 3 Logistic regression analysis to show odds ratio of HBA1c as a predictor of morbidity, broken down by presence or absence of diabetes (95 % CI)

Post-operative complication	Diabetic	Non-diabetic	All patients
Infective complication	0.986 (0.932, 1.043)	1.032 (0.973, 1.094)	1.033 (1.004, 1.063)*
Non-infective complication	0.980 (0.913, 1.051)	1.047 (0.982, 1.126)	1.020 (0.989, 1.052)
Re-admission <30 days pot-operatively	1.001 (0.937, 1.068)	1.003 (0.888, 1.134)	1.026 (0.984, 1.069)

* Statistically significant ($p < 0.05$)

Discussion

Diabetes leads to increased morbidity and length of stay of surgical patients [7]. According to Frisch et al. [8], the perioperative mortality rate is reported to be up to 50 % higher than in the non-diabetic population. Within gynaecological oncology the proportion of undiagnosed diabetic patients is unknown. In 2012, there were 2.5 million people in England with diabetes and it is estimated that there are a further 85,000 people in the UK that have diabetes but are unaware or have no confirmed diagnosis [9]. The incidence of detection of previously unknown impaired glucose tolerance/diabetes was 17.3 % in this study.

Preoperative HBA1c has been reported to help predict hyperglycaemia and adverse outcome after colorectal surgery [10]. Hudson et al. showed that in non-diabetics, an elevated preoperative HBA1c level (>6.0 %) was independently associated with significantly greater early mortality risk after elective cardiac surgery. Such findings suggested that HBA1c may have value as a screening tool to identify high-risk non-diabetic cardiac surgery patients [11]. O'Sullivan et al. also showed that elevated plasma HBA1c level

was associated with increased postoperative morbidity and mortality in patients undergoing vascular surgical procedures [12]. This is the first time that HBA1c has been proven to significantly impact on gynaecological oncology patients' perioperative course. HBA1c should be tested in all gynaecological oncology patients and when elevated results are detected, strategies to reduce preoperative HBA1c (where appropriate) should be adopted in all patients.

Our study consisted of prospectively collected, consecutive data on a moderate scale and 10 % of the women were diabetics. Cancer stage at the time of surgery was similar across all groups whilst the diabetic group had a statistically elevated BMI compared to their non-diabetic peers.

Outcome measures including length of peri-operative hospital stay and non-infective complications showed no difference between diabetics and non-diabetics, however, other measures including infective complications and rate of re-admission to hospital showed markedly elevated incidences. The apparent increase in complications amongst non-diabetic women with even mildly elevated HBA1c may prove to be clinically significant. The power of the study to detect statistical differences would evidently be improved if the study population size was increased.

When the data relating to HBA1c values and clinical outcomes are interrogated based independent of the presence of diabetes, one may begin to appreciate the potential value of HBA1c testing in pre-operative patients. As HBA1c value increased, body mass index increased in parallel. This alone may have implications for peri-operative issues, e.g. anaesthesia and wound healing. The increasing incidence of infective complications, non-infective complications and re-admission to hospital due to complications is supported by these data and the project was large enough to detect several statistical differences. The elevated infection rate with increasing HBA1c values in this paper was comparable to that found recently in a study of cardiac surgical patients.

In the future, peri-operative care could be modified for women with elevated HBA1c. Possible alterations may include prolonged pre- or post-operative antibiotics, closer follow-up (either in community or in the secondary care setting). Specific advice for these women regarding the signs and symptoms of infection along with education of all members of the healthcare team may prove beneficial.

Conclusion

Elevated pre-operative HBA1c. levels are known to be associated with increased morbidity and mortality in some sub-specialties of surgical practice. This study was scientifically sound and the project could readily be replicated in other centres. An association with elevated HBA1c. and increased post-operative morbidity has been demonstrated in a gynaecological oncology population. Pre-operative HBA1c. optimisation and alterations in peri-operative care for high-risk individuals may improve patient outcomes.

Compliance with ethical standards

Conflict of interest I certify that no actual or potential conflict of interest in relation to this article exists.

References

1. Jeppsson J-O, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umwnoto M, Weykamp C (2005) Approved IFCC reference method for the measurement of HBA1c in human blood. Clin Chem Lab Med 40(1):78–89
2. McCullough ML, Patel AV, Patel R, Rodriguez C, Fiegelson HS, Bandere EV, Gansler T, Thun MJ, Calle EE (2008) Body mass and endometrial cancer risk in hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 17:73–79
3. Lindermann K, Vatten LJ, Ellstrom-Engh M, Eskild A (2008) Body mass, diabetes and smoking, and endometrial cancer risk: a follow up study. Br J Cancer 98:1582–1585
4. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D (2007) Million Women Study Collaboration. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort. Br Med J 335:1134
5. Iyer R, Gentry-Maharaj A, Nordin A, Burnell M, Liston R, Manchanda R, Das N, Desai R, Gornall R, Beardmore-Gray A, Nevin J, Hillaby K, Leeson S, Linder A, Lopes A, Meechan D, Mould T, Varkey S, Olaitan A, Rufford B, Ryan A, Shanbhag S, Thackeray A, Wood N, Reynolds K, Menon U (2015) Predictors of complications in gynaecological oncological surgery: a prospective multicentre study (UKGOSOC-UK gynaecological oncology surgical outcomes and complications). Br J Cancer 112(3):475–484
6. Raja SG, Rochon M, Jarman JW (2015) Brompton Harefield Infection Score (BHIS): development and validation of a stratification tool for predicting risk of surgical site infection after coronary artery bypass grafting. Int J Surg 16(Pt A):69–73
7. Dhatariya N, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, Hilton L, Jairam C, Leyden K, Lipp A, Lobo D, Sinclaire-Hammersley M, Rayman G (2012) NHS guidelines for the perioperative management of the adult patient with diabetes. Diabet Med 29:420–433
8. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, Hudson M, Mendoza J, Johnson R, Lin E, Umpierrez GE (2010) Prevalence and clinical outcome of hyperglycaemia in the perioperative period in noncardiac surgery. Diabetes Care 33(8):1783–1788
9. Diabetes UK (2012) State of the Nation 2012, England. Diabetes UK, London
10. Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J (2009) Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg 96(11):1358–1364
11. Hudson CC, Welsby IJ, Phillips-Bute B, Mathew JP, Lutz A, Chad Hughes G, Stafford-Smith M, Cardiothoracic Anesthesiology Research Endeavors (C.A.R.E.) Group (2010) Glycosylated hemoglobin levels and outcome in non-diabetic cardiac surgery patients. Can J Anaesth 57(6):565–572
12. O'Sullivan CJ, Hynes N, Mahendran B, Andrews EJ, Avalos G, Tawfik S, Lowery A, Sultan S (2006) 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 32(2):188–197