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Hemoglobin A1c and the relationship to stage and grade of endometrial cancer

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Abstract
Objectives To determine if elevated markers of poor glycemic control (HgA1c and fasting glucose levels) in patients surgically staged for type I endometrial cancer is related to a higher stage or higher grade at the time of diagnosis. Also, to assess if these markers impact overall survival.
Methods A retrospective chart review was performed from January 2000 to June 2010 at three academic medical centers. Patients were included if they underwent surgical staging and had HgA1c drawn within 3 months before surgery. Demographic data, fasting blood glucose levels and overall survival data were also obtained.
Results Eighty-two patients fitting the inclusion criteria were identified during the study period. There was a strong positive correlation between HgA1c and fasting glucose. There was no statistical difference with regard to stage alone, grade alone, or when stratified together with regard to HgA1c or fasting glucose levels. There was a trend toward increased mean HgA1c across increasing stages, but this was not statistically significant. Diabetes, HgA1c and tumor grade did not affect overall survival, but advanced stage was a poor prognostic measure for overall survival.
Conclusions Elevated preoperative HgA1c has a trend toward a higher stage at the time of diagnosis. Advanced stage is a poor prognostic measure for overall survival.

Keywords Hemoglobin A1c (HgA1c) · Endometrial cancer · Diabetes · Surgery

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Introduction

Endometrial cancer is the fourth most common malignancy in women, with an estimated 46,470 diagnoses and 8,120 deaths in the USA in 2011 [1]. Type I endometrial cancer is characterized by endometrioid type histology and is associated with excess estrogen as well as mutations in the PTEN tumor suppressor gene [2]. It has identifiable risk factors including hypertension, obesity, diabetes, nulliparity and anovulation [3].

Hyperinsulinemia and impaired glucose metabolism have been hypothesized to increase the risk of many cancers, including those of the breast, genitourinary and gastrointestinal [3–11]. Glucose, acting on the production of insulin and insulin like growth factor (IGF)-1, may enhance tumor development by stimulating cell proliferation and

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inhibiting apoptosis [6, 7]. Through this mechanism, it is possible that hyperglycemia and hyperinsulinemia may contribute to the association between type 2 diabetes and cancer in general. Glycosylated hemoglobin (HgA1c) can be used as a surrogate measure for glycemic control. This marker reflects overall glucose levels for 3 months prior to testing and is often used to regularly monitor diabetes. This is often favored over fasting or random blood glucose measurement because of the ability to assess glycemic control over a longer period of time.

Although many studies examine the risk of development of cancer with elevated HgA1c, few studies examine the role of glycemic control in the overall prognosis. In colon cancer, poor glycemic control has been shown to be related to poor overall prognosis. Patients with a measured HgA1c >7.5 % had a significantly more aggressive clinical course than those with improved glycemic control [8]. These patients with poor glycemic control were also found to be younger, and have more advanced cancers and a worse 5-year survival.

In endometrial cancer, impaired glucose tolerance as measured by HgA1c was found to be significantly increased in endometrial cancer cases when compared with a representative patient population with other cancers [12]. Diabetes itself is a known independent risk factor for the development of type I endometrial cancer [3]. The mere presence of self-reported diabetes has been associated with poorer overall survival in endometrial cancer, independent of tumor stage or grade [13]. However, markers of diabetes and diabetic control, including fasting glucose levels and HgA1c, were not included for analysis in that study. Therefore, the authors could only postulate that hyperglycemia or hyperinsulinemia may contribute to the worsened survival rate.

The risk of developing a more aggressive endometrial cancer in patients with poor glycemic control, as shown through a higher stage or grade of the tumor at the time of diagnosis, has yet not been examined in the literature. In this study, we sought to determine if poor gylcemic control, as defined by HgA1c and postoperative day 1 (POD #1) fasting glucose measurements, is related to a higher stage or higher grade at the time of diagnosis in patients surgically staged for type I endometrioid adenocarcinoma of the uterus. We also examined if poor glycemic control or diabetes itself was related to overall survival.

Materials and methods

A retrospective chart review was performed from January 2000 to June 2010 at three academic medical centers. Patients diagnosed with endometrioid adenocarcinoma of the uterus were identified from the tumor registry records. Inclusion criteria in our study included a hemoglobin A1c performed within 3 months of surgery and surgical staging, including a minimum of hysterectomy and bilateral salpingoopherectomy. The decision to perform a lymph node dissection was determined by the attending surgeon at the time of surgery based on their routine practice. Since the majority of our patients were diagnosed prior to the FIGO 2009 revised staging for uterine corpus, the staging was recorded based on the FIGO 1988 staging system for uterine corpus. Standard FIGO pathological criteria were used to determine tumor grade. Demographic characteristics including age and preoperative diagnosis of diabetes were determined through review of medical records and tumor registry data. Additionally, fasting POD #1 glucose levels were collected as an additional assessment of glycemic control. Overall survival data on each patient were obtained from review of the tumor registry, medical record and the Social Security Death Index. Statistical analysis, including non-parametric tests and Kaplan–Meier survival curves, were conducted in SPSS version 20.

Results

A total of 618 patients were identified with endometrioid adenocarcinoma during the study period. Of these, 82 had an HgA1c done within 3 months of surgery and were surgically staged. These 82 patients comprised our study group. The demographic characteristics of the study population are displayed in Table 1. The mean and median age was 62 years (range 34–86); 57.3 % of the study population had been diagnosed preoperatively with type 2 diabetes mellitus. The stage distribution favored early-stage disease, with 63 patients surgically staged as stage 1, 10 as stage 2, 8 as stage 3 and 1 as stage 4. In terms of tumor grade, 45.1 % had a grade 1 tumor, 29.3 % had a grade 2 tumor, and 25.6 % had grade 3. Table 2 shows the distribution of all the patients by stage and grade.

The overall average HgA1c was 6.69 ± 1.50 (range 4.4–12.8). The mean fasting POD#1 glucose ($n = 70$) was 175.8 ± 60.8 (range 83–355). There is a significant positive correlation between HgA1c and POD#1 glucose ($r = 0.481$, $p < 0.001$), but no correlation between age and either measure of glycemic control (HgA1c $p = 0.20$, POD#1 glucose $p = 0.65$). There was no statistical difference with regard to age when stratifying by stage (Kruskal–Wallis, $p = 0.19$), but there was a difference in distribution of age by grade (Kruskal–Wallis, $p = 0.01$). Low grade tumors tended to be younger than higher grade tumors; grade 1 tumors had a mean age of 58 ± 11.9 years, compared to grade 2 (63 ± 9.0 years) and grade 3 (67.5 ± 9.6 years) tumors. There was no statistical difference between HgA1c or POD#1 glucose levels in low-grade

Table 1 Demographic characteristics of the study population (study subjects $n = 82$)

Age		
Mean	62	
Median	62	
SD	11.2	
Range	34–86	
	Number of patients	Percentage
Diabetes mellitus		
Non-diabetic	35	42.7
Diabetic	47	57.3
Stage (FIGO 1988)		
Stage I	63	76.8
IA	22	
IB	31	
IC	10	
Stage II	10	12.2
IIA	3	
IIB	7	
Stage III	8	9.8
IIIA	4	
IIIC	4	
Stage IV	1	1.2
IVB	1	
Grade		
1	36	43.9
2	24	29.3
3	22	26.8

versus high-grade tumors (Table 3). There was no statistical difference between HgA1c or POD#1 glucose levels in early-stage versus later-stage cancers, but there was a trend toward significance with increasing HgA1c levels in later-stage cases (Table 4). When stratifying by stage and grade together, no significant difference was found between the groups with regard to HgA1c (Table 5) or POD#1 glucose (Kruskal–Wallis, $p = 0.83$, not shown). Finally, there was no difference in survival between the different tumor grades, but there was a significant difference in survival based on the stage of disease. See Fig. 1 for Kaplan–Meier survival plots.

With regard to diabetics versus non-diagnosed diabetics, there is a significant difference between HgA1c levels in diabetics and non-diabetics. (Mann–Whitney U, $p < 0.001$) Diabetics had a higher average HgA1c ($M = 7.29$, SD = 1.59, range 5.1–12.8) versus non-diabetics ($M = 5.87$, SD = 0.89, range 4.4–8.6). There was also a significant difference between POD#1 glucose levels in diabetics and non-diabetics. (Mann–Whitney U, $p < 0.001$). Diabetics had a higher average POD#1 glucose level ($M = 204.5$, SD = 60.9, range 94–355) versus non-diabetics ($M = 139.6$, SD = 36.4, range 83–244). Despite these differences, there was no difference in survival shown between the diabetics and non-diabetics. When evaluating HgA1c using a cutoff of HgA1c $\geq$7.5, there was no difference in survival between the groups. See Fig. 1 for Kaplan–Meier survival plots.

Discussion

Prognostic factors for endometrial cancer encompass clinical, surgical, pathologic and biologic/molecular factors. Poor prognostic factors have included advancing age, higher tumor grade, non-endometrioid histologic subtype, deeper myometrial invasion, presence of lymphovascular space invasion, amount of extrauterine spread and amplification of oncogenes, especially HER-2/neu [14]. Favorable biologic and molecular factors include the presence of steroid receptors, especially the progesterone receptor, and diploid tumor ploidy determined by flow cytometry [14]. With the exception of age, all of these factors were only determined after surgical management of endometrial cancer. Poor prognostic factors identified prior to surgery, such as HgA1c, could aid the clinician with regard to both surgical and treatment planning for the subset of patients where surgery is not an option.

In this retrospective study, we did not find a significant relationship between poor preoperative glycemic control and advanced stage or grade of endometrial cancer. Specifically, there was no relationship between POD#1 glucose and stage, grade, or when stage and grade were stratified together. There was also no relationship between HgA1c and grade, though we did see a trend toward significance

Table 2 Distribution of patients by stage and grade of endometrioid adenocarcinoma

	Stage 1	Stage 2	Stage 3	Stage 4	Total
Grade 1	34 (41.5 %)	1 (1.2 %)	1 (1.2 %)	0	36 (43.9 %)
Grade 2	17 (20.7 %)	5 (6.1 %)	2 (2.4 %)	0	24 (29.3 %)
Grade 3	12 (14.6 %)	4 (4.9 %)	5 (6.1 %)	1 (1.2 %)	22 (26.8 %)
Total	63 (76.8 %)	10 (12.2 %)	8 (9.8 %)	1 (1.2 %)	82 (100 %)

Table 3 Hemoglobin A1c and POD#1 fasting glucose versus grade of tumor

Grade	No. of patients	HgA1c	POD #1 glucose
1	HgA1c ($n = 36$)	$M = 6.74$	$M = 185.0$
	POD #1 ($n = 31$)	SD = 1.61	SD = 73.1
2	HgA1c ($n = 24$)	$M = 6.46$	$M = 176.5$
	POD #1 ($n = 21$)	SD = 0.85	SD = 52.3
3	HgA1c ($n = 22$)	$M = 6.63$	$M = 158.9$
	POD #1 ($n = 18$)	SD = 1.45	SD = 42.0

Independent samples Kruskal–Wallis: HgA1c ($p = 0.99$) and POD #1 ($p = 0.60$)

Table 4 Hemoglobin A1c and POD#1 fasting glucose versus stage of cancer

Stage	No. of patients	HgA1c	POD #1 glucose
1	HgA1c ($n = 63$)	$M = 6.63$	$M = 175.6$
	POD #1 ($n = 54$)	SD = 1.41	SD = 64.5
2	HgA1c ($n = 10$)	$M = 6.14$	$M = 161.7$
	POD #1 ($n = 9$)	SD = 0.58	SD = 36.6
3 and 4	HgA1c ($n = 9$)	$M = 7.69$	$M = 195.3$
	POD #1 ($n = 7$)	SD = 2.32	SD = 56.2

Independent samples Kruskal–Wallis: HgA1c ($p = 0.07$) and POD #1 ($p = 0.52$)

Table 5 Distribution of HgA1c by stage and grade of endometrioid adenocarcinoma

	Stage 1	Stage 2	Stage 3/4	Total
Grade 1	$M = 6.74$	$M = 6.8$	$M = 6.6$	$M = 6.74$
	SD = 1.65			SD = 1.61
Grade 2/3	$M = 6.50$	$M = 6.07$	$M = 7.83$	$M = 6.64$
	SD = 1.08	SD = 0.56	SD = 2.45	SD = 1.45
Total	$M = 6.63$	$M = 6.14$	$M = 7.69$	$M = 6.69$
	SD = 1.41	SD = 0.58	SD = 2.33	SD = 1.50

Independent Samples Kruskal–Wallis ($p = 0.57$)

with regard to stage, with advancing stage showing a higher average HgA1c level.

The relationship of glycemic control to stage and grade of endometrial cancer is a concept that has not been explored previously in this manner within the gynecologic oncology literature. Folsom et al. [13] showed that diabetes mellitus was associated with poorer survival after endometrial cancer, independent of tumor stage and grade. However, HgA1c or glucose levels were not explicitly investigated as markers in that study. Our study did not find that diabetes had a worse overall survival when compared with non-diabetic patients. Almost half of our study population was non-diabetic; however, six of these patients had an HgA1c level >6.5, which was clinically diagnostic of diabetes, and six had levels between 6 and 6.5, considered by many to be "pre-diabetic."

We also limited our glucose measurements to fasting blood glucose levels obtained on POD#1. Although stress of surgery itself can affect glycemic control, all of the patients underwent surgery, so this effect could be negated. However, some patients did not have a fasting glucose level drawn until after their diet was advanced or glucose was not included in the postoperative day 1 laboratory testing, so not all patients were included in this sub-analysis.

Elevated HgA1c has been shown to have an association with increased risk of many cancers. For instance, elevated levels are an independent predictor of aggressive clinical behavior in colorectal cancer patients [8, 9]. In our study, using a similar cut point of 7.5 % as Siddiqui did [8], we did not find elevated HgA1c to purport a worse overall survival as compared to those with HgA1c <7.5 %.

A strength of the study was the use of three medical centers which allowed for increased numbers of subjects who had HgA1c testing. Although demographic characteristics of race and ethnicity were not collected, the location of the hospitals allows for a diverse patient population to be represented. Also, we had similar numbers of diabetics and non-diabetic patients who had HgA1c level drawn, somewhat eliminating the possible bias that those with levels drawn were likely known type 2 diabetics.

Since the study was conducted retrospectively, it has inherent weaknesses. Only 13.3 % of the patients with endometrioid adenocarcinoma of the uterus had HgA1c drawn in the period of time established during the study. Because of the retrospective nature, it is unclear why certain subjects had HgA1c drawn while others did not. Regardless that one hospital drew HgA1c routinely at preoperative testing, one still might postulate that this subset of patients may be inherently different and contribute to the lack of statistical significance.

Also, there were more patients with low-grade, low-stage endometrial cancers than high-stage and/or high-grade cancers. As many as 68 % of endometrial cancers are diagnosed at an early stage in the USA; this is thought to be because postmenopausal bleeding in the most common symptom and the bleeding prompts the patient to visit a gynecologist [1]. This rate of early-stage disease is comparable to our patient population, where 76 % were stage I. The lack of advanced-stage cancers in general as well as in our study itself limits the ability to conclude that there is no potential relationship between poor glycemic and stage and/or grade of endometrial cancer.

Although it was not established in this study, it does seem plausible that there may be a relationship between HgA1c and other measures of poor glycemic control with an elevated stage or grade of endometrial cancer. Insulin

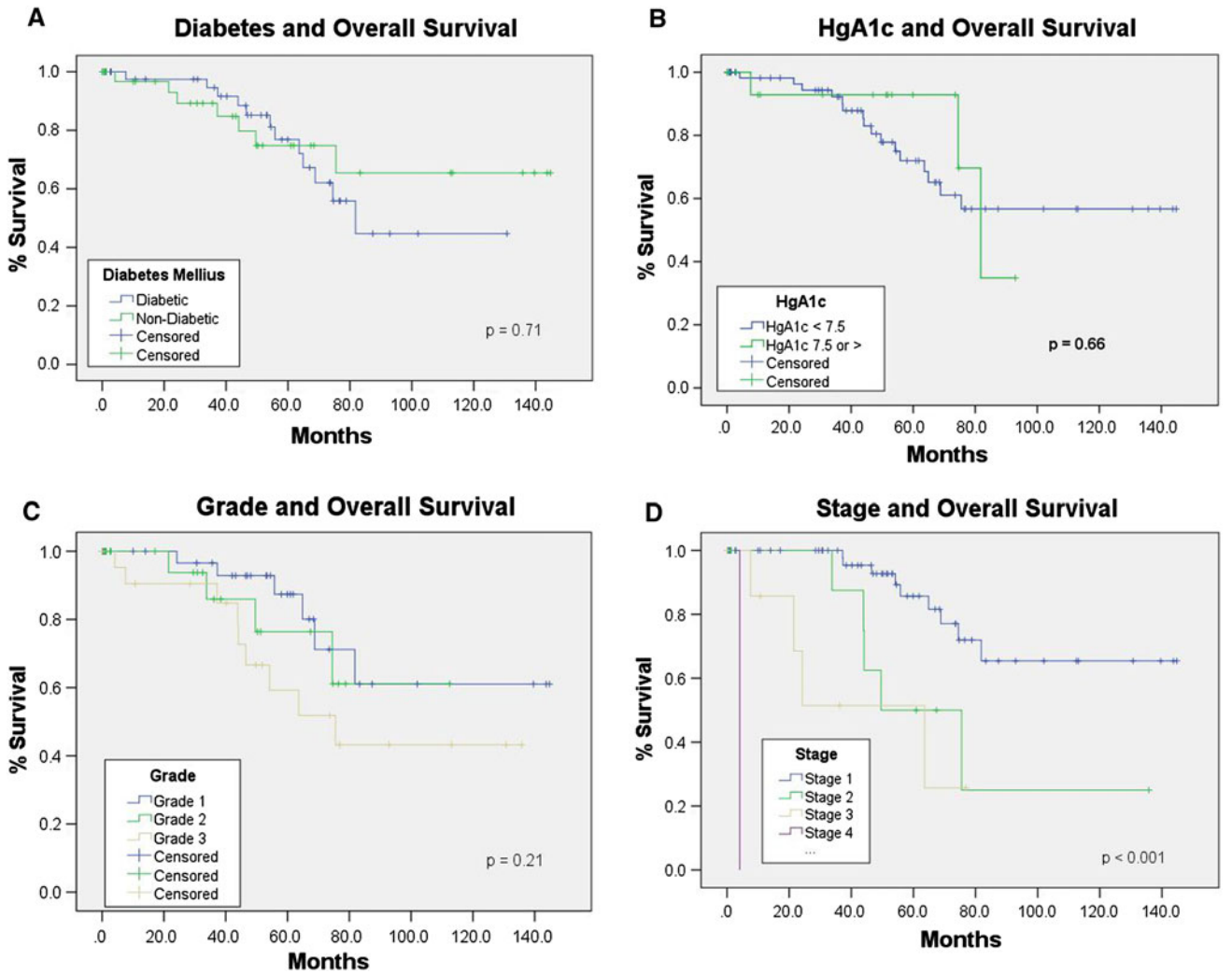

Fig. 1 Kaplan Meier overall survival plots and statistical significance for **a** Diabetes, **b** HgA1c, **c** Grade, **d** Stage

resistance and hyperinsulinemia are established as key biologic mechanisms underlying the relationship between obesity and tumor development, and HgA1c is seen as a surrogate marker for this biologic process. We propose a prospective study that routinely checks HgA1c levels pre-operatively on all patients with type I endometrial cancer. If a relationship is established, this would be an additional argument for improved control of diabetes in patients at risk for development of endometrial cancer.

Conflict of interest None.

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