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Research Article

Predictive value of different glycemic control markers in total hip or knee arthroplasty: A prospective study

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ABSTRACT

Objective: The optimal glycemic control marker before total hip or knee arthroplasty remains inconclusive. Hemoglobin A1c (HbA1c) is widely used, while fructosamine may be valuable for predicting periprosthetic joint infection (PJI). Fructosamine levels can be affected by serum albumin levels; albumin-corrected fructosamine (AlbF) can be calculated to overcome this issue. The objective of this study was to evaluate the predictive value of different markers for complications after primary total hip or knee arthroplasty.

Methods: This prospective cohort study included 304 patients (mean age: 65 years [range, 16-85), mean follow-up: 32 months (range, 12-49)] who underwent primary total hip or knee arthroplasty between 2018 and 2021. Of them, 156 patients had diabetes. Mean HbA1c was 6.5% (range, 4.8%-13%), fructosamine 244 μmol/L (range, 98-566 μmol/L), and AlbF 632 (range, 238-2308). Patients who did and did not have diabetes were matched 1 : 1. Hemoglobin A1c 7% and fructosamine 292 μmol/L were used as cutoff. Complications were documented. Glycemic markers were compared using logistic regression analyses, with a special focus on PJI.

Results: In the logistic regression analyses, HbA1c was strongly associated with total complications [adjusted odds ratio (OR): 3.61; 95% CI, 1.65-7.91, $P = .001$], while fructosamine was associated with PJI (adjusted OR: 13.68; 95% CI, 1.39-134.89, $P = .025$). Albumin-corrected fructosamine did not show any additional benefits.

Conclusion: Preoperative assessment before total hip or knee arthroplasty must not focus on a single marker; HbA1c is a good predictor of total complications, while fructosamine is a better predictor of PJI. To the best of our knowledge, in its first orthopedic study, AlbF did not show any advantages.

Level of Evidence: Level II, Prognostic Study.

Introduction

Periprosthetic joint infection (PJI) is a devastating complication of total hip or knee arthroplasty, while uncontrolled diabetes mellitus (DM) is a risk factor for PJI.[1-3] Various markers have been used to assess glycemic control, including hemoglobin A1c (HbA1c), fasting, and random glucose measurements. HbA1c is the most widely studied marker; however, different cutoff values have been proposed. The American Diabetes Association has designated the threshold for uncontrolled diabetes as 7%.[4] The predictive value of this threshold for arthroplasty was questioned in a meta-analysis, and a cutoff of 7% was not depicted.[1] Higher values, such as 7.7%, may be more strongly correlated with adverse outcomes; however, further studies are required in this regard.[5]

Serum fructosamine, which reflects the level of glycated serum proteins, has a half-life of 2-3 weeks and thus represents a shorter period of glycemic control. Fructosamine has recently been shown to be a more valuable marker than HbA1c and is more strongly associated with postoperative complications, including PJI.[6-8] However, a potential limitation of this marker is that it is correlated with total protein and albumin levels,[9] and basal albumin levels may be outside the normal range, especially in older patients and those with comorbidities.[10,11] Correcting fructosamine with respect to other serum proteins may be performed to overcome this problem.[12] In previous studies, albumin-corrected fructosamine (AlbF) has shown higher performance in detecting diabetes with a higher clinical value compared to fructosamine.[10,11,13] Patients undergoing total hip or knee arthroplasty may be prone to fluctuations in serum protein levels owing to the advanced age and comorbidities; therefore, AlbF may have a potential benefit over fructosamine. To the best of our knowledge, AlbF has not been previously evaluated in the arthroplasty literature.

The aim of this study was to investigate the effects of DM and different glycemic control markers (HbA1c, fructosamine, and AlbF) on the postoperative complications after primary total hip and knee arthroplasty, with a special focus on PJI.

Material and methods

This prospective cohort study was conducted simultaneously at 3 different institutions. Informed consent was obtained from the participants. Local

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ethical committee approval was obtained from Istanbul Research and Training Hospital Ethics Committee (Approval no: 1201) prior to the study. Patients who underwent primary elective total hip or knee arthroplasty between June 2018 and January 2021 were included. Each patient with a diagnosis of DM was matched in a 1 : 1 ratio to a control patient without DM with the nearest operation date. Exclusion criteria were patients undergoing revision arthroplasty, with previous infection at the joint, with <1 year of follow-up and lost to follow-up.

Demographic data, diagnosis of DM, preoperative HbA1c, fructosamine, AlbF, fasting and postoperative glucose levels, the American Society of Anesthesiologists (ASA) classification and Charlson comorbidity index (CCI), type (hip or knee), number (uni- or bilateral) of arthroplasty, and data on additional comorbidities were collected. Preoperative glycemic control parameters were measured 2-4 weeks before surgery and after at least 8 hours of fasting. Patients with an HbA1c level ≥6.5% were considered to have diabetes. Patients were grouped according to their preoperative HbA1c levels (<7% and ≥7%) and fructosamine levels (<292 μmol/L and ≥292 μmol/L).

Patients with a preoperative HbA1c level of ≥7% were informed about the potential risks, and the decision to undergo the procedure or to postpone was made together with the patient. If the decision was made to postpone, the patient was referred to endocrinology for diabetes management and reevaluated in 3 months.

After excluding 2 patients as they were lost to follow-up, 304 patients were included in the study (male/female: 67/237), with a mean age of 64.5 years (range, 16-85 years). Mean follow-up period was 32 months (range, 12-49 months). Two hundred nine (69%) patients underwent total knee arthroplasty (TKA), 95 (31%) underwent total hip arthroplasty (THA), and 5 (2%) underwent bilateral TKAs.

One hundred fifty-six (51%) patients had diabetes, while 148 (49%) did not (4 patients were diagnosed after the matching). The mean HbA1c level was 6.5% (range, 4.8-13%), fructosamine was 244 μmol/L (range, 98-566 μmol/L), AlbF was 632 (range, 238-2308), preoperative fasting glucose was 123 mg/dL (range, 73-394), and postoperative glucose was 138 mg/dL (range, 73-394 mg/dL). Two hundred thirty-four patients (77%) had an HbA1c level <7%, while 70 (23%) had a level of ≥7%. Two hundred forty-five (84%) patients had a fructosamine level < 292 μmol/L, while for 59 (16%) the level was ≥292 μmol/L. The characteristics of the study groups are shown in Table 1.

To evaluate the outcomes; complications, readmissions, and reoperations were documented. Superficial and deep infections, aseptic loosening, instability, periprosthetic fractures, joint stiffness, and medical complications (deep vein thrombosis, pulmonary thromboembolism, myocardial infarction, arrhythmia, pneumonia, urinary tract infection, cerebrovascular disease, gastrointestinal bleeding, and mental status changes) within 90 days of surgery were recorded. Deep infection was diagnosed according to the Musculoskeletal Infection Society criteria.[14] Lengths of hospital stay were also documented.

The threshold for uncontrolled diabetes was designated as HbA1c ≥ 7% and fructosamine ≥ 292 μmol/L (as determined in a previous study).[8] The AlbF was calculated using the following equation proposed by Lamb et al.[12]

$$AlbF = \frac{fructosamine(\mu mol/L) \times 100}{albumin(g/L)}$$

Statistical analysis

Descriptive statistics are presented as mean ± SD and range. To confirm a normal distribution, Shapiro–Wilk's test, histograms, skewness/kurtosis calculations, and detrended Q–Q plots were consulted. Chi-square and Fisher's exact tests were used to compare the categorical data. The student's *t*-test or Mann–Whitney *U*-test was used to compare the numerical data. Logistic regression analysis was performed, with complications (total complications or PJI) as the dependent variable. Independent variables with $P < .25$ were included in the multiple regression analysis. The results of logistic regression are presented as odds ratios (OR) with 95% CI. The fragility index (FI) of the results was also calculated.[15] The threshold for statistical significance was designated as $P < .05$. Statistical analyses were performed using the software package Statistical Package for the Social Sciences Statistics version 23.0 (IBM SPSS Corp., Armonk, NY, USA).

Results

Complications in the study groups are shown in Table 2. A total of 39 (13%) patients experienced complications, 10 (3%) underwent reoperations, and 16 (5%) were readmitted to the hospital. One mortality (1%) was noted within the first 90 days. Five (2%) patients were diagnosed with PJI, of which 4 had both fructosamine and HbA1c levels above the threshold, while 1 had lower levels for both markers. When total complication rates were compared, the FI values were calculated as follows: 7 for the comparison between DM subgroups, 30 for HbA1c, and 4 for fructosamine. When the PJI rates were compared, the FI values were calculated as follows: 2 for the comparison between HbA1c subgroups and 3 for fructosamine.

The results of the logistic regression analysis are shown in Tables 3 and 4. For total complications as the dependent variable, diagnosis of diabetes, HbA1c group, fructosamine group, age at surgery, ASA score, and CCI were found to be associated in the univariate analysis. In the multivariate analysis, the HbA1c group and CCI were the only factors shown to have a significant relationship with the total complications. For PJI as the dependent variable, the HbA1c group, fructosamine group, and AlbF values were found to be associated in the univariate analysis. In the multivariate analysis, only the fructosamine group was significantly associated with PJI.

Discussion

This prospective multi-institutional study on a 1 : 1 matched cohort of patients with and without diabetes revealed that the diagnosis of DM and elevated HbA1c and fructosamine levels were associated with a higher rate of total complications, while the elevated HbA1c and fructosamine levels were associated with a higher incidence of PJI. When further evaluated with logistic regression analysis, the preoperative HbA1c (≥7%) was found to have the highest predictive value for total

HIGHLIGHTS

- Optimum glycemic control marker before total hip or knee arthroplasty is inconclusive, and different markers may be more valuable in predicting different types of complications.
- Albumin-corrected fructosamine has not been previously studied in the arthroplasty literature, and it has not shown any clear benefit.
- Fructosamine is more valuable for predicting periprosthetic joint infection; however, hemoglobin A1c is better for predicting total complications.

Table 1. Demographic characteristics and perioperative details of the study population (p values written in bold indicate statistical significance for the given comparisons).

	Diagnosis of diabetes			HbA1c (%)			Fructosamine (μmol/L)		
	− (n=148)	+− (n=156)	*P*	<7	≥7	*P*	<292	≥292	*P*
Age at surgery, years (range)	60.8 (16-84)	67.9 (37-85)	**<.001**	63.4 (16-84)	67.2 (50-85)	**.007**	64.1 (16-84)	65.9 (22-85)	.279
Follow-up, months (range)	29.5 (15-49)	31.2 (12-47)	.245	30.4 (12-48)	30.3 (12-49)	.794	30.1 (12-48)	31.5 (12-49)	.336
Gender (male/female)	37/111	30/126	.182	50/184	17/53	.624	50/195	17/42	.162
BMI kg/m^2 (range)	29.2 (17-40)	32.1 (24-48)	**<.001**	30.3 (17-48)	32.5 (24-46.1)	**.001**	30.4 (17-48)	32 (21-46.1)	**.025**
ASA score		**<.001**			**<.001**			**.008**	
1	46 (31%)	6 (4%)	–	50 (21%)	2 (2%)	–	45 (18%)	7 (12%)	–
2	86 (59%)	90 (57%)	–	142 (61%)	34 (49%)	–	148 (60%)	28 (48%)	–
3	14 (10%)	62 (39%)	–	42 (18%)	34 (49%)	–	52 (22%)	24 (40%)	–
CCI		**<.001**			**<.001**			**.005**	
0	11 (7%)	0	–	11 (5%)	0	–	9 (4%)	2 (3%)	–
1	35 (24%)	4 (2%)	–	38 (15%)	1 (1%)	–	37 (15%)	2 (3%)	–
2	33 (23%)	25 (17%)	–	52 (22%)	6 (9%)	–	50 (20%)	8 (13%)	–
3	34 (23%)	38 (24%)	–	60 (26%)	12 (17%)	–	59 (24%)	13 (22%)	–
4	21 (14%)	34 (21%)	–	40 (17%)	15 (22%)	–	44 (18%)	11 (19%)	–
5	10 (7%)	30 (19%)	–	24 (10%)	16 (23%)	–	28 (11%)	12 (20%)	–
6	1 (1%)	18 (11%)	–	7 (3%)	12 (17%)	–	14 (6%)	5 (9%)	–
7	0	8 (5%)	–	1 (1%)	7 (10%)	–	3 (1%)	5 (9%)	–
8	0	1 (1%)	–	0	1 (1%)	–	0	1 (2%)	–
9	1 (1%)	0	–	1 (1%)	0	–	1 (1%)	0	–
HbA1C, % (range)	5.6 (4.8-8.7)	7.1 (5.3-13)	**<.001**	5.8 (4.8-6.9)	8.5 (7-13)	**<.001**	6 (4.9-9)	8.1 (4.8-13)	**<.001**
Glucose									
Preoperative mg/dL (range)	95 (73-155)	144 (76-394)	**<.001**	106 (73-208)	187 (95-394)	**<.001**	108 (73-254)	170 (87-394)	**<.001**
Postoperative mg/dL (range)	110 (76-200)	165 (87-436)	**<.001**	122 (76-256)	210 (109-436)	**<.001**	124 (76-256)	196 (107-436)	**<.001**
Fructosamine μmol/L (range)	220 (105-393)	265 (125-566)	**<.001**	220 (105-393)	325 (153-566)	**<.001**	215 (105-289)	360 (292-566)	**<.001**
AlbF (range)	557 (238-1191)	692 (291-2308)	**<.001**	561 (284-1191)	884 (425-2308)	**<.001**	559 (284-979)	941 (724-2308)	**<.001**

AlbF, albumin-corrected fructosamine; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; HbA1c, hemoglobin A1c.

complications, while fructosamine (≥292 μmol/L) levels were most strongly associated with PJI. Both markers may have important roles in the perioperative management of patients scheduled to undergo elective arthroplasty.

In this study cohort, patients with DM had a higher rate of total complications, and the univariate analysis showed an OR of 3.57 (95% CI, 1.63-7.81). The difference in the PJI rates (3% vs. 0%, *P*=.061) was not significant; however, the 5 patients who were diagnosed with PJI were all in the subgroup with diabetes. The effect of DM on postoperative complications after total hip or knee arthroplasty has been extensively studied. In a meta-analysis of 40 THA studies, Ren et al[16] found that the DM diagnosis was associated with a higher risk of PJI (risk ratio: 1.64, *P* < .001). Kremers et al[17] also found an increased risk of PJI; however, when adjusted for confounding variables (body mass index, age, sex, surgery type, ASA score, and operative time), the effect of being diagnosed with DM diminished. Diabetes causes immune suppression through various mechanisms, including altered cytokine production, leukocyte dysfunction, and defects in pathogen recognition.[18] Hyperglycemia may alter immune functions independent of diabetes diagnosis, which is demonstrated at the cellular and molecular levels.[19,20] Patients with DM comprise a very heterogeneous population, and being diagnosed with DM may not necessarily lead to an increased risk of complications, considering that an excellent glycemic control can be maintained by some patients. Uncontrolled diabetes will undoubtedly increase the risk of complications; however, patient-specific assessments and quantification of the risks for each complication will require considering more variables, such as the duration and severity of dysglycemia. Consequently, patient evaluation focusing on glycemic control using different markers may be helpful in achieving a more accurate assessment of complication risks and identifying the safest option for each patient.

The HbA1c reflects the average plasma glucose level over the past 2-3 months. It is the most widely used glycemic control marker and is currently the gold standard; however, its optimum threshold value is difficult to determine. In a meta-analysis, Shohat et al[1] observed a relationship between elevated HbA1c levels and surgical site infections following total hip or knee arthroplasty (OR: 1.49, *P*=.09); however, when a subgroup analysis was performed with a designated threshold of HbA1c ≥ 7%, this correlation diminished. This limitation of using HbA1c as a glycemic control marker prior to arthroplasty led researchers to seek different markers with a higher predictive value. Fructosamine is a glycoprotein formed by the attachment of a sugar molecule to serum proteins, mainly albumin.[21] It is a short-term marker that provides information about blood glucose levels over the past 2-3 weeks. While evaluating 829 patients undergoing total hip or knee arthroplasty, Shohat et al[8] found that a fructosamine level of ≥292 μmol/L was significantly associated with PJI (adjusted OR: 6.2, *P*=.009), whereas HbA1c levels did not show a significant correlation. These results were confirmed separately for THA and TKA in larger patient populations.[6,7] In the current study, subgroups with elevated levels of HbA1c and fructosamine both showed increased rates of PJI (Table 2). Univariate regression analysis also revealed a significant relationship between both markers and PJI; however, in the multiple regression analysis, fructosamine levels of ≥292 μmol/L remained

Table 2. Complications and the length of hospital stay in the study groups (p values written in bold indicate statistical significance for the given comparisons).

	Diagnosis of DM			HbA1c (%)			Fructosamine (μmol/L)		
	−	+	*P*	<7	≥7	*P*	<292	≥292	*P*
Total complications, n (%)	9 (6%)	30 (19%)	**.001**	17 (7%)	22 (31%)	**<.001**	25 (10%)	14 (24%)	**.005**
PJI, n (%)	0	5 (3%)	.061	1 (1%)	4 (6%)	**.011**	1 (1%)	4 (7%)	**.006**
Reoperations, n (%)	1 (1%)	9 (6%)	**.014**	5 (2%)	5 (7%)	**.039**	5 (2%)	5 (8%)	**.014**
Readmissions, n (%)	3 (2%)	13 (8%)	**.016**	5 (2%)	11 (16%)	**<.001**	10 (4%)	6 (10%)	.067
Length of hospital stay (days)	4.9 ± 3.3	4.8 ± 2.9	.565	4.9 ± 2.9	4.9 ± 3.6	.858	4.8 ± 3.1	5.1 ± 3.3	.705

DM, diabetes mellitus; HbA1c, hemoglobin A1c; PJI, periprosthetic joint infection.

Table 3. Logistic regression model analyzing the effects of different variables on total complications (p values written in bold indicate statistical significance for the given comparisons).

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	***P***	**Adjusted odds ratio (95% CI)**	***P***
Diagnosis of diabetes	3.82 (0.42-34.55)	.233	–	.798
HbA1c group	14.12 (1.55-128.5)	**.019**	–	.592
Fructosamine group	17.36 (1.9-158.3)	**.011**	13.68 (1.39-134.89)	**.025**
Albumin-corrected fructosamine	1.002 (1.001-1.005)	**.035**	–	.614
Bilateral surgery	<0.001	.999	–	–
Age at surgery	1.05 (0.94-1.16)	.395	–	–
BMI	1.11 (0.93-1.32)	.237	–	.446
ASA score	2.29 (0.53-9.91)	.269	–	–
CCI	1.57 (0.96-2.56)	.073	–	.436

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; HbA1c, hemoglobin A1c.

Table 4. Logistic regression model analyzing the effects of different variables on the occurrence of periprosthetic joint infection (p values written in bold indicate statistical significance for the given comparisons).

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	***P***	**Adjusted odds ratio (95% CI)**	***P***
Diagnosis of diabetes	3.57 (1.63-7.81)	**.001**	–	.729
HbA1c group	5.85 (2.89-11.85)	**<.001**	3.61 (1.65-7.91)	**.001**
Fructosamine group	3.06 (1.48-6.29)	**.002**	–	.129
Albumin-corrected fructosamine	1.001 (0.99-1.002)	.248	–	.813
Bilateral surgery	4.72 (0.76-29.2)	.095	–	.290
Age at surgery	1.04 (1.001-1.08)	**.044**	–	.172
BMI	1.03 (0.96-1.11)	.378	–	–
ASA score	1.93 (1.11-3.33)	**.019**	–	.740
CCI	1.6 (1.29-1.97)	**<.001**	1.37 (1.09-1.72)	**.008**

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; HbA1c, hemoglobin A1c.

the only variable that increased the risk of PJI by over 13-fold. These results support the current trend on the importance of fructosamine as a glycemic control marker in the orthopedic literature.

Complications that might occur after total hip or knee arthroplasty are numerous and, although of utmost importance, PJI comprises only a fraction. Assessment of glycemic control must focus on complications as a whole. In the current study, subgroups with elevated fructosamine and HbA1c levels showed significantly higher rates of total complications (Table 2). Univariate analysis also showed significant relationships between total complications and these markers (Table 3); however, in the multiple regression analysis, HbA1c ≥ 7% remained the only glycemic control marker with a significant relationship, increasing the risk of total complications over 3-fold. This difference in the results of the analyses based on PJI and total complication rates may be due to the underlying mechanisms of these complications. As mentioned above, immune dysfunction is mainly a result of ongoing hyperglycemia rather than a chronic process. Short-term markers, such as fructosamine, may be more accurate in reflecting hyperglycemic periods perioperatively. In contrast, most of the other complications are not directly immune related, and the underlying mechanisms may be based on micro- and macrovascular complications (e.g., atherosclerosis causing myocardial infarction), which are of a more chronic nature; HbA1c levels may be more valuable for predicting such events.

The different markers were highly correlated, and in most situations, they were both above or below the designated threshold levels (e.g., 4 of the 5 patients with PJI had elevated levels of both fructosamine and HbA1c). However, when these levels are divergent (one marker is above and the other is below the threshold), the clinical situation may be confusing and difficult to manage. The safest approach for the surgeon may be to consider the patient at a high risk for complications and postpone the surgery until the glycemic control is optimal.

By calculating the levels of AlbF,[12] we tried to eliminate the possible confounding effect of fluctuating serum protein levels on fructosamine measurements. As this marker has not been evaluated previously in the orthopedic literature, a cutoff value has not been established. As a continuous variable, AlbF was included in the regression analysis; however, it had no significant relationship with total complications (Table 3). When analysed for PJI as shown on Table 4, AlbF showed significant association in the univariate analysis, which dropped out when moved forward with the multivariate analysis. For PJI (Table 4), AlbF showed a significant association in univariate analysis, which dropped out in multivariate analysis. As expected, our study population included a significant number of elderly patients with comorbidities; however, correcting fructosamine levels with respect to albumin did not seem to increase its value in predicting complications. Further studies on selected subpopulations may reveal the potential benefits of this marker.

This study has certain limitations. First, the sample size was limited; a larger cohort would allow us to make subgroup analyses by separating THAs and TKAs, with more accurate assessment of risk quantifications. The FI may be used in this setting as an adjunct to statistical significance, and FI < 2 indicates that the study is underpowered, as stated by the American Academy of Orthopedic Surgeons guidelines.[22] Considering the given FI values, this study was statistically robust when analyzing total complications, and for PJI, the mean FI was still above the threshold of 2. The FI values were also no less than the number of patients lost to follow-up. The mean follow-up period was also limited, which may have affected the complication

rates. Another important limitation is the possible multicollinearity between different glycemic control markers. Since all these markers reflect the same entity (i.e., serum glucose concentration) over different time periods, it is expected that a certain correlation exists between them. This multicollinearity is known to result in unstable regression analysis results because the independent variables may not be *truly independent*. A separate analysis between HbA1c and fructosamine levels showed a correlation coefficient of $r = 0.696$, which urges caution in interpreting the results of this study. However, we believe that any study focusing on similar parameters will be prone to this limitation.

The results of this matched prospective cohort study revealed that in patients scheduled to undergo total hip or knee arthroplasty, a successful assessment of glycemic control cannot be sufficiently performed with a single marker, and both HbA1c and fructosamine have significant predictive values. Hemoglobin A1c is a good predictor of total complications, and fructosamine is most strongly associated with PJI. In addition, the correction of fructosamine based on albumin levels, which had not been studied previously in the orthopedic literature, did not show any additional benefit.

Ethics Committee Approval: This study was approved by Ethics Committee of Istanbul Research and Training Hospital (Approval No: 1201, Date: 2018).

Informed Consent: Written informed consent was obtained from the participants who agreed to take part in the study.

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