SIRS Is Valid in Discriminating Between Severe and Moderate Diabetic Foot Infections

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OBJECTIVE—This retrospective, single-center study was designed to distinguish severe diabetic foot infection (DFI) from moderate DFI based on the presence or absence of systemic inflammatory response syndrome (SIRS).

RESEARCH DESIGN AND METHODS—The database of a single academic foot and ankle program was reviewed and 119 patients were identified. Severe DFI was defined as local infection associated with manifestation of two or more objective findings of systemic toxicity using SIRS criteria.

RESULTS—Patients with severe DFI experienced a 2.55-fold higher risk of any amputation (95% CI 1.21–5.36) and a 7.12-fold higher risk of major amputation (1.83–41.05) than patients with moderate DFI. The risk of minor amputations was not significantly different between the two groups (odds ratio 1.02 [95% CI 0.51–2.28]). The odds of having a severe DFI was 7.82 times higher in patients who presented with gangrene (2.03–44.81) and five times higher in patients who reported symptoms of anorexia, chills, nausea, or vomiting (2.22–11.25). The mean hospital length of stay for patients with severe DFI was ~4 days longer than for patients with moderate DFI, and this difference was statistically significant.

CONCLUSIONS—SIRS is valid in distinguishing severe from moderate DFI in hospitalized patients. Patients with severe DFI, as by manifesting two or more signs of systemic inflammation or toxicity, had higher rates of major amputation and longer hospital stays and required more surgery and more subsequent admissions than patients who did not manifest SIRS.

Diabetes Care 36:3706–3711, 2013

In 2004, the Infectious Disease Society of America (IDSA) classified diabetic foot infections (DFIs) as mild, moderate, and severe based on local and systemic manifestations of infection (1). Individuals with mild infections are typically treated as outpatients but some patients with moderate infections and all patients with severe infections require hospitalization and potential surgical intervention. The International Working Group on the Diabetic Foot devised a similar classification system (1). Severe infections are distinguished from moderate infections by the presence of systemic toxicity or metabolic instability (fevers, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia). A validation study of the IDSA classification demonstrated that as infection severity increased, there was an increased risk of amputation and hospitalization (2). Neither the initial guideline nor the validation study precisely defined what constituted leukocytosis, tachycardia, hypotension, severe hyperglycemia, or azotemia (1,2). Recently, the IDSA updated their guidelines and recommended using systemic inflammatory response syndrome (SIRS) as a method for distinguishing between moderate and severe DFI (3). To the best of our knowledge, the use of SIRS has not yet been validated as a method of discriminating between moderate and severe DFI.

The aim of this study was to classify infection severity in a group of hospitalized diabetic patients based on the presence or absence of SIRS. The reason for hospitalization in this group of patients was their DFI. Our hypotheses are that patients with DFI who manifest SIRS (i.e., severe infection) will have longer hospital stays and higher rates of major amputation than patients who don't manifest SIRS (i.e., moderate infection).

RESEARCH DESIGN AND METHODS

After approval by our local institutional review board, the database of a single academic foot and ankle program was reviewed for patients hospitalized with a DFI from 2006 to 2012. Inpatient and outpatient electronic medical records were reviewed, and 119 patients were identified. We used the IDSA guidelines to classify infection severity (3). Mild infections were defined as having an infection that was limited to the skin and subcutaneous tissues with erythema of <2 cm (3). Moderate infections were defined as local infection with erythema >2 cm or involvement of structures deeper than the skin and subcutaneous tissues (abscess, osteomyelitis, septic arthritis, or fasciitis) in patients who did not manifest SIRS (3). Severe DFI was defined as local infection associated with manifestation of two or more objective findings of systemic toxicity using SIRS criteria (3,4). The findings of systemic toxicity include temperature (T) >38°C or <36°C, heart rate >90 bpm, respiratory rate >20 breaths/minute or partial pressure of arterial carbon dioxide <32 mmHg, and a white blood cell count (WBC) $>12,000$ cells or $<4,000$ cells/μL (3,4). The foot infections were classified as moderate or severe at the time of admission, and the extent of periwound erythema was documented during the initial assessment.

The University of Texas San Antonio (UTSA) wound classification was also used to grade the depth of the wound,

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Received 6 May 2013 and accepted 23 June 2013.
DOI: 10.2337/dc13-1083

and since this represents a study of hospitalized patients, no superficial wounds were observed. All of the wounds were infected, and the wounds were classified as either 2B, 2D, 3B, or 3D (5). Grade 2 wounds penetrate to tendon or capsule, and grade 3 wounds involve the joint, capsule, or bone. Nonischemic infected wounds are labeled as B, and infected ischemic wounds are labeled as D. Deep-tissue specimens were obtained after appropriate skin and wound preparation and sharp debridement. Tissue specimens (soft tissue and/or bone) were obtained in lieu of swab cultures. For the purposes of this study, we counted bacteria based on the number of different bacteria recovered on deep-tissue culture. For example, a deep-tissue culture that grew *Staphylococcus aureus* and *Escherichia coli* was counted as having two infecting organisms.

Major amputations were defined as amputation at the level of the ankle joint or more proximal (6). Minor amputations were defined as removal of a part of the foot at or distal to the transverse tarsal joint (6). By definition, minor amputations preserved a part of the foot. For the purposes of this study, limb salvage was defined as preservation of a part of the foot and equated to having no amputation or a minor amputation (6–8).

Statistical analysis

Descriptive statistics were summarized as frequencies or as mean ± SD. Examinations of normal distribution assumptions for continuous data were determined by q-q plots, histograms, and Shapiro-Wilk test. For nonnormally distributed continuous data, median and interquartile range are also presented. Two-sample Student *t* test or Mann-Whitney *U* test was performed to determine differences between moderate and severe infection groups for continuous data. Pearson χ^2 or Fisher exact test, as appropriate, was used to compare the frequency distribution of categorical variables between moderate and severe infection groups. Univariate logistic regression was applied to assess the strength of association between predictor variables (e.g., albumin, gangrene, infection, etc.) and the dichotomous outcome of interest (e.g., infection or amputation). The magnitude of associations between the predictor variable and outcome was quantified using the odds ratio (OR) and the corresponding 95% CI. Those predictor variables showing independent association with the outcome of interest (e.g., major amputation), in terms of OR and significance level $P < 0.05$, were selected for model fitting in a subsequent multiple logistic regression analysis using a stepwise approach. The level of significance to enter or remain in the model was set to 0.03 to allow only one variable in the model (9). OR and 95% CI were calculated from the β coefficient. Performance of the model was tested by means of the Hosmer-Lemeshow goodness-of-fit test. All tests were two-sided, and the significance level was set to 0.05. All analyses were conducted using SAS version 9.3 statistical software (SAS Institute, Inc., Cary, NC).

RESULTS—Of the 119 patients who were hospitalized for DFI, 65 patients were diagnosed with moderate infection and 54 with severe infection using SIRS. There were no significant differences between the two groups with regard to age, sex, BMI, tobacco use, type of diabetes (DM) (type 1 or 2), insulin use, duration of DM, presence of peripheral artery disease, and neuropathy or Charcot neuroarthropathy (Table 1). We did not identify a significant difference in the prevalence of osteomyelitis between those with severe and moderate infection (Table 2).

Patients with severe DFI experienced a 2.55-fold higher risk of any amputation than patients with moderate infection (95% CI 1.21–5.36) and a 7.12-fold higher risk of major amputation (1.83–41.05). The risk of minor amputations was not significantly different between the two groups (OR 1.07 [95% CI 0.51–2.28]). The odds of having a severe DFI was 7.82 times higher in patients who presented with gangrene (2.03–44.81) and five times higher in patients who reported symptoms of anorexia, chills, nausea, or vomiting (2.22–11.25). Laboratory and clinical data are recorded in Table 2. There was not a significant difference in the need for vascular surgery between those with moderate (9%) and severe (17%) DFI ($P = 0.22$) (Table 2).

The mean hospital length of stay for patients with severe DFI (11.39 ± 8.67 days) was ~4 days longer than for patients with moderate DFI (7.82 ± 6.65 days), and this difference was statistically significant (Table 2). Patients with severe DFI on average required more subsequent admissions to the hospital than those with moderate DFI ($P = 0.04$). The distribution of severe and moderate infections was not significantly different when using the UTSA wound classification with the exception of UTSA 2B wounds. Patients with moderate infections were more likely to have wounds that were less deep (UTSA 2B) than patients with severe infections ($P < 0.0001$).

Major amputation was identified in 17 (14%) of the 119 patients. On univariate analysis, several variables were significantly associated with major amputation, including younger age, higher Michigan Neuropathy Screening Index (MNSI), Charcot neuroarthropathy, elevated erythrocyte sedimentation rate (ESR), lower serum albumin, elevated anion gap, subjective symptoms (nausea, vomiting, chills, and anorexia), elevated WBC on discharge,

Table 1—*Demographic data*

	Moderate infection ($n = 65$)	Severe infection ($n = 54$)	*P* value
Age (years)	60 ± 12	57 ± 11	0.1401
Sex (female)	18 (28%)	10 (19%)	0.2402
BMI (kg/m^2)	31.53 ± 6.32	32.37 ± 7.82	0.5225
Tobacco use (active tobacco use/former tobacco use)	17 (26%)/6 (9%)	11 (20%)/5 (9%)	0.7406
Type 1 or 2 DM	10 (15%)/55 (85%)	7 (13%)/47 (87%)	0.7070
Insulin use	45 (69%)	44 (81%)	0.1255
Duration of DM (years)	14.22 ± 10.75	17.26 ± 10.35	0.1204
MNSI	7.29 ± 1.92	7.73 ± 1.45	0.1577
Charcot neuroarthropathy	16 (25%)	20 (37%)	0.1419
Osteomyelitis	41 (63%)	38 (70%)	0.4017
Peripheral artery disease	31 (48%)	22 (41%)	0.4475
Number of surgeries	1.4 ± 1.1	2.1 ± 1.6	0.0092

Data are mean ± SD unless otherwise indicated.

Table 2—*Comparison of laboratory results and clinical parameters between patients with moderate and severe DFI*

	Moderate infection (n = 65)	Severe infection (n = 54)	P value
ESR (mm/h)	70.89 ± 40.80 (63.00–49.00)	107.20 ± 34.72 (117.00–65.00)	<0.0001
CRP (mg/mL)	9.29 ± 10.34 (6.00–12.40)	19.36 ± 9.10 (19.57–9.50)	<0.0001
Serum albumin (g/dL)	2.96 ± 0.64	2.41 ± 0.61	<0.0001
Prealbumin (mg/dL)	15.05 ± 5.86	10.22 ± 5.19	0.0005
Hemoglobin (g/dL)	11.55 ± 2.20	10.57 ± 1.66	0.0066
HbA_{1c} (%), (mmol/L)	9.01 ± 2.39, 75 ± 26.1	8.61 ± 2.21, 71 ± 24.2	0.3573
Platelet count (cells/mm^3 in thousands)	265.55 ± 98.49	347.46 ± 126.50	0.0001
BUN (mg/dL)	22.52 ± 13.96	29.89 ± 18.88	0.0194
Creatinine (mg/dL)	1.77 ± 1.92 (1.00–1.00)	2.19 ± 1.91 (1.49–0.81)	0.0030
BUN/creatinine ratio	16.02 ± 5.93	15.33 ± 5.41	0.5134
Glucose admission (mg/dL)	256.20 ± 129.70	314.78 ± 160.06	0.0294
Glucose discharge (mg/dL)	181.10 ± 63.51	146.91 ± 52.63	0.0024
Change in glucose from admission to discharge	0.10 ± 0.72 (0.21–0.49)	0.38 ± 0.47 (0.51–0.36)	0.0008
Number of organisms (mean)	2.19 ± 1.21	2.83 ± 1.34	0.0087
Number of surgeries (mean)	1.42 ± 1.07	2.09 ± 1.59	0.0092
Any amputation (minor and major)	26 (40%)	34 (63%)	0.0126
Minor amputation	23 (35%)	20 (37%)	0.8518
Major amputation	3 (5%)	14 (26%)	0.0012
Vascular surgery during admission	6 (9%)	9 (17%)	0.2237
Number of subsequent admissions (r mean)	0.35 ± 0.65	0.70 ± 1.04	0.0418
UTSA grade 2B	12 (18%)	0	<0.0001
UTSA grade 2D	1 (2%)	1 (2%)	1.000
UTSA grade 3B	38 (58%)	36 (67%)	0.3581
UTSA grade 3D	14 (22%)	17 (31%)	0.2186
Systolic blood pressure (mmHg)	136.31 ± 22.36	138.15 ± 23.87	0.6654
Heart rate (bpm)	83.69 ± 15.24	102.94 ± 16.78	<0.0001
Admission T, mean	37.12 ± 0.39	38.05 ± 0.79	<0.0001
Respiratory rate (breaths per minute)	17.85 ± 1.96	19.94 ± 3.19	<0.0001
Serum CO_2 level (mmol/L)	25.36 ± 3.37	23.87 ± 3.86	0.0264
Serum anion gap (mEq/L)	10.47 ± 3.95	12.56 ± 4.33	0.0068
Number of patients with symptoms of nausea, vomiting, anorexia, and/or chills	13 (20%)	30 (56%)	<0.0001
WBC admission (cells/mm^3 in thousands)	9.38 ± 2.70	15.61 ± 4.74	<0.0001
WBC discharge (cells/mm^3 in thousands)	8.15 ± 4.07 (7.50–3.15)	10.05 ± 4.61 (8.65–5.20)	0.0067
WBC change (cells/mm^3 in thousands)	1.39 ± 3.85	5.80 ± 5.09	<0.0001
% Neutrophils admission	72.19 ± 10.82	83.30 ± 6.66	<0.0001
% Neutrophils discharge	65.39 ± 10.26	70.88 ± 12.02	0.0127
Change in neutrophils during admission	0.09 ± 0.15 (0.09–0.19)	0.15 ± 0.16 (0.18–0.19)	0.0195
Gangrene	3 (5%)	15 (28%)	<0.0001
Glucose >200 mg/dL	39 (60%)	40 (74%)	0.1056
WBC >12,000 cells/mm^3	10 (15%)	46 (85%)	<0.0001
36°C< T >38°C	2 (3%)	30 (56%)	<0.0001
Respiratory rate (breaths per minute) >20	2 (3%)	16 (30%)	<0.0001
Heart rate (bpm) >90	17 (26%)	43 (80%)	<0.0001
Cumulative number of SIRS criteria	34 (52%)/31 (48%)/0/0/0	0/0/32 (59%)/17 (31%)/5 (9%)	<0.0001
Length of stay (days)	7.82 ± 6.65 (5.00–5.00)	11.39 ± 8.67 (9.50–9.00)	0.0005

Data presented as mean ± SD or frequency (%), (median, interquartile range) when appropriate.

and admission oral T >38°C (Table 3). Multiple logistic regression analysis using a stepwise approach demonstrated that serum albumin was a significant predictor of major amputation status (OR 0.19 [95% CI 0.07–0.49]). A negative estimated coefficient for serum albumin (−1.68) suggests that the risk of major amputation decreases with one unit increase in serum albumin levels. The mean number of organisms recovered on wound culture was 2.5 per infection, and patients with severe DFI had significantly more infecting organisms than patients with moderate DFI (2.83 vs. 2.19 organisms, P = 0.0087). Twenty different bacteria and one fungus were recovered from wound cultures, and methicillin-sensitive *S. aureus* (44%), *Streptococci* (40%), and methicillin-resistant *S. aureus* (30%) were the most common pathogens. All of these organisms were recovered from deep-tissue cultures obtained after debridement and were considered pathogenic by

Table 3—*Univariate analysis of variables associated with major amputation*

	OR (95% CI)
Age	**0.937 (0.889–0.988)**
Sex	5.703 (0.808–250.349)
BMI	0.941 (0.867–1.022)
Active tobacco use	2.313 (0.661–7.740)
Type 1 or 2 DM	0.744 (0.173–4.547)
Duration of DM	0.996 (0.948–1.046)
Insulin use	1.111 (0.306–5.093)
MNSI	**1.755 (1.130–2.726)**
Presence of Charcot neuroarthropathy	**4.176 (1.442–12.097)**
HbA_{1c}	0.872 (0.680–1.117)
Osteomyelitis	4.409 (0.943–41.843)
Peripheral artery disease	1.960 (0.691–5.561)
ESR	**1.023 (1.007–1.039)**
Albumin	**0.187 (0.071–0.491)**
CRP	1.025 (0.982–1.070)
Hemoglobin	0.940 (0.734–1.205)
Platelet count	1.004 (1.000–1.008)
BUN	1.015 (0.988–1.044)
Creatinine	1.230 (0.993–1.525)
BUN/creatinine ratio	0.944 (0.858–1.037)
Number of organisms	1.398 (0.941–2.078)
Vascular surgery	1.607 (0.402–6.419)
UTSA wound grade	0.224 (0.000–1.263)
Each UTSA wound grade (1, 2, 3)	1.519 (0.000–13.354)
vs. Grade 4	0.539 (0.163–1.871)
Anion gap	**1.132 (1.004–1.275)**
Acidosis	2.156 (0.742–6.261)
Nausea/vomiting	**2.987 (1.044–8.546)**
WBC admission	1.102 (0.997–1.217)
WBC discharge	**1.165 (1.038–1.307)**
Gangrene	1.240 (0.204–5.268)
Prerenal azotemia	0.629 (0.107–2.515)
Hyptotension	12.952 (0.639–801.878)
Hyperglycemia	1.251 (0.372–4.907)
Tachycardia	2.678 (0.806–10.430)
WBC >12,000 cells/mm^3	2.322 (0.798–6.762)
T >38	**3.864 (1.339–11.149)**
Respiratory rate >20	1.922 (0.400–7.497)

Significant findings are highlighted in bold font.

our infectious disease consultants. The most common metabolic perturbation observed in this study was hyperglycemia, as 79 of 119 patients (66%) presented with a serum glucose >200 mg/dL. Patients with severe DFI (314.78 mg/dL) had significantly higher mean admission glucose levels than moderate infections (256.20 mg/dL) ($P = 0.0294$). Long-term glycemic control as measured by HbA_{1c} was not significantly different between the two groups (Table 2). Other significant abnormalities included 60 patients (50%) with tachycardia (heart rate >90 beats minute), 56 patients (47%) with a WBC >12,000 cells/mm^3, 32 patients (27%) with T >38°C, 32 patients (27%) with reduced serum CO_2 levels (<22 mmol/L), 29 patients (24%) with prerenal azotemia (serum urea nitrogen/creatinine ratio >20), 18 patients (15%) with respiratory rate >20 breaths per minute, 18 patients (15%) with an increased anion gap (>15 mEq/L), and 3 patients (2%) with systolic blood pressure <90 mmHg. Fifteen of the 119 patients (13%) underwent open or endovascular revascularization during the hospitalization.

CONCLUSIONS—This study validates the most recent recommendation of the IDSA to use SIRS as a method to distinguish severe from moderate DFI. Hospitalized patients with DFI who presented with SIRS had higher rates of major amputation, had longer hospital stays, required more surgery, required more subsequent admissions, and grew more organisms on wound culture than patients who did not manifest SIRS. SIRS has also been associated with inferior outcomes in other areas of surgery (10,11). Patients undergoing emergent colorectal surgery who presented with SIRS experienced 1.9 times higher risk of 30-day mortality compared with patients who did not manifest SIRS (11). A study of 179 acute surgical admissions demonstrated that patients who presented with SIRS had more therapeutic interventions (39.7 vs. 16.4%, $P = 0.001$), surgical interventions (33.3 vs. 3.4%, $P < 0.0001$), longer hospital stay (median 6 vs. 2 days, $P < 0.001$), and more frequent deaths (11.1 vs. 2.6%, $P < 0.05$) than patients who did not present with SIRS (10). Patients with DFI may not mount the normal inflammatory response, such as leukocytosis or fever due to immune dysfunction, and consequently those who do are at higher risk for adverse outcome (12,13). In our cohort of hospitalized patients, only 47% presented with a WBC >12,000 cells/mm^3 and 27% with a fever >38°C. Consequently, clinicians should be observant for other signs of infection. In addition to manifesting signs of SIRS, patients with severe DFI demonstrated significant differences in many laboratory parameters when compared with patients with moderate DFI. Inflammatory markers (ESR and C-reactive protein [CRP]), measurements of renal function (blood urea nitrogen [BUN] and creatinine), serum glucose, platelet count, and anion gap were significantly higher in patients with severe DFI (9). Conversely, serum albumin, prealbumin, and CO_2 levels were significantly lower in patients with severe DFI. These perturbations are consistent with a robust inflammatory response that accompanies more severe infection. Subjective symptoms of fever, chills, nausea, vomiting, and anorexia were also more likely to be associated with severe infection, and heightened awareness of a serious infection should be entertained in those patients who report those symptoms.

Although the potential for major amputation is sevenfold higher in patients with severe DFI, patients with moderate DFI are also at risk as 5% of our patients required a transtibial amputation. Both groups are at significant risk for minor amputations, and approximately one-third of patients in both groups required a minor amputation. Our results are consistent with

recent studies evaluating the outcomes of patients with DFI. A report from France demonstrated that nearly 48% of patients treated at specialized centers for DFI underwent lower-limb amputation during the first year of treatment (14). Another study of 141 patients (115 moderate and 26 severe DFI) reported an overall amputation rate of 43%; however, the major amputation rate was only 3.5% (15). Lavery et al. (2) reported that 77% of patients with a severe DFI required some type of amputation and that major amputations were performed in nearly 30% of patients.

The use of SIRS requires only vital signs and WBC at the time of admission, and this simplistic approach is a valid method of distinguishing severe from moderate DFI. As expected, patients with severe DFI had higher mean WBC and higher mean percentage of neutrophils on admission and discharge than patients with moderate DFI. The mean percentage improvement in WBC from admission to discharge was also significantly better in patients with severe DFI (36%) compared with moderate DFI (15%). Correction of hyperglycemia from admission to discharge was also more pronounced in patients with severe infection. The most likely explanation for this is that patients with severe DFI presented with significantly higher values, and consequently the response to treatment was more dramatic.

This study has several weaknesses that need to be acknowledged. Retrospective studies rely on the accuracy of the medical records, and data analysis is only as good as the quality of the information obtained from the medical record. The nature of our surgical practice potentially introduces bias into this study, since our service is only consulted for the most serious DFIs. The overwhelming majority of patients (110 of 119) underwent surgery for their DFI, and only 8% (nine patients) were treated nonsurgically. At our institution, patients with less serious infections are typically admitted to the medical service and do not require surgical consultation. Although this is a limitation of this study, it also provides further support for the use of SIRS. Our study group represents a cohort of hospitalized patients with limb-threatening infections, and SIRS was able to meaningfully distinguish severe from moderate infection. Approximately 30% of our patients had Charcot neuroarthropathy, and this may not be representative of a normal diabetic foot population. The most likely explanation for this is that our hospital serves as a referral center for the inpatient management of complex diabetic foot disorders such as Charcot neuroarthropathy. Another weakness of this study is that we did not evaluate the specific antibiotic regimen or the duration of antibiotic use. Our inpatient diabetic foot service uses a multidisciplinary approach using the consultative services of hospital medicine, infectious disease, endocrinology, and renal and vascular surgery, and our infectious disease consultants manage the antibiotic regimen during the hospitalization and after discharge. One of the major goals of the inpatient diabetic foot team is to reduce the rate of major amputations. Because of the small number of patients who underwent major amputation (n = 17), we were limited to one variable when constructing the logistic regression analysis model for significant variables associated with major amputation on univariate analysis (16). With larger numbers, it is possible that other variables in addition to serum albumin would be associated with major amputation on multiple logistic regression analysis. Although patients with severe DFI grew more organisms on culture than patients with moderate DFI, this study did not permit us to compare the various organisms recovered between patients with severe and moderate DFI.

Patients with DFI who manifest SIRS have longer hospital stays, more subsequent admissions, and higher rates of major amputation than patients who do not manifest SIRS. The use of SIRS is a valid method of classifying infection severity in hospitalized patients with DFI. Other metabolic perturbations and laboratory abnormalities are also associated with severe DFI, and physicians should recognize that not all patients will manifest a robust inflammatory response in the presence of a severe infection. Our overall limb salvage rate was 86% in a high-risk group of patients, and patients who manifested SIRS (severe infection) had lower-limb salvage rates than patients who did not manifest SIRS (74 vs. 95%).

Acknowledgments—The project described was supported by the National Institutes of Health through grants UL1-RR-024153 and UL1-TR-000005.

No potential conflicts of interest relevant to this article were reported.

D.K.W. researched the data and wrote the manuscript. K.B.H. and K.M.R. researched the data and edited the manuscript. B.L.R. performed the statistical analyses and edited the manuscript. D.K.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, Illinois, 21–25 June 2013.

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