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ORIGINAL ARTICLE

The Use of Optical Coherence Tomography to Determine the Effect of Thiazolidinediones on Retinal Thickness in Patients with Type 2 Diabetes

Aaron K. Tarbett, O.D.,[1] LTC Ronald C. VanRoekel, O.D.,[2] Robin S. Howard, M.A.,[3] and COL MC Robert A. Vigersky, M.D.[4]

Abstract

Objective:

Thiazolidinediones (TZDs) are insulin-sensitizing agents that are associated with peripheral edema and have been reported to be associated with diabetic macular edema (DME). We hypothesized that TZDs produce subclinical increases in retinal thickness that may be detected by optical coherence tomography (OCT) but are not seen on routine dilated funduscopic examination.

Research Design and Methods:

We used OCT to screen for subclinical DME in a cross-sectional study of patients with type 2 diabetes; 29 patients were taking TZDs and 58 were not taking TZDs. We analyzed data using multiple linear regression analysis to investigate associations of retinal thickness with clinical characteristics.

Results:

There was no significant difference between the central subfield retinal thickness in the non-TZD group (206.4 ± 28.0 microns; $n = 59$) and TZD group (204.1 ± 26.1 microns; $n = 29$) ($p = .72$) nor were there significant differences in any other retinal subfield. There was no significant correlation of retinal thickness with laboratory results studies—peripheral edema, gender, age, duration of diabetes, individual, or combinations of medications. Retinal thickness differences between regions displayed normal anatomical variation. However, ethnic differences were found in which African-Americans had thinner retinas in all regions than Caucasians regardless of whether or not they used TZDs.

Conclusions:

These data suggest that TZDs do not cause subclinical DME in a demographically diverse patient population with diabetes. The established normal ranges for macular thickness may require adjustment based on ethnicity.

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Author Affiliations: [1]Optometry Clinic, Walter Reed Army Medical Center, Washington, District of Columbia; [2]DiLorenzo Tricare Health Clinic, Washington, District of Columbia; [3]Department of Clinical Investigation, Biostatistics Section, Walter Reed Army Medical Center, Washington, District of Columbia; and [4]Endocrinology Service, Walter Reed Army Medical Center, Washington, District of Columbia

Abbreviations: (BDR) background diabetic retinopathy, (CI) confidence interval, (DME) diabetic macular edema, (HbA1c) hemoglobin A1c, (LDL) low-density lipoprotein, (OCT) optical coherence tomography, (RM ANOVA) repeated measures analysis of variance, (SD) standard deviation, (TZD) thiazolidinedione, (WRAMC) Walter Reed Army Medical Center

Keywords: diabetic macular edema, optical computerized tomography, oral antidiabetic agents, retinal thickness, type diabetes 2 diabetes mellitus, thiazolidinediones

Corresponding Author: Robert A. Vigersky, M.D., Endocrinology Service, Walter Reed Army Medical Center, 6900 Georgia Avenue NW, Washington, DC 20307-5001; email address robert.vigersky@amedd.army.mil

Introduction

Thiazolidinediones (TZDs) are insulin-sensitizing drugs that can be used as monotherapy or in combination with other oral or injectable glucose-lowering medications (including insulin) for glycemic control in type 2 diabetes. Thiazolidinediones increase insulin sensitivity by acting on muscle and liver to increase glucose utilization and decrease glucose production through their binding to peroxisome proliferator-activated receptors.[1] Pioglitazone (ACTOS®) and rosiglitazone (AVANDIA®) are the only two TZDs available in the United States and the latter only to a limited degree. Among the known adverse effects of TZDs is peripheral edema, which is found in 5–7% of patients using TZDs alone and up to 15% of patients when a TZD is used in combination with insulin.[2] Because systemic fluid retention in cases of congestive heart failure or renal disease is associated with diabetic macular edema (DME),[3] it has been hypothesized that peripheral edema and fluid retention associated with TZDs may increase the risk of DME. Indeed, a few case reports and research support this.[4–8] DME is a common complication of diabetes mellitus and is one of the most frequent causes of vision loss in patients with diabetes mellitus.[9] The purpose of this study is to determine if TZDs cause subclinical DME defined as macular thickening not seen on routine funduscopic examination but identified by optical coherence tomography (OCT), a technology that can provide objective measurements of retinal thickness.

Methods

This is a cross-sectional study of patients with type 2 diabetes comparing retinal thickness in subjects on glucose-lowering regimens that did not contain TZDs with those that did include TZDs. The TZD group had been taking a TZD for at least 6 months and the non-TZD group had been taking a regimen that did not include a TZD for the previous 6 months. The patients had to be age 18 years and older, had type 2 diabetes for at least 1 year, and had been taking one or more glucose-lowering medications. Patients were excluded if they had a history of congestive heart failure or renal failure, DME, any known diabetic retinopathy or diabetic retinopathy found at the time of screening for inclusion in the study, glaucoma, any visually significant cataracts (greater than Grade 1), or spherical equivalent refractive error greater than 6 diopters. The study was approved by the Human Use Committee/Institutional Review Board at the Walter Reed Army Medical Center (WRAMC). All subjects gave their written, informed consent to participate. Enrollment occurred in the Optometry Service during a 2-year period at WRAMC beginning August 2007.

All subjects entered the study after a comprehensive dilated eye exam had ruled out any of the preestablished exclusion criteria noted above. The primary outcome measure was the difference in retinal thickness measured by OCT between the TZD group and the non-TZD group. This study used a Stratus OCT3 model (Carl Zeiss Meditec, Dublin, CA), which has a tissue and thickness resolution limit of 10 microns axially. Optical coherence tomography is a safe, noninvasive, rapid, and reproducible method of producing high-resolution, cross-sectional images of the retina using a near-infrared, 820-nm light beam in a process similar to an ultrasound examination.[10] It is a commonly used instrument in the clinical setting for evaluation, analysis, and thickness measurements of the retina.[11] Subjects' pupils were dilated and the macular thickness map scan protocol and retinal thickness/volume tabular OU (both eyes) analysis algorithm were used to measure the central 6 mm of the macular region that includes the central 1 mm (foveal area) defined as the central subfield. Normative values for central subfield thickness vary between studies.[12–16] The current study uses a mean ± standard deviation (SD) of 212 ± 20 microns. Subjects with measurements that were more than 232 microns were considered to have DME. Two consecutive macular thickness map scans per eye were taken and averaged. If the initial two central subfield thickness measurements differed by more than 10 microns, a third measurement was taken and the two measurements that were closest were used as the average. If the repeated scans happened to be equidistant from the initial values, the lower two values of the three scans were averaged. Scans of inadequate quality (e.g., signal strength score <5) were repeated until they met the specified quality metrics or were excluded from the study if standards were unattainable.

Secondary outcomes of this study included the association of the following with TZD use: 1) distal extremity edema; 2) diabetes-related laboratory data including glycosylated hemoglobin A1c (HbA1c), serum creatinine level, the presence and quantity of urinary microalbumin, and serum low density lipoprotein (LDL) and triglyceride levels obtained within 90 days of the OCT study; 3) central subfield and peripheral zone retinal thicknesses; and 4) medication history as obtained from the electronic medical record.

The presence of pitting edema in the lower extremities was assessed by observing the persistence of an indentation of the skin following pressure behind the medial malleolus and anterior tibia. It was graded as follows: 0 = no edema; 1+ = present only behind the medial malleolus; 2+ = present behind the medial malleolus and up to one third of the tibia; 3+ = present behind the medial malleolus and up to two thirds of the tibia; and 4+ = present behind the medial malleolus and extending to the knee or above.

Statistical Consideration

The Shapiro-Wilk test was used to evaluate if continuous data satisfied assumptions of normality; most data describing baseline characteristics were not normally distributed, are presented as the median and range, and were analyzed using the Wilcoxon rank sum test. Categorical data were compared between groups using Fisher's exact test. Retinal thicknesses were examined using data for all eyes and also by subject, using data from the eye with the thickest central subfield. Overall retinal thickness for all nine subfields (using the subject's eye with the thickest central subfield) was compared between groups using repeated measures analysis of variance (RM ANOVA). Results for each subfield are presented using the mean ± SD and were compared using the two-sample *t*-test. To examine the association between each clinical characteristic and central subfield thickness, a simple linear regression model was used. Multiple linear regression analysis was used to examine differences in central subfield thickness between TZD groups while controlling for clinical characteristics. In all regression analyses, the actual value of each variable was used. All *p* values are two-sided. Data were analyzed using SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL).

Results

Patient demographics and clinical characteristics are shown in **Table 1**. The groups are generally well matched for most relevant clinical parameters except that those in the TZD group had a longer duration of diabetes (8 vs 5 years; $p = .039$) and were more likely to be on a sulfonylurea (69 vs 45%; $p = .042$) compared to those in the non-TZD group. All but one in the TZD group were

Table 1.
Patient Demographics

	All subjects	Non-TZD	TZD	*p* value
Number	87	58	29	
Age median (range) (years)	59 (40–77)	59 (40–77)	60 (43–74)	.84
Gender (male), *n* (%)	46 (53)	30 (52)	16 (55)	.82
Ethnicity, *n* (%) African-American Caucasian Other (Hispanic, Asian, Indian)	 46 (53) 35 (40) 6 (7)	 33 (57) 19 (33) 6 (10)	 13 (45) 16 (55) 0 (0)	.056
Duration of diabetes median (years) (range)	6 (1–26)	5 (1–26)	8 (2–25)	.039
HbA1c median (range)	6.7 (4.9–14.2)	6.5 (4.9–10.8)	6.9 (5.7–14.2)	.093
Serum creatinine median (range)	1.0 (0.5–7.9)	1.0 (0.5–1.5)	0.9 (0.6–7.9)	.51
Microalbumin Creatinine median (range) (mg/g) >30 mg/g creatinine, *n* (%)	 7.1 (0.5–2149.4) 19 (22)	 6.7 (1.0–2149.4) 10 (17)	 9.7 (0.5–465.6) 9 (31)	 .48 .17
LDL cholesterol median (range) (mg/dl)	92 (49–161)	95 (49–161)	86 (53–132)	.39
Triglycerides median (range) (mg/dl)	134 (41–569)	142 (41–569)	126 (55–307)	.17
Presence of peripheral edema	21 (24)	15 (26)	6 (21)	.79
Duration TZD use median (range) (months)		N/A[a]	33.9 (12.3–85.7)	N/A[a]
Sulfonylurea use, *n* (%)	46 (53)	26 (45)	20 (69)	.042
Insulin use, *n* (%)	9 (10)	6 (10)	3 (10)	.99
Use of ACE[a] inhibitor or ARB[a], *n* (%)	55 (63)	35 (60)	20 (69)	.49

[a] N/A, not applicable; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

on pioglitazone. Fifty-eight subjects (116 eyes) were in the non-TZD group and 29 (58 eyes) in the TZD group. The median duration of TZD use was 33.9 months. Excluded from analysis were 24 eyes [7 were excluded from the TZD group (12%) and 17 of 116 eyes were excluded from the non-TZD group (15%)] for the following reasons: 10, unreliable measurement; 5, cataract; and 9, retinal hemorrhages or other retinal defects. The results of the OCT scan on those taking and not taking TZDs are shown in **Figure 1A**. The thickness differences between regions display the normal anatomical variations that occur throughout the retina. There was no statistically significant regional difference in retinal thickness (including the central subfield) between those who had a TZD included in their regimen and those who did not (RM ANOVA, $p = .72$) (**Table 2**). However, there was a significant difference in thicknesses between ethnic groups, with African-American subjects having thinner OCT3 thicknesses than Caucasian subjects regardless of TZD usage (RM ANOVA, $p < .0005$) (**Figure 1B** and **Table 3**). There was no significant correlation between retinal thickness and any of the laboratory studies—peripheral edema, gender, age, duration of diabetes, and individual or combinations of medications (**Table 4**).

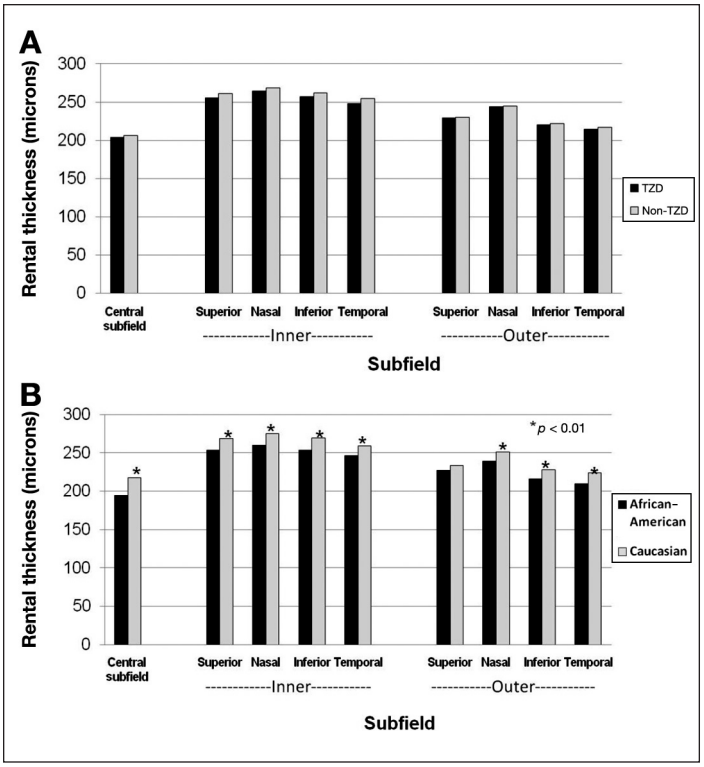

Figure 1. Retinal thickness in TZD vs non-TZD users **(A)** and in Caucasians vs African-Americans **(B)**.

Table 2.
Retinal Thickness for TZD and Non-TZD Users for All Subfields

Subfield	All subjects	Non-TZD	TZD	Mean difference (95% CI)	*p* value[b]
All subjects[a]	*n* = 87	*n* = 58	*n* = 29		
Central subfield	205.6 ± 27.2	206.4 ± 28.0	204.1 ± 26.1	2.2 (-10.1 to 14.6)	.72
Inner superior	259.3 ± 25.2	261.2 ± 22.2	255.3 ± 30.4	5.9 (-5.5 to 17.3)	.30
Inner temporal	252.4 ± 20.5	254.6 ± 19.3	248.1 ± 22.4	6.5 (-2.7 to 15.7)	.16
Inner inferior	260.1 ± 22.0	261.7 ± 21.1	256.9 ± 24.0	4.8 (-5.1 to 14.8)	.34
Inner nasal	267.0 ± 21.5	268.6 ± 20.4	264.0 ± 23.7	4.6 (-5.1 to 14.3)	.35
Outer superior	229.8 ± 17.5	230.1 ± 17.8	229.3 ± 17.3	0.9 (-7.1 to 8.8)	.83
Outer temporal	216.4 ± 19.0	217.2 ± 20.9	214.7 ± 14.5	2.5 (-6.1 to 11.2)	.56
Outer inferior	221.4 ± 20.4	222.0 ± 21.8	220.4 ± 17.7	1.5 (-7.7 to 10.8)	.74
Outer nasal	244.3 ± 20.3	244.7 ± 20.8	243.5 ± 19.6	1.2 (-8.1 to 10.4)	.80
All eyes	*n* = 150	*n* = 99	*n* = 51		
Central subfield	201.7 ± 26.8	202.1 ± 27.7	201.0 ± 25.3	1.1 (-8.1 to 10.2)	.82
Inner superior	260.8 ± 22.8	262.7 ± 20.4	257.2 ± 26.7	5.5 (-2.2 to 13.3)	.16
Inner temporal	252.4 ± 19.3	254.0 ± 18.5	249.3 ± 20.5	4.7 (-1.8 to 11.3)	.16
Inner inferior	260.6 ± 20.4	262.3 ± 19.6	257.5 ± 21.7	4.8 (-2.1 to 11.7)	.17
Inner nasal	266.1 ± 20.2	267.3 ± 19.3	263.9 ± 21.9	3.5 (-3.4 to 10.4)	.32
Outer superior	229.7 ± 16.8	230.4 ± 17.1	228.3 ± 16.2	2.1 (-3.6 to 7.8)	.47
Outer temporal	215.0 ± 17.0	215.8 ± 18.2	213.6 ± 14.4	2.2 (-3.6 to 8.0)	.46
Outer inferior	222.0 ± 18.8	223.1 ± 19.8	220.1 ± 16.8	3.0 (-3.4 to 9.4)	.36
Outer nasal	244.5 ± 19.6	245.6 ± 19.9	242.4 ± 18.9	3.2 (-3.5 to 9.8)	.35

[a] One eye per subject (eye with the highest central field thickness) analyzed.
[b] Groups compared by two sample *t*-test.
Data presented as mean ± SD or mean difference (95% CI of the difference.)

Table 3.
Central Subfield Thickness by Ethnicity

	Caucasian n = 46	African-American n = 35	p value[a]
All subjects	217.9 ± 24.9	194.4 ± 25.4	<.0005
Non-TZD	216.1 ± 27.9	198.3 ± 27.5	.03
TZD	220.0 ± 21.6	184.6 ± 16.0	<.0005

[a] Groups compared by two sample t-test.

Discussion

We had hypothesized that TZDs may cause subclinical retinal thickening in many patients, only a small fraction of whom progress to DME. However, we conclude that TZDs do not cause subclinical macular edema in a demographically diverse patient population with type 2 diabetes, whether the TZD was taken as monotherapy, combined with noninsulin glucose-lowering agents including sulfonylureas, or insulin. Our study is unique

Table 4.
Central Subfield Thickness in TZD and Non-TZD Users According to Clinical Characteristics

Clinical characteristic	n	Central subfield mean ± SD	p value[a]	Non-TZD		TZD		Multiple regression	
				n	Central subfield mean ± SD	n	Central subfield mean ± SD	p value clinical variable	p value for TZD
Overall	87	205.6 ± 27.2		58	206.4 ± 28.0	29	204.1 ± 26.1		.72
Age[b]			.66					.66	.73
<55 years	28	205.8 ± 29.4		19	200.6 ± 28.0	9	216.7 ± 30.8		
≥55 years	59	205.6 ± 26.4		39	209.2 ± 27.9	20	198.5 ± 22.3		
Gender			.15					.15	.69
Women	41	201.2 ± 28.5		28	203.2 ± 30.8	133	196.9 ± 23.3		
Men	46	209.6 ± 25.7		30	209.3 ± 25.2	16	210.0 ± 27.5		
Ethnicity			<.0005					<.0005	.38
African-American	46	194.4 ± 25.4		33	198.3 ± 27.5	13	184.6 ± 16.0		
Caucasian	35	217.9 ± 24.9		19	216.1 ± 27.9	16	220.0 ± 21.6		
Duration of diabetes[b]			.061					.067	.99
<10 years	59	206.7 ± 28.6		45	205.9 ± 29.3	14	209.4 ± 27.3		
≥10 years	21	201.8 ± 24.0		10	207.2 ± 20.9	11	196.8 ± 26.5		
HbA1c[b]			.12					.13	.93
<8%	66	205.7 ± 26.8		45	204.9 ± 28.7	21	207.5 ± 22.5		
≥8%	14	195.6 ± 20.4		8	201.8 ± 21.0	6	187.3 ± 18.1		
<7%	48	208.5 ± 25.5		33	207.1 ± 28.1	15	211.4 ± 19.4		
≥7%	32	197.1 ± 25.4		20	199.9 ± 26.7	12	192.5 ± 23.4		
Serum creatinine[b]			.13					.14	.93
Female <1.4; Male <1.5	79	204.8 ± 27.0		53	205.2 ± 27.7	26	204.0 ± 26.1		
Female ≥1.4; Male ≥1.5	3	190.8 ± 23.2		1	187.5	2	192.5 ± 32.5		
Microalbumin[b]			.72					.74	.77
≤30 mg/g creatinine	68	208.9 ± 27.9		48	209.8 ± 28.0	20	206.8 ± 28.2		
>30 mg/g creatinine	19	193.9 ± 21.5		10	190.0 ± 22.2	9	198.3 ± 21.1		
LDL Cholesterol[b]			.94					.91	.79
<100 mg/dl	49	207.8 ± 27.0		30	206.0 ± 26.9	19	210.6 ± 27.7		
≥100 mg/dl	34	201.4 ± 25.7		24	205.4 ± 27.6	10	191.9 ± 18.1		
Triglycerides[b]			.72					.74	.93

(Continued) →

Table 4. Continued

Clinical characteristic	*n*	Central subfield mean ± SD	*p* value[a]	Non-TZD		TZD		Multiple regression	
				n	Central subfield mean ± SD	*n*	Central subfield mean ± SD	*p* value clinical variable	*p* value for TZD
<250 mg/dl	78	204.3 ± 26.6		50	204.9 ± 27.2	28	203.2 ± 26.1		
≥250 mg/dl	6	210.3 ± 29.6		5	206.2 ± 31.1	1	231.0		
Peripheral edema			.88					.87	.71 71
Yes	21	204.8 ± 27.2		15	202.8 ± 29.9	6	210.0 ± 20.3		
No	65	205.8 ± 27.7		43	207.6 ± 27.5	22	202.4 ± 28.2		
Sulfonylurea use			.81					.87	.76
Yes	46	204.9 ± 24.2		26	205.8 ± 26.0	20	203.8 ± 22.2		
No	41	206.4 ± 30.6		32	206.8 ± 29.9	9	204.8 ± 34.8		
Insulin use			.76					.76	.72
Yes	9	208.3 ± 23.7		6	219.1 ± 14.4	3	186.7 ± 25.9		
No	78	205.3 ± 27.7		52	204.9 ± 28.9	26	206.2 ± 25.9		
Use of ACE or ARB			.25					.26	.79
Yes	55	203.0 ± 26.3		35	200.1 ± 26.4	20	208.2 ± 25.9		
No	32	210.0 ± 28.7		23	215.9 ± 28.1	9	195.1 ± 25.7		

[a] Based on simple linear regression.
[b] Actual value of clinical variable used in regression analyses.
[c] ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

in that it is cross-sectional and is the only study that used OCT and controlled for background diabetic retinopathy (BDR) (by excluding anyone whose screening dilated retinal examination showed any retinal hemorrhages or other retinal defects) as well as the only study to screen for subclinical macular edema. Studies suggesting that TZDs increase the risk have been retrospective,[4,5] have not controlled for BDR (i.e., have included such patients in their study),[4,5,17] and have not used OCT to detect DME.[4,5,17,18] All but one of our TZD patients were on pioglitazone, reflecting an institutional preference. Thus, our data are applicable to most patients using TZDs at this time given the limitation on rosiglitazone use in the United States and its withdrawal from European markets.

While our study was not powered to detect differences among the various TZD combinations, it is reassuring that there appears to be no trend toward increased retinal thickness in those patients on a TZD with insulin because this combination is associated with a higher incidence of peripheral edema and/or congestive heart failure.[19] The mechanism of DME in patients taking TZDs is unclear. It may be related to an independent effect of the TZD or a secondary effect from related systemic fluid retention.[4–7]

Diabetic retinopathy is associated with microalbuminuria and nephropathy but we found no correlation between retinal thickness and microalbuminuria. Also, no significant correlation was found with duration of diabetes, combinations of medications, or gender.

We found a significant difference in the central subfield thickness between Caucasian subjects and African-American subjects. African-Americans have been shown to have thinner central subfield thickness than Caucasian subjects[13,14] and our results confirm this. The cause of this difference is unclear but some have implicated melanin and its light-altering properties affecting the OCT light beam. Given the findings in our study and those of others, it may be necessary to adjust the criteria for abnormalities in retinal thickness based on race.

A strength of our study is that it was a cross-sectional study that employed OCT and controlled for BDR. A weakness of our study is that in controlling for BDR, while helpful in isolating the TZD effect on DME, seeing an effect of the TZDs on patients with already established microvascular disease of the retina may have been precluded. A prospective study is needed to evaluate causality and elucidate more fully the impact of

TZDs on patients with or without diabetic retinopathy. Another limitation is the smaller number of subjects enrolled for the TZD group, which reflected the limited use of this drug class in our institution. However, we terminated the study because it was clear from the 95% confidence intervals (CIs) for the differences between TZD and non-TZD groups for all regions of the eye that further recruitment was highly unlikely to prove the original study hypothesis.

Conclusions

Thiazolidinediones do not cause subclinical macular edema in demographically diverse patient populations with diabetes. The established normal ranges for macular thickness may require adjustment based on ethnicity.

Acknowledgements:

Robert A. Vigersky conceived the original idea of the study, contributed to the discussion, and wrote the manuscript. Aaron K. Tarbett researched data, designed the study, and wrote the manuscript. Robin S. Howard designed the study and contributed to the discussion. Ronald C. VanRoekel researched data and contributed to the discussion.

Disclosures:

The opinions expressed in this paper reflect the personal views of the authors and not the official views of the United States Army or the Department of Defense.

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