A Multi-Institutional Observational Study of Testosterone Levels after Testosterone Pellet (Testopel®) Insertion

Andrew R. McCullough, MD, FACS,* Mohit Khera, MD, MBA, MPH,† Irwin Goldstein, MD,‡ Wayne J.G. Hellstrom, MD, FACS,§ Abraham Morgentaler, MD,¶ and Laurence A. Levine, MD**

*Albany Medical College, Albany, NY, USA; †Scott Department of Urology—Baylor College of Medicine, Houston, TX, USA; ‡San Diego Sexual Medicine at Alvarado Hospital and UC San Diego, San Diego, CA, USA; §Tulane University School of Medicine, New Orleans, LA, USA; ¶Harvard Medical School, Boston, MA, USA; **Rush University Medical Center, Chicago, IL, USA

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ABSTRACT

Introduction. Implantable testosterone pellets were approved by the Food and Drug Administration in 1972 for the treatment of testosterone deficiency syndrome (TDS). Clinical use of this testosterone delivery modality has been limited until its recent reintroduction (Testopel®, Slate Pharmaceuticals, Durham, NC, USA). Six academic institutions collaborated and combined their databases to more fully characterize serum testosterone levels after the pellet implantations.

Aims. To assess the time-dependent serum testosterone levels after subcutaneous testosterone pellets in clinical practice for the treatment of TDS.

Methods. Data were retrospectively pooled and analyzed from data in six academic institutions. Variables included patient age, total testosterone concentrations before and after implantation, the number of testosterone pellets implanted, and the time from implantation to measurement of serum testosterone concentrations. Three hundred eighty men undergoing 702 insertions were included for analysis using JMP (version 4.0.4; SAS Institute, Cary, NC, USA).

Main Outcome Measures. Main outcome measures were postimplantation total testosterone levels and investigator-reported adverse events. Testosterone levels as a function of the number of pellets implanted and time from implantation were assessed.

Results. Implantation of six to ≥10 testosterone pellets (450 to ≥750 mg) increased total testosterone into the therapeutic range at 1 month postimplantation and sustained therapeutic levels (>300) for 4–6 months. Higher pellet numbers (10–12 pellets) were associated with higher, more consistent, and longer maintenance of testosterone levels within the therapeutic range. Four extrusions and three hematomas were reported early in our experience; other investigator-reported adverse events were generally mild to moderate in nature and transient in duration. No subjects required analgesics.

Conclusions. Testosterone pellets (Testopel®, Slate Pharmaceuticals) provide sustained levels of testosterone for at least 4 months and up to 6 months in men with TDS. Implantation of ≥8 pellets achieved optimal results with respect to peak mean testosterone level and duration of effect. Testosterone pellets were generally well tolerated.

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Key Words. Hypogonadism; Testosterone Pellet; Subcutaneous Testosterone; Testosterone Replacement Pharmacokinetics; Testosterone Replacement

Introduction

Testosterone is a sex steroid that is critical for the structure and function of genital tissues, especially penile erectile tissue. Testosterone deficiency syndrome (TDS), hypogonadism, androgen insufficiency syndrome, andropause, and male menopause are all synonyms used to describe the clinical syndrome of low serum testosterone. The symptoms of TDS include one or more of the following: decrease in sexual activity, loss of libido or sexual interest, thoughts, or fantasies, erectile dysfunction, decrease in volume of ejaculate, decreased orgasmic intensity, irritability, nervousness, generalized weakness, loss of muscle mass, lack of energy, osteoporosis, fractures, decrease of body hair, and abdominal obesity. These symptoms in conjunction with a biochemical measure of low testosterone such as low "calculated free testosterone" may be indicative of TDS in men [1,2].

Normal testosterone levels range from 300 to 1,000 ng/dL, and levels below 300 ng/dL are typically required for a diagnosis of TDS [3–5]. This syndrome is estimated to occur in 5 million men in the United States alone, with a prevalence of 39% in men at least 45 years of age [6]. Prevalence appears to increase as a function of age, occurring in relatively low levels in men younger than 49 years of age and increasing to 49% (as determined by total testosterone levels) or 91% (as determined by free testosterone index) in men in their 80s [4]. With the aging of the American population, TDS is likely to afflict a growing number of men.

Testosterone replacement therapy has been shown to improve multiple symptoms of testosterone deficiency [7–9]. Studies demonstrate that use of exogenous testosterone can improve sexual function and mood, increase muscle mass, strength, fat-free mass, and bone density, and decrease cholesterol in men with testosterone deficiency [8–14].

Multiple formulations of exogenous testosterone have been used to treat TDS, including short acting (e.g., gels, patches, oral formulations, and buccal systems) and long acting (e.g., injectable testosterone undecanoate [not approved in the United States] and implantable testosterone pellets) [3,15]. The approved formulations have been shown to increase testosterone into the normal physiologic range [3,15]. Unlike the short-acting formulations, which require daily dosing, testosterone pellets can provide sustained increases in serum testosterone for a period of 4 to 6 months [3,15–17]. The long-acting testosterone pellets may provide a more patient-friendly treatment modality that has the potential to increase compliance and improve patient outcomes.

The sustained activity of implantable testosterone pellets makes this formulation an attractive approach to treat TDS. Previous reports on subcutaneous testosterone pellet therapy have shown that this formulation is generally well tolerated and reported mostly minor adverse events such as local pain and tenderness, swelling and bruising of the buttocks, minor ecchymosis, infection of the pellet or insertion track, wound infection, and pellet extrusion [15,17–22].

At the present time, the only long-acting testosterone replacement therapy approved by the U.S. Food and Drug Administration (FDA) is Testopel® (75 mg testosterone per pellet) (Slate Pharmaceuticals, Durham, NC, USA). Despite its approval by FDA in 1972, little is known about the pharmacokinetics of this formulation. In a retrospective review of the medical records of 80 patients, Cavender and Fairall reported that total testosterone concentrations were an average of 70% higher than baseline at approximately 60 days after pellet implantation [15]. Kaminetsky et al. conducted a prospective study of testosterone pellets in a clinical setting, which demonstrated that this formulation can normalize testosterone levels and improve the symptoms of TDS for 3–6 months. Though a prospective study, the study is limited to 28 patients [17]. These results are consistent with the pharmacokinetics of other testosterone pellet formulations that are not marketed in the United States [16,18,23–26]. Testosterone pellets in the USA are also produced generically by independent compounding pharmacies with unknown and varying phamacodynamic properties. The pellets used in this study were exclusively the FDA approved testosterone pellets. The results should be considered unique to this preparation and should not be generalized to other testosterone pellet preparations, commercial or generic.

Aims

The objective for this study was to provide a larger experience on total testosterone levels after subcutaneous testosterone pellets used in clinical practice for the treatment of TDS. Serum testosterone concentrations and the number of pellets administered were collected by retrospective chart review for all patients who received treatment with testosterone pellets.

Table 1 Patient characteristics

Characteristics	Overall	Baylor	Harvard	NYU	Center rush	San Diego	Tulane
Number of patients	380	176	41	120	11	12	20
Number of pellet insertion procedures	702	299	80	234	18	23	48
Patient age (years) at pellet insertion							
Mean (SD)	59 (129)	57 (133)	589 (11)	66 (15.4)	57 (10.1)	59 (7.0) 52	55 (11.6)
Total testosterone (ng/dL) before pellet implantation							
Mean (SD)	235 (110)	246 (95)	162 (36)	227 (160)	262 (95)	224 (94.8)	238 (00)
Lower and upper 5%	221, 249	230, 261	144, 181	192, 263	198, 326	NA	192, 284
Number of insertions N (% of procedures)							
Six or seven pellets (450 or 525 mg)	73 (10)	8 (2.6)	17 (21.5)	18 (7.8)	5 (25.0)	0	18 (37.5)
Eight or nine pellets (600 or 675 mg)	189 (27)	22 (73)	40 (49.4)	64 (27)	13 (75.0)	12 (52.4)	19 (39.6)
10 or more pellets (≥750 mg)	440 (63)	269 (90)	23 (29)	152 (65)	0	11 (47.6)	11 (22.4)
Days after implant for follow-up testosterone level							
Mean (SD)	74 (75)	44 (35)	59 (45)	95 (95)	73 (62)	58 (58)	101 (63)
Lower and upper 95%	68, 80	39, 49	49, 69	84, 106	38, 107	26, 90	83, 120

As some patients had more than one pellet insertion, N exceeds the number of patients
N = number of observations; NA = not applicable; NYU = New York University; SD = standard deviation

Methods

Data were retrospectively and anonymously collected from patient records at each research center to further characterize the effect to testosterone pellet insertions on serum total testosterone levels. At each center, an Institutional Review Board reviewed the study and granted an informed consent waiver. Data from adult males of any age with TDS who received at least one insertion procedure with subcutaneous testosterone pellets were included in this analysis.

From each eligible patient's medical records, the following data were tabulated: patient age, total serum testosterone concentrations before and after implantation, the number of testosterone pellets implanted, and the time from implantation to measurement of serum testosterone concentrations. Data were summarized and analyzed using JMP (version 4.0.4; SAS Institute, Cary, NC, USA). Data were categorized by institution and the number of testosterone pellets implanted (grouped as six or seven pellets, eight or nine pellets, and 10 or more pellets). The time between pellet implantation and subsequent visits or data were grouped by month, with a month defined as 30 days (for example, differences of 29 and 31 days were categorized as 1 and 2 months, respectively).

Main Outcome Measures

The main outcome measures were postimplantation total serum testosterone levels and investigator-reported adverse events. Changes in total testosterone as a function of the number of pellets implanted were assessed.

Results

Medical records for 380 men who had pellet implantations from March 2008 through September 2009 were included in this investigation. Patient characteristics at baseline are shown in Table 1. Mean total serum testosterone, which was assessed prior to the implantation procedures, was 235 (110) ng/dL. Mean preimplantation testosterone for subjects receiving six or seven, eight or nine, or ≥10 pellets were 182 (112), 209 (91), and 239 (102) ng/dL, respectively. A total of 702 implantation procedures were performed in 380 men. Of the 702 procedures, six or seven (450 or 525 mg) pellets were implanted in 73 (10%) procedures, eight or nine (600 or 675 mg) pellets were implanted in 189 (27%) procedures, and 10 or more pellets (≥750 mg) were implanted in 404 (63%) procedures. The mean time to follow-up was 74 days (confidence interval [CI] 68, 80).

Total testosterone levels at various time points following testosterone pellet implantation are summarized in Table 2 and shown in Figure 1. Regardless of the number of pellets implanted, mean peak testosterone levels were observed at 1 month following implantation, reaching 712, 719, and 795 ng/dL for the six to seven, eight to nine, and ≥10 pellet groups, respectively. Total testosterone remained above 300 ng/dL at 4 months for all groups with 95% confidence in the 8–9 and 10–12 pellet groups. For subjects receiving eight or nine pellets, mean total testosterone was 305 and 298 ng/dL at 5 and 6 months, respectively, after implantation. In patients receiving at least 10 pellets, total testosterone was 356 and 206 ng/dL at these same time points. Median levels and percentage of testosterone measurements greater

Table 2 Total testosterone levels after pellet implantation

Total testosterone (ng/dL) by testopel dose	Baseline	Time after pellet implantation					
		1 month	2 months	3 months	4 months	5 months	6 months
Six or seven pellets							
Number of measurements		18	17	27	17	5	21
Mean (SD)	182 (112)	712 (210)	476 (209)	468 (127)	366 (177)	199 (44)	249 (159)
Median	197	787	478	439	314	218	240
Lower and upper 5%	151, 214	578, 845	336, 617	370, 565	254, 479	89, 309	164, 334
Minimum, maximum		233, 966	238, 1,010	335, 673	126, 764	149, 231	26, 573
% of measurements >300 ng/dL	22	91	81	99	55	5	28
Eight or nine pellets							
Number of measurements		72	60	58	60	30	34
Mean (SD)	209 (91)	719 (328)	558 (210)	402 (130)	364 (150)	305 (97)	298 (166)
Median	193	661	572	423	328	301	311
Lower and upper 5%	101, 225	624, 824	477, 637	353, 452	306, 422	251, 359	216, 380
Minimum, maximum		221, 1,078	216, 1,037	210, 686	164, 825	168, 439	56, 725
% of measurements >300 ng/dL	22	94	83	72	53	53	53
10 or more pellets							
Number of measurements		128	104	82	78	54	32
Mean (SD)	239 (102)	795 (297)	670 (192)	467 (127)	398 (168)	358 (150)	206 (214)
Median	240	782	686	666	367	318	186
Lower and upper 5%	228, 251	740, 851	634, 706	431, 563	346, 441	304, 413	148, 263
Minimum, maximum		257, 1,762	382, 1,100	172, 1,172	170, 715	178, 745	92, 800
% of measurements >300 ng/dL	30	98	98	80	74	59	20

Time is categorized by month (e.g., 1–30 days = 1 month, ≥151 days = 6 months)
SD = standard deviation

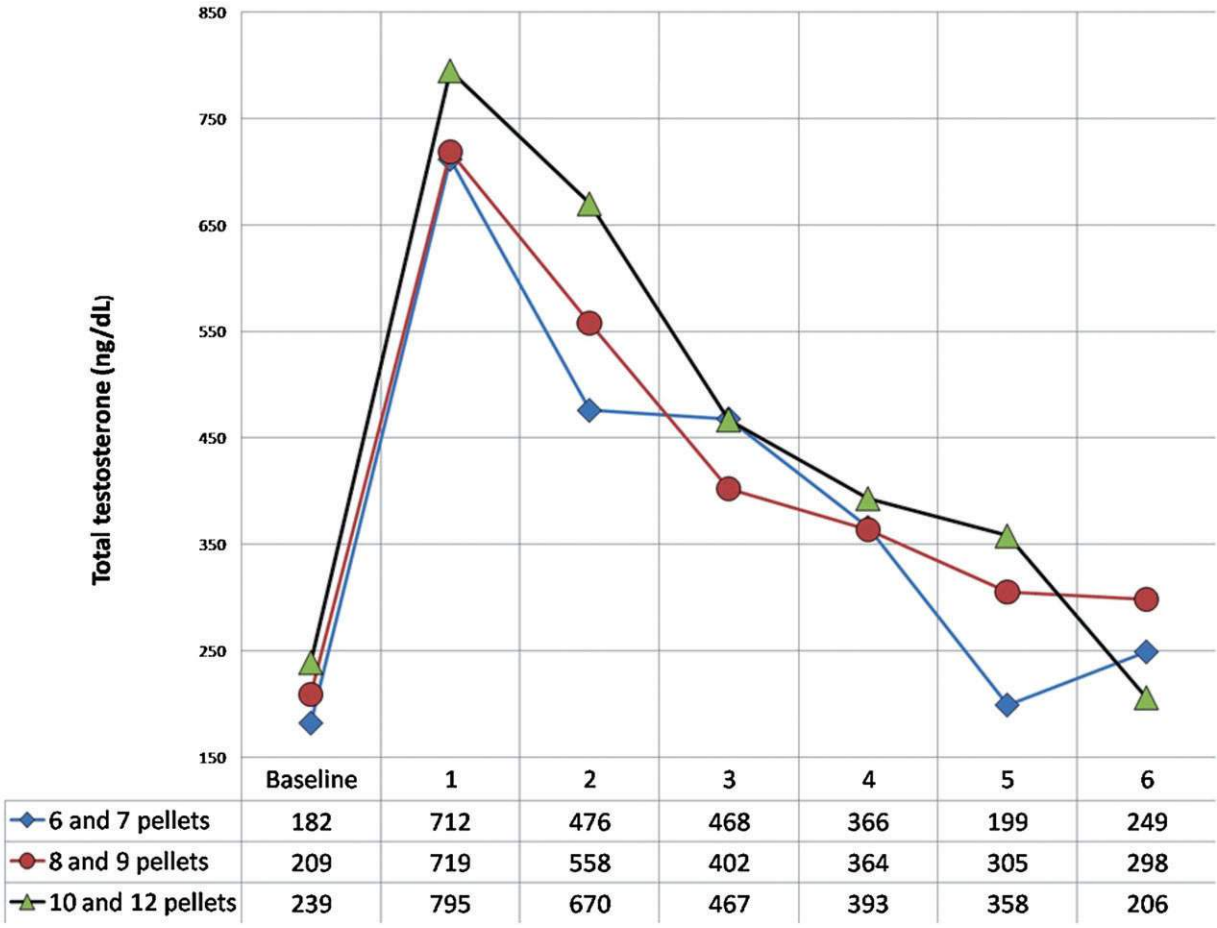

Figure 1 Total testosterone levels by month from insertion.

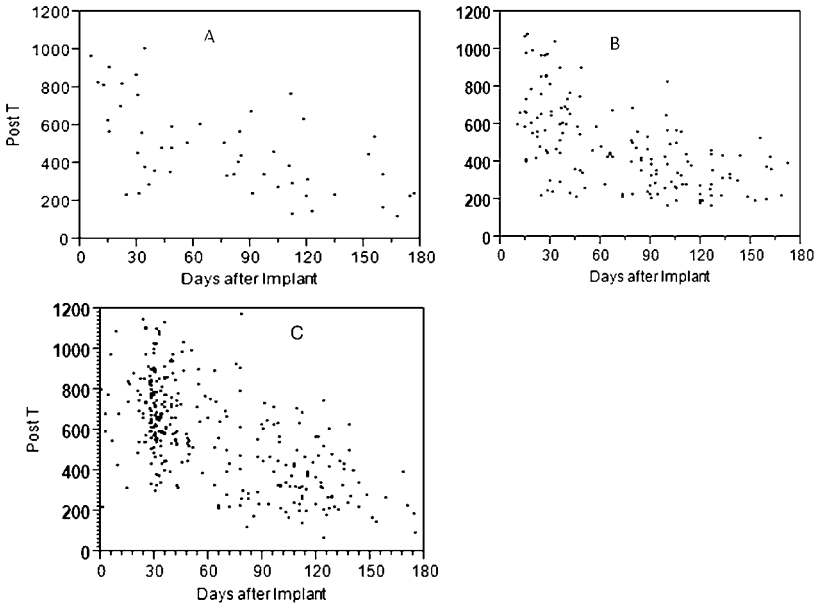

Figure 2 Testosterone Levels (ng/dl) by days from Implant. (A) 6–7 pellets. (B) 8–9 pellets. (C) 10 or more pellets.

than 300 ng/dL favored the implantations with 10 or more pellets. Supraphysiologic testosterone levels were uncommon at all levels. Serum testosterone concentrations over time for the study subjects receiving six to seven, eight to nine, or ≥10 pellets are shown in Figure 2.

Differences between total serum testosterone in the ≥10 pellet group and the other groups were significant in the second month after implantation ($P < 0.001$). There were no significant differences in testosterone levels between subjects receiving six to seven or eight to nine pellets at any time point. Statistical comparison between groups was of questionable value as there was no standardization of criteria for treatment, interval of determination of postimplantation testosterone measurements, and low number of patients in the six to seven pellet group.

Investigator-reported adverse events comprised four extrusions and three hematomas occurring early in the experience. Other adverse events, which were mild to moderate in nature and transient in duration, included pain, tenderness, redness/erythema, and ecchymosis at the implantation site. No patients required analgesics.

Discussion

This observational study demonstrates the safety and efficacy of testosterone pellets as experienced in multiple clinical practices. Mean serum testosterone was maintained at a therapeutic level (≥300 ng/dL) for 4 months following implantation, regardless of pellet number (six or seven, eight or nine, or ≤10 pellets). Higher pellet numbers were associated with higher short-term testosterone levels and with maintenance of testosterone levels in the therapeutic range for longer periods of time. Peak mean testosterone levels were observed 1 month following implantation. These results are consistent with a recent prospective study of testosterone pellets conducted in 28 men with TDS. In this prospective study, mean testosterone remained above 300 ng/dL for at least 12 weeks, and 86% of subjects had testosterone >315 ng/dL 16 weeks following implantation. The small number of patients limited the analysis of testosterone levels by the number of pellets. We were able to show the effect of increasing the number of pellets per implantation on serum testosterone levels. Peak mean testosterone levels in our study occurred 1 month following implantation and increased with increasing pellet number.

The stratification of patients as a function of the number of pellets (six or seven, eight or nine, or ≤10) implanted was based on the clinical practice of the various investigators, unlike the Kaminetsky study where the dosing of testosterone was based on body mass index (BMI). The choice of dose for any individual patient was based on the observed responses that each investigator had experienced when using testosterone pellets in previous patients, which was different for each investigator.

These data suggest that testosterone pellets provide an effective approach for treating TDS.

Unlike other testosterone formulations that require more frequent administration, testosterone pellets may have a compliance advantage because it is administered only three times per year. Improved compliance rates remain to be investigated.

The testosterone pellets used are the only long-acting testosterone formulation approved by the FDA available to men in the United States with TDS. A study comparing testosterone pellets with a long-acting injectable formulation of testosterone undecanoate (not available in the United States) found that over the short term of the study (54 weeks), subjects preferred the injectable formulation, due largely to ease of administration. It should be noted that the testosterone pellets used in that study were different from those used in our study. The product used is marketed only in Europe and Australia. The pellets are larger (8×15 mm vs. 3×8 mm), are stored surrounded by wool or cotton material in a glass ampule, require a larger insertion trochar, and are associated with a higher rate of extrusion (8–12%) and infection [15,24]. Patient preferences may be different with the testosterone pellets used in our study, which has been shown to have a lower incidence of extrusion and infection than the historical data for other testosterone pellets. With the need for intramuscular (IM) injection of testosterone in 4 cm^3 of castor oil every 10–12 weeks, long-term (greater than 1 year) patient preferences might be different.

A weakness of this study is that it is a retrospective analysis of data from multiple clinical practices, and complete data are not available for every patient. While this is not unexpected given the design of the study, it makes it more difficult to provide a comprehensive analysis of patients' experiences. Additionally, as a retrospective study, the clinical laboratory values used in this analysis were obtained from a variety of clinical labs due to variations in patients' insurance providers, as is common. The potential for interlaboratory variability in testosterone measurements between patients, or for patients who had their baseline and follow-up testosterone assessments conducted by different laboratories, may impact the results reported here. Similarly, lack of standardization of selection criteria for the treatment of TDS, insertion techniques, and assessment periods make it somewhat more difficult to analyze data from multiple clinical practices. The strength of the study lies in the large number of patients and testosterone determinations and its reflection on general urological practice.

Despite these limitations, this study is the largest analysis of the safety and efficacy of testosterone pellets reported to date. Comprising data from 380 subjects, 702 implantation procedures, and nearly 2,000 individual testosterone measurements, this larger data set continues to support the efficacy of testosterone pellets and expands our understanding of testosterone pellets in clinical practice. Moreover, these results reflect the testosterone pellet experience in actual clinical practice, which may provide a more realistic perspective than data from highly controlled clinical trials. The data presented allow the clinician a better understanding of postimplantation serum testosterone level decay with differing doses of testosterone pellets.

Conclusions

These data expand the understanding and experiential base related to the use of testosterone pellets in clinical practice. The investigator-reported extrusion rate was well below that previously reported, <1% (4/702). Implantation of six to ≥10 pellets resulted in therapeutic testosterone levels (>300 ng/dL) for 4 months (95% CI 336, 426), with implantation of a higher number of pellets (e.g., 10–12 pellets) achieved more consistent and sustained short- and long-term results compared with six to nine pellets. These data represent the largest analysis of testosterone levels after testosterone pellet insertions to date and support the efficacy of this testosterone formulation for the treatment of TDS.

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Corresponding Author: Andrew McCullough, MD, FACS, Director of Men's Health—Albany Medical College, Albany, NY 12208, USA. Tel: 518-262-3341; Fax: 518-262-6660; E-mail: amccullough@communitycare.com

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Andrew McCullough
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Abraham Morgentaler, MD

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Wayne J.G. Hellstrom,
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VIVUS—Advisor/Consultant, Investigator
Mohit Khera, MD, MBA, MPH
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Statement of Authorship

Category 1

(a) Conception and Design
Andrew R. McCullough; Mohit Khera; Irwin Goldstein; Wayne J.G. Hellstrom; Abraham Morgentaler; Laurence A. Levine

(b) Acquisition of Data
Andrew R. McCullough; Mohit Khera; Irwin Goldstein; Wayne J.G. Hellstrom; Abraham Morgentaler; Laurence A. Levine

(c) Analysis and Interpretation of Data

Category 2

(a) Drafting the Article
Andrew R. McCullough; Mohit Khera; Irwin Goldstein; Wayne J.G. Hellstrom; Abraham Morgentaler; Laurence A. Levine

(b) Revising It for Intellectual Content
Andrew R. McCullough; Mohit Khera; Irwin Goldstein; Wayne J.G. Hellstrom; Abraham Morgentaler; Laurence A. Levine

Category 3

(a) Final Approval of the Completed Article
Andrew R. McCullough; Mohit Khera; Irwin Goldstein; Wayne J.G. Hellstrom; Abraham Morgentaler; Laurence A. Levine

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