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Deterioration of Sleep Quality According to Glycemic Status

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Background: Type 2 diabetes mellitus (T2DM) is a progressive disease with multiple complications. The present study aimed to determine the effects of glycemic status on sleep quality in individuals with T2DM, prediabetes, and normal glucose tolerance (NGT).

Methods: A total of 90 participants were categorized into three groups, T2DM ($n=30$), prediabetes ($n=30$), and NGT ($n=30$). Objective sleep quality was measured with the actigraph wrist-worn device over 3 nights and subjective sleep quality was evaluated with a questionnaire.

Results: The duration of diabetes in the T2DM group was 2.23 years and the glycosylated hemoglobin (HbA1c) levels in the T2DM, prediabetes, and NGT groups were 7.83%, 5.80%, and 5.31%, respectively. Sleep efficiency decreased across the T2DM, prediabetes, and NGT groups (86.25%, 87.99%, and 90.22%, respectively; $P=0.047$). Additionally, HbA1c levels revealed a significant negative correlation with sleep efficiency ($r=-0.348$, $P=0.001$). The sleep quality questionnaire results were similar among the three groups.

Conclusion: Although the participants in the present study were not necessarily conscious of their sleep disturbances, deterioration in sleep quality progressed according to glycemic status.

Keywords: Actigraphy; Diabetes mellitus, type 2; Glycated hemoglobin A; Prediabetic state; Sleep

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and beta cell dysfunction [1,2]. As T2DM progresses, diabetic complications related to quality of life and mortality can develop; thus, the management of T2DM involves the regulation of glucose levels as well as the identification and control of diabetic complications [3]. These diabetes-related complications also progress with T2DM and regular examinations are recommended to prevent and slow the course of the disease. For example, diabetic neuropathy is a common and serious diabetic complication that affects approximately half of diabetic patients with various symptoms

[4,5]. It is also known that diabetic neuropathy is associated with the occurrence of sleep disorders [6].

The sleep quality of patients with diabetes is affected by a variety of conditions including frequent nocturia, neuropathic pain, nocturnal hypoglycemia, obstructive sleep apnea, restless leg syndrome, depression, and respiratory disturbances with congestive heart failure [7]. Approximately 25% of diabetic patients with autonomic neuropathy experience sleep apnea [8] and, conversely, sleep disorders alter insulin resistance and aggravate the glycemic status [9]. Furthermore, sleep deprivation increases insulin resistance by altering the levels of stress hormones and appetite-associated hormones, as well as the metabolism of glucose and lipids [10]. Thus, the quality and quan-

tity of sleep are profoundly associated with obesity and the development of diabetes [11].

Although the onset of diabetic neuropathy has not been associated with the duration of diabetes, both a longer duration of diabetes and poor control of glucose and lipid levels are associated with the acceleration of neural damage and aggravation of neuropathic pain [12,13]. Additionally, the presentation of peripheral neuropathies can also occur in patients with early or new-onset diabetes, prediabetes, or even normal glucose control status. Recently, Lee et al. [14] assessed the prevalence of peripheral neuropathy based on data from the Prospective Metabolism and Islet Cell Evaluation longitudinal cohort study. These authors found that the prevalence rates of peripheral neuropathy were 50% in patients with new-onset diabetes, 49% in adults with prediabetes, and 29% in adults with normal glycemic status.

The development of diabetes involves the continuous deterioration of bodily metabolic pathways away from a normal glucose control status [15]. Although the pathogenesis of peripheral neuropathies may parallel these metabolic changes, the onset and prevalence of sleep disorders in patients with prediabetes or early diabetes remain unclear. Thus, the present study recruited patients without overt symptomatic neuropathy and compared sleep quality among those with normal glucose tolerance (NGT), prediabetes, and early T2DM. Additionally, the relationship between glycemic status and sleep quality was analyzed in each group.

METHODS

Study population

This study was approved by the Institutional Review Board of Eulji University Hospital, School of Medicine (EMC 2016-08-017-002). Participants were recruited from among outpatients who visited the Department of Endocrinology at Eulji University Hospital from March 2017 to July 2017. A total of 90 men and women, aged between 18 and 50 years and who voluntarily agreed to participate and signed informed consent forms, were selected for the study. The participants were divided into three groups according to glycemic status: T2DM, prediabetes, and NGT. The T2DM group included early diabetic patients whose duration of diabetes was less than 5 years. Non-diabetic patients performed the 75 g oral glucose tolerance test (OGTT) for categorization into either the prediabetes or NGT group.

Prediabetes was diagnosed based on fulfilment of any one of

the following criteria: fasting glucose level of 100 to 125 mg/dL, a 2-hour glucose level of 140 to 199 mg/dL during the 75 g OGTT, and/or a glycosylated hemoglobin (HbA1c) level of 5.7% to 6.4%. Patients who were taking or had a history of taking neuropathic drugs (e.g., pregabalin, alpha lipoic acid, and duloxetine), tranquilizer and sedative were excluded. Patients who were suffering from uncontrolled thyroid, hepatic, renal diseases and chronic alcoholics, were excluded from the study. Patients with insulin administration in T2DM were excluded to avoid the effect of hypoglycemia. We also excluded patients with experience of symptomatic hypoglycemia within recent 1 month. Severe obese patients with body mass index (BMI) >30 kg/m² and patients with history of sleep apnea syndrome were also excluded. Additionally, all participants were prohibited from drinking alcohol prior to sleep throughout the study period.

Study design

The present investigation was a prospective case control study. All participants were evaluated for body weight (kg), height (cm), and BMI during their first visit. Additionally, blood samples were drawn to assess the following parameters: HbA1c levels; lipid profiles, which were based on low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglyceride levels; creatinine levels, which were based on the calculated estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study (MDRD) equation; and thyroid function, which was based on triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone (TSH) levels. The participants completed the subjective sleep quality questionnaire in an office. Following instructions on how to use the Actigraph device (Actigraph Corp., Pensacola, FL, USA), the participants took it home to wear for 3 days while sleeping. Upon return to the hospital, the Actigraph data for sleep quality were downloaded and explained to each participant (Fig. 1).

Objective measurement of sleep quality

Sleep quality was assessed using the Actigraph device, which is a wristband instrument that measures wrist movements with an accelerometer of an XYZ coordinate axis system, and the lightness of the room. The Actigraph wristbands were provided to the participants after inputting their personal data (initial name, height, weight, and age) using a PC with a USB port. The participants attached the Actigraph to their right wrists prior to sleep, slept as they normally would, and then removed the Acti-
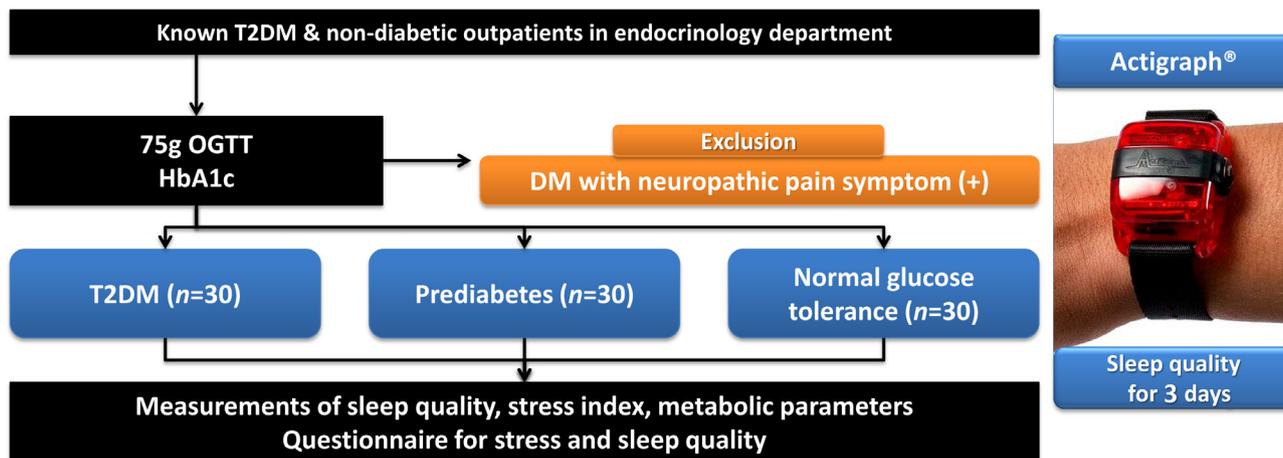
Fig. 1. Study protocol (left image) and photo of the Actigraph device (Actigraph Corp.) on a wrist (right image). T2DM, type 2 diabetes mellitus; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin; DM, diabetes mellitus.

graph in the morning without operating it. After three nights, the participants returned the Actigraph to the hospital and the sleeping sections from the "asleep" to "wake up" files were downloaded from the Actigraph using a PC. The Actigraph program analyzed movement and lightness and recorded total sleep time, s0leep efficiency, wake up after sleep onset (WASO), waking frequency, and average awake time. Data from the Actigraph were downloaded and analyzed using ActiLife version 6.11.9 (Actigraph Corp.).

Subjective measurement of sleep quality

The present study administered the Verran and Snyder-Halpern Sleep Scale, which is an effective instrument that measures sleep disturbances and sleep effectiveness in adults without pre-existing sleep difficulties [16]. This scale is composed of eight items that assess sleep quality and sleep fragmentation. Each item is scored on a numeric rating scale that ranges from 0 (poor) to 10 (good) (Supplementary Table 1); a higher total score is indicative of better sleep quality. All participants completed the questionnaire within a short time based on their sleeping experience over the past 1 week.

Measurement of stress index

We measured heart rate, the stress index, and heart rate variability (HRV) using Canopy 9 (Jawon Medical Corp., Seoul, Korea), which is a portable device that measures these parameters according to a light sensor on the finger with sitting on chair in quiet, isolated room. After the analysis of HRV during

5 minutes, stress index and HRV results were reported.

Statistical analysis

All data were analyzed with SPSS software for Windows version 23.0 (IBM Corp., Chicago, IL, USA). The baseline characteristics and sleep quality data of the participants in the three groups were analyzed by analysis of variance. The effects of the metabolic parameters on sleep quality were analyzed by correlation analyses and a multiple regression analysis. Two-tailed P values <0.05 were considered to indicate statistical significance.

RESULTS

Baseline characteristics of the participants

The participants were categorized into three groups based on glycemic status: T2DM ($n=30$), prediabetes ($n=30$), and NGT ($n=30$). The baseline characteristics of the three groups are shown in Table 1. The mean ages of the T2DM, prediabetes, and NGT groups were 47.3±10.7, 52.5±11.0, and 42.9±12.5 years, respectively, and there was a significant difference in age among the groups ($P=0.007$), where the NGT group was younger than the prediabetes group ($P=0.005$). The ratio of males in the T2DM group (76.7%) was higher than in the prediabetes (26.7%) and NGT (30%) groups. The duration of diabetes in the T2DM group was 2.23±2.32 years; only early diabetic patients were recruited to this group, to exclude the effects of complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, and other vascular diseases.

Table 1. Baseline characteristics of the study participants

Characteristic	T2DM ($n=30$)	Prediabetes ($n=30$)	NGT ($n=30$)	P value
Age, yr	47.3±10.68	52.5±11.03	42.9±12.45	0.007
Sex, male/female	23/7 (76.7)	8/22 (26.7)	9/21 (30)	<0.001
DM duration, yr	2.23±2.32	-	-	
BMI, kg/m²	25.74±4.49	26.23±3.13	24.90±3.28	0.372
HbA1c, %	7.83±2.01	5.80±0.24	5.31±0.22	<0.001
LDL, mg/dL	95.33±49.78	108.63±35.48	104.67±27.57	0.402
Triglyceride, mg/dL	155.56±66.83	159.03±100.98	143.58±100.87	0.792
HDL, mg/dL	43.56±11.82	53.53±15.69	51.13±15.97	0.026
Total cholesterol, mg/dL	156.06±50.22	181.13±38.59	178.46±30.61	0.036
eGFR, mL/min/1.73 m²	122.87±21.00	118.57±36.68	121.08±34.07	0.867
Creatinine	0.70±0.13	0.64±0.23	0.68±0.19	0.448
Hemoglobin, g/dL	14.73±1.93	14.10±1.34	13.67±1.44	0.040
T3, ng/dL	91.30±19.19	109.28±33.03	107.96±18.05	0.025
Free T4, ng/dL	1.22±0.17	1.20±0.23	1.19±0.17	0.834
TSH, μIU/mL	1.49±1.14	1.85±1.47	1.73±1.55	0.645

Values are presented as mean±standard deviation or number (%).
T2DM, type 2 diabetes mellitus; NGT, normal glucose tolerance; DM, diabetes mellitus; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

Table 2. Comparisons of objective sleep quality measurements from the Actigraph among the three groups

Variable	T2DM	Prediabetes	NGT	P value
Total sleep time, min	362.23±89.37	363.24±60.86	345.71±41.84	0.525
Sleep efficiency, %	86.25±7.09	87.99±6.44	90.22±4.53	0.047
WASO, frequency	56.72±35.29	49.05±26.84	37.34±19.90	0.031
Awake, frequency	19.73±7.22	17.92±6.62	15.21±5.04	0.025
Average awake, frequency	2.81±1.03	2.65±0.79	2.49±1.26	0.500

Values are presented as mean±standard deviation.
T2DM, type 2 diabetes mellitus; NGT, normal glucose tolerance; WASO, wake after sleep onset.

The BMI values of the three groups did not differ significantly (T2DM: 25.74±4.49 kg/m², prediabetes: 26.23±3.13 kg/m², and NGT: 24.90±3.28 kg/m²). The HbA1c level of the T2DM group at the time of recruitment was 7.83%±2.01%. The HbA1c levels of the prediabetes and NGT groups at the time of recruitment were 5.80%±0.24% and 5.31%±0.22%, respectively; these levels were significantly different (P<0.001). The lipid profiles of the three groups, which included assessments of LDL-C and triglyceride levels, did not differ significantly. However, 60% ($n=18$) of the T2DM patients were taking a statin, which is a lipid-lowering agent, whereas there were no

statin users in the prediabetes or NGT groups. There were no significant differences in the renal (P=0.867) or thyroid (free T4, P=0.834; TSH, P=0.645) function tests.

Objective sleep quality results

The present study analyzed factors that influenced sleep fragmentation and reflected sleep quality and sleep deterioration (Table 2). Sleep quality data were acquired using the Actigraph device during sleep over three nights (Fig. 2). The average total sleep time was over 300 minutes in each of the three groups and did not significantly differ among the groups. However, there
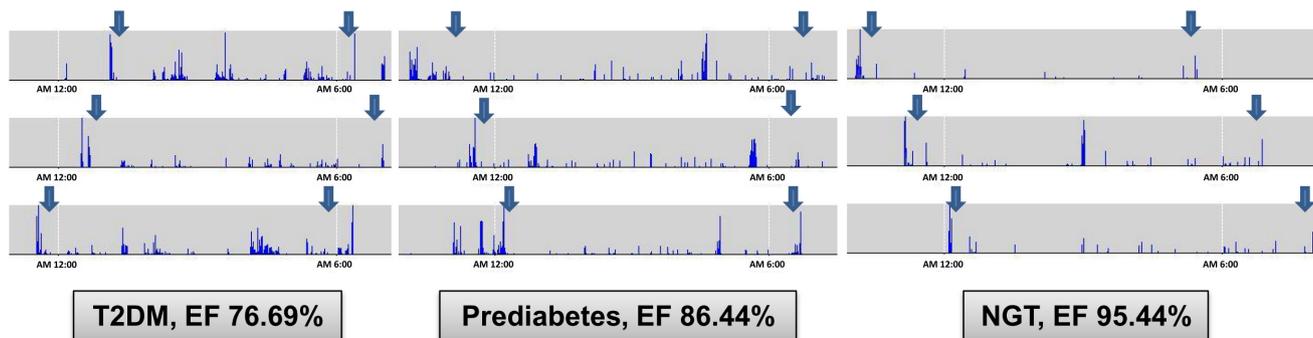
Fig. 2. Sleep quality data acquired with the Actigraph (Actigraph Corp.) in the type 2 diabetes mellitus (T2DM), prediabetes, and normal glucose tolerance (NGT) groups; arrows indicate the sleep onset and wake up points (representative data of each group). EF, efficiency.

Table 3. Correlation analysis of sleep efficiency, wakening frequency and metabolic parameters

Variable	Age	BMI	HbA1c	LDL	TG	HDL	TC	eGFR	Hb
Efficiency	−0.069	−0.209	−0.348	0.070	0.073	0.093	0.126	−0.098	−0.080
P value	0.517	0.054	0.001	0.518	0.496	0.384	0.237	0.359	0.454
Awake	0.155	0.038	0.215	−0.143	−0.016	−0.081	−0.155	−0.019	0.078
P value	0.144	0.728	0.042	0.184	0.883	0.449	0.145	0.861	0.465

BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; TC, total cholesterol; eGFR, estimated glomerular filtration rate; Hb, hemoglobin.

was a significant difference in sleep efficiency among the three groups ($P=0.047$). Sleep efficiency was 90.22%±4.53% in the NGT group, which reflects healthy sleep. Sleep efficiency decreased in the prediabetes group (87.99%±6.44%) and was lowest in the T2DM group (86.25%±7.09%). WASO induces sleep fragmentation, which is a marker of sleep deterioration. The longest WASO duration was in the T2DM group (56.72±35.29 minutes), followed by the prediabetes group (49.05±26.84 minutes) and the NGT group (37.34±19.90 minutes); these values were significantly different ($P=0.031$). The frequency of awakening was highest in the T2DM group (19.73±7.22), lower in the prediabetes group (17.92±6.62), and lowest in the NGT group (15.21±5.04; $P=0.025$).

Correlations between sleep efficiency and the metabolic parameters

Correlation analyses revealed that the HbA1c level was significantly associated with sleep efficiency ($r=-0.348$, $P=0.001$) and waking frequency ($r=0.215$, $P=0.042$) (Table 3) but there were no significant correlations with age, BMI, cholesterol, HbA1c, or renal function. A multiple regression analysis adjusted for age and BMI revealed that the HbA1c level was sig-

Table 4. Multiple regression analysis of HbA1c level and sleep efficiency after adjusting for age and BMI

Sleep efficiency	B	β	t	P value	VIF
Constant	106.871		18.292	<0.001	
Age	−0.046	−0.088	−0.856	0.394	1.020
BMI	−0.334	−0.195	−1.906	0.060	1.025
HbA1c	−1.279	−0.328	−3.234	0.002	1.007

HbA1c, glycosylated hemoglobin; VIF, variance inflation factor; BMI, body mass index.

nificantly associated with sleep efficiency (B=−1.279, $P=0.002$) (Table 4).

Subjective sleep quality questionnaire results
The sleep quality questionnaire sum scores were similar among the three groups (T2DM: 50.48±10.74, prediabetes: 50.4±13.90, and NGT: 53.28±12.54, $P=0.596$); the NGT group had a relatively, but not significantly, higher score. The scores for participant satisfaction with sleep quality were similar among the three groups regardless of the differences in objective sleep quality as measured by the Actigraph device.

DISCUSSION

In the present study, sleep quality significantly differed among the three groups such that the T2DM group experienced the worst sleep quality despite the absence of neuropathic symptoms. Interestingly, the prediabetes group also showed a deterioration of sleep quality compared to the NGT group. HbA1c was the only metabolic marker of glycemic status that was associated with differences in sleep quality between the T2DM and prediabetes groups. Thus, deterioration of sleep quality may be prevalent in the prediabetes and early T2DM phases of the disease course.

Although the mechanisms underlying deterioration in sleep quality during the early phases of glycemic alterations have yet to be fully elucidated, many researchers have offered hypotheses. For example, Fujihara et al. [17] reported that diabetic patients with peripheral neuropathy or autonomic neuropathy had a twofold higher prevalence of sleep apnea syndrome. Mallien et al. [18] analyzed the effects of autonomic neuropathy on sleep quality by measuring HRV in patients with postural orthostatic tachycardia syndrome. HRV is a physiological phenomenon, in which there are variations in the time intervals between heartbeats that can be measured based on the beat-to-beat interval (R-R interval in an electrocardiogram). Previous studies have shown that T2DM patients exhibit a decreased HRV, and that this technique can be applied as a tool for assessing cardiac autonomic neuropathy [19]. The present study measured heart rate, the stress index, and HRV using Canopy 9. Although it was not possible to assess HRV during sleep in this study, as it could only be measured in the hospital, there were significant differences in the stress index and HRV among the three groups (Supplementary Table 2). The stress index was highest in the T2DM group (7.36 ± 2.20), slightly lower in the prediabetes group (7.20 ± 1.74), and lowest in the NGT group (5.40 ± 2.49, $P=0.001$). The HRV index was lowest in the T2DM group (6.60 ± 2.13), higher in the prediabetes group (7.49 ± 2.56), and highest in the NGT group (8.97 ± 2.88, $P=0.002$) (Supplementary Table 2). It is possible that autonomic neuropathy was present in the prediabetes and early T2DM patients, even though there were no overt neuropathic symptoms [20,21]. Further research that measures HRV during sleep will be required to elucidate the relationship between cardiac autonomic neuropathy and sleep quality in patients with prediabetes and early T2DM.

The Actigraph device used in the present study was a wrist-band that was wearable during sleeping and walking. Although polysomnography (PSG) is the gold standard for sleep research, actigraphy has been utilized by many researchers for over 30 years. Some studies have compared the efficacy and sensitivity of sleep quality measurements using actigraphy and PSG and reported that actigraphy produces highly correlated data with respect to total sleep time, sleep efficiency, and WASO in older patients and those with diabetes [22,23]. Although actigraphy cannot be used to evaluate respiration patterns, oxygen content, brain waves, or eye movements, it has several advantages over PSG. For example, the device is comfortable, does not affect sleeping behavior, and is much more affordable than PSG. Additionally, it is not necessary to change the location where a subject sleeps because the Actigraph device can be worn in one's own bed at home, which eliminates the possible confounding effect of changing the sleeping location [24].

The present study had several limitations that should be noted, because there are a variety of factors that can affect sleep quality. Although patients with neuropathy were excluded from the present analyses, neuropathic symptoms were only assessed using a subjective report and nerve conduction velocity tests were not performed. Asymptomatic diabetic peripheral neuropathies are reported in up to 50% of T2DM patients [25] and, thus, the present study only excluded the effects of symptomatic peripheral neuropathies in prediabetes and early T2DM patients. Another limitation was the effect of hypoglycemia, because the participants in the T2DM group were taking glucose-lowering agents with exclusion of insulin user. Although these participants were relatively young and had short-duration T2DM, it was not possible to completely exclude the effects of nocturnal hypoglycemia [26]. Hypoglycemia in children with type 1 diabetes mellitus is associated with a decrease in sleep quality [27] and, thus, the use of a continuous glucose monitoring system in future research will be required to fully exclude the effects of nocturnal hypoglycemia. Gender difference of our study was a confounding factor for the analysis. In each gender, there were also differences of sleep efficiency with glycemic status. However, the number of patients was too small to validate the results. Finally, it was not possible to accurately control participant behaviors prior to sleeping. The participants were instructed to avoid alcohol, snacking, and smoking prior to sleep because these behaviors can affect sleep quality and the Actigraph cannot detect their presence.

The present study assessed participants without overt diabetic symptomatic neuropathy and demonstrated that sleep

quality deteriorated in patients with prediabetes or early T2DM relative to individuals with NGT. Although the participants were not necessarily consciously aware of sleep disturbances, deterioration in sleep quality progressed with changes in glycemic status. These findings indicate that sleep disorders should be considered in patients with early T2DM or prediabetes, even when diabetic neuropathic symptoms are not present and patients do not report sleep disturbances.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0125.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: M.H.H., J.H.H.
Acquisition, analysis, or interpretation of data: M.K.L., K.S., J.H.H.
Drafting the work or revising: M.H.H., M.K.L., K.S., J.H.H.
Final approval of the manuscript: M.H.H., J.H.H.

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