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Sleep Quality in Psoriasis Patients and its Relations with Possible Affecting Factors

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Abstract

Objectives: Psoriasis (PS) is a chronic, immune-mediated inflammatory skin disease. PS may lead to significant effects on health-related quality of life (HRQoL) and other outcomes. In the present study, an investigation into sleep quality (SQ), and its possible relations with factors which may affect SQ were aimed.

Methods: A total of 74 subjects from both sexes were enrolled in this study, between January and July 2017. Patients were evaluated with their demographics, body mass index (BMI), Psoriasis Area Severity Index (PASI), Pittsburgh Sleep Quality Index (PSQI), Psoriasis Quality of Life Index (PQLI), Self Perception Scale (SPS). Additionally, accompanying chronic diseases, disease duration and severity of pruritus were recorded. Obtained PSQI values were compared with the mentioned parameters concerning the significance of their relations with it. SPSS version 24, 2016 was used to analyse the data, and significance was evaluated with p-values of <0.05, 0.01, and 0.001, and rho (r) values of <0.2, =0.2-0.4, =0.4-0.6, =0.6-0.8 and >0.8.

Results: Thirty-seven female and 37 male were studied. The mean age of total of the study population was 47.21±13.91. Mean BMI and mean duration were 30.09± 4.68 kg/m², and 10.58±9.1 months. Mean values of PASI, PSQI, SPS, and PQLI of the study group were 19.79±16.99, 9.14±5.09, 142.12±23.83, and 21.94±16.31, respectively. Approximately thirty-one percent of them had at least one chronic disease. Alcohol and smoking rates were 17.56%, 50%. PASI was positive/strongly correlated with PQLI and negative/ weakly correlated with SPS. No correlation was detected between PSQI values and age, gender, BMI, and SPS values. PSQI was moderately correlated with PQLI, diabetes mellitus (DM), and pruritus severity, whereas it was weak correlated with PASI, hypertension (HT), thyroid diseases and disease duration. PASI and DM showed a predictive effect on SQ.

Conclusion: SQ is affected by certain factors, such as QoL, disease severity, disease duration, pruritus severity, accompanying disorders, such as HT, DM and thyroid diseases, in which disease severity and DM have predictive effects on SQ in PS patients. Controls of disease activation and prevention of progression in DM may provide to keep SQ in PS.

Keywords: Causality; demographic factors; diabetes mellitus; psoriasis; sleep; quality of life.

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Psoriasis (PS) is a chronic, immune-mediated inflammatory skin disease of a genetic basis, which characterized by sharp limited, erythemasquamous plaques. Its prevalence is between 1.5% and 5%. The disease can easily be diagnosed with chronic and frequently recurrent bright-red colored plaques, which are coated with silvery and brittle scales, on the extensor surfaces of extremities, knees, elbows, hip, and scalp.^[1] The disease has a considerable impact on the quality of life (QoL) because both having a chronic and repetitive course and being a visual and cos-

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metic problem that can almost be comparable to the impacts that arise from systemic diseases. Indeed, especially in recent years, it has begun to defined as a disease spectrum or a multisystemic disease rather than being a skin-confined disease.^[2] These comorbidities have been described as cardiovascular diseases, psychological/psychiatric disorders, inflammatory disorders, sexual dysfunctions, fatty liver disease, alcoholism, smoking, metabolic syndrome as a whole or its individual components, such as hypertension (HT), dyslipidemia, high blood glucose, or atherosclerosis.^[3] On the other hand, sleeping is both a stationary state and active renovation phase of an organism in which the whole body is recharged and prepared for life during this process. ^[3,4] Sleep disorders result in some changes in immune functions. Additionally, it has been proposed that these dysfunctions in sleep patterns may lead to chronic inflammation in the metabolism, an increasing in activation of the diseases, and so a decrease in Health-related Quality of Life (HRQoL). It is thought that the mechanism of these effects can be dependent on underlying dysfunctions in the immune regulatory system. The importance of improvement of sleep dysfunctions should not be ignored in the management of chronic inflammatory diseases.^[4] Some recent reports regarding PS and sleep disturbances suggest that another comorbidity for PS is obstructive sleep apnea/ hypopnea (OSAHS) syndrome, and there is a higher prevalence in relation to the general population. Although it is thought that the relationship stemmed from the increased prevalence of obese PS patients, strongly probable effects of inflammatory mediators should not be neglected.^[5] Similarly, Shutty et al.^[6] stated the positive relation between insomnia and PS. Moreover, it is suggested that pruritus, pain and emotional factors might have predictor effects on sleep disturbances in PS patients, and sleep disorders may be risk factors for the development and activation of PS.^[7] However, the exact relationship between the PS and sleep disorders is still inconsistent, and available data on detailed questioning of sleep quality (SQ) and related conditions are very limited and unsatisfying.^[3, 5-8] Thus, in this study investigating overall SQ, sleep subcomponents, and determining of correlations of SQ and factors that may affect it, in PS patients were aimed.

Methods

A total of 74 subjects (37 male and 37 female) were enrolled in this study, who referred to our dermatology clinic between January and July 2017. After the Local Ethics Committee approval and the required written informed consent was obtained, volunteer patients were included in this study. PS diagnosed with clinical and/or histopathological examination findings. Inclusion criteria were as follows: volunteering to work, ≥ 18 years of age, clinical and/ or histopathological diagnosis of PS, having the ability to understand the questions. Subjects with cognitive impairment, psychiatric and other dermatological disorders, and subjects who underwent any systemic therapy for their PS except for topical therapies were excluded from this study. Subjects' age, gender, smoking and drinking habits, any coexistent chronic diseases (diabetes mellitus (DM), hypertension (HT), heart disease, chronic kidney disease, chronic liver disease, thyroid disease) and disease duration were questioned. After the heights and weights of the subjects were measured, Body Mass Index (BMI) was calculated as weight (kilograms) divided by height (square meters) for an estimate of obesity. The evaluation of body weight was made as <25= normal and $\geq 25=$ overweight, whereas determining of obesity was made as follows: non obese= \leq 29.9 kg/m², and obese = \geq 30 kg/m².^[9] PS severity was evaluated using the Psoriasis Area Severity Index (PASI) scoring, which is the golden standard for determining in disease severity in PS.^[10] PASI is an evaluation of the average redness, thickness and desquamation of the lesions (grades 0-4), weighted by the area of involvement. The minimum score is 0 (no disease) and the maximum score is 72 (maximal disease), whereas values of 10 and above are considered moderate/severe disease. SQ was evaluated with the Pittsburgh Sleep Quality Index (PSQI).^[11] It is a self-administered questionnaire that subjectively measures SQ over the previous month. The guestionnaire includes 19 guestions that must be answered by patients and five questions that must be rated by their bed or room partner (if exists). The questions form the component scores, each of which has a range of 0-3 points. A score of 0 indicates no difficulty in sleep, while a score of 3 indicates severe difficulty. The seven component scores that subjective SQ, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction finally give one total score (0-21 points). A total score of \geq 5 indicates bad SQ. This system was tested and validated by Agargun et al., in the Turkish population.^[12] Disease-related QoL of the subjects was evaluated using the Psoriasis Quality of Life Index (PQLI), which is determined by a Likert type survey. This PS-specific scale was first developed in our country by Aydemir et al., in 2003, and was integrated to QoL studies associated with PS, after its validity and reliability were confirmed. The scale is comprised of 17 questions organized in three categories, which include disease findings, social and sexual live properties of patients, and use of disease-specific medication. The scale is entirely composed of yes-no questions and all "yes" answers should further be rated in four different severity categories. There is no cutoff value for this index. It provides a categorical evaluation

in QoL of the PS patients. As PQLI score increases, diseaserelated QoL is proportionally and adversely impacted. Pruritus was assessed in five categories according to answers given in guestion five of the PQLI scale (no, yes/but it does not affect at all, yes/it affects a little, yes/it is guite effective, yes/very effective).^[13] The perception of body image was determined by Self Perception Scale (SPS), which was developed by Secord and Jourard in 1953. This scale consisted of a total of forty questions in five categories that regard different body images. The Turkish validity and reliability were performed by Hovardaoğlu et al. in 1992. The scale is composed of 40 items. Each item is related to an organ or a part of the body. Each item includes five-grade answer options (I do not like it at all, I do not like it, I'm undecided about it, I like it, I like it very much) that can takes values from 1 to 5. The cut-off point of the scale is 135, and the total score can take values from 40 to 200. A value under 135 indicates low self-perception.^[14] This study was conducted in accordance with the "World Medical Association Declaration of Helsinki, ethical principles for medical researches involving human subjects, 2013".

Statistical Analysis

Obtained data was evaluated with the Statistical Package for Social Sciences (SPSS Statistics for Mac, version 24, New York, USA, 2016). Descriptive statistics were used as mean, standard deviation (SD), median, and frequency. The normality assumption of the variables was checked with the Kolmogorov-Smirnov test. Because our all variables were distributed asymmetrically, Mann-Whitney U non-parametric analysis was used for comparing different parameters. Pearson correlation test was used for determining in a relation of qualitative and quantitative variables which were distributed normal, whereas Spearman's rho test was used for variables that were distributed asymmetrically. A p-value of < 0.05 was considered as significant in binary comparisons, whereas p-values of <0.05, 0.01, and 0.001 were considered as significant in relations in which they were interpreted as weak, moderate, and strong relation, respectively. Correlation results were interpreted according to rho (r) values, as follows: r<0.2 is very weak/no correlation, r=0.2-0.4 is weak correlation, r=0.4-0.6 is moderate correlation, r=0.6-0.8 is strong correlation, and, r>0.8 is very strong correlation. Finally, predictivity of determinant factors which show positive correlation on SQ was detected with multiple linear regression analysis methods.

Results

A total of 74 PS subjects were enrolled in this study (37 female/37 male). General characteristics of the study population are seen in Table 1. The mean age of the subjects was Table 1. General characteristics of totally of the study population

Variables	n (%)	Mean (±SD)	Min	Мах
Gender	37(50)/37(50)			
(Female/Male)				
Age		(47.21±13.91)	21	73
BMI *		30.09±4.68	21.90	42.90
Disease duration		10.58±9.10	1	45
(year/s)				
PASI**		19.79±16.99	1.5	70
SPS***		142.12±23.83	63	199
PLQI ****		21.94±16.31	0	51
PSQI*****		9.14±5.09	1	20
PSQI components				
Sleep quality		1.83±0.82	0	3
Sleep latency		1.59±1.10	0	4
Sleep duration		1.39±1.20	0	3
Sleep efficiency		0.85±1.10	0	3
Sleep disturbances	;	1.41±0.57	0	3
Use of sleeping dru	ıg	0.68±0.79	0	3
Daytime dysfunction	on	1.55±0.99	0	3
PMI*: Pody Mass Inde	NY DI OI**** Deoria	cic Life Quality Inde		

BMI*: Body Mass Index; PLQI****: Psoriasis Life Quality Index; PASI**: Psoriasis Area Severity Index; PSQI*****: Pittsburgh Sleep Quality Index; SPS***: Self-perception scale.

47.21±13.91 (min. 21/max. 73). The mean BMI of subjects was 30.09±4.68 kg (min. 21.9/max. 42.9), and the majority of them (n=36, 48.6%) were obese. Approximately half of them (n=31, 41.89%) had at least one chronic disease, which were 25 hypertension (33.78 %), 20 diabetes mellitus (27.02%), five thyroid diseases (6.75%), 13 alcohol users (17.56%) and 37 smokers (50%), respectively. Subjects' SQ was evaluated based on the total PSQI scores. Mean PSQI of the subjects was 9.14±5.09 (min.1/max. 20), and most subjects (n=58, 78.3%) had bed SQ. Subjects' mean PASI value was found as 19.79±16.99 (min.1.5/max. 70). A little more of the subjects had moderate/severe disease severity (n=46, 62.16%). Mean score for PLQI was 21.94±16.31 (min. 0/max.51), and there was a very significant difference between PASI groups according to PLQI values (p<0.001). Mean SPS was 142.12±23.83 (min. 63/max.199). The difference in SPS values, according to PASI groups was significant (p<0.05). The mean disease duration was 10.58±9.10 years (min.1/max.45 years). The linear relationships with PASI and PLQI scores and PASI and SPS scores are seen in Table 2. There was a positive and very strong correlation between PASI and PLQI values (r=0.823), whereas negative and weak correlation was obtained between PASI and SPS scores (r=-0.287). Comparison of the PSQI values according to cut-off values of SPS, PASI and BMI (overweight/normal) is seen in Table 3. Moderate/severe PASI groups had worse SQ than the other group, whereas there was no difference accord-

Table 2. Comparison of the PSQI values of the study population
according to cut-off values of SPS, PASI and BMI.

n=74	Median (±SD)	U	р	Effect size
SPS*				
<135, (n=23)	8.91±3.89 (9)	576.50	0.907	0.00
>=135, (n=51)	9.25±5.57 (8)			
PASI**				
<10 Weak, (n=28)	6.10±3.30 (6)	289.50	<0.0001*	0.46
>=10 Moderate-	11.00±5.12 (12)			
Severe, (n=46)				
BMI***				
<25, (n=10)	8.20±4.46 (9)	281.50	0.542	0.07
>=25, (n=64)	9.29±5.19 (9)			

Mann-Whitney U test; [†]p<0.0: SPS*: Self-perception; PASI**: Psoriasis Area Severity Index; BMI***: Body Mass Index.

Table 3. Correlations of disease severity with PLQI and SPS values			
n=74	PLQI*	SPS**	
PASI***	0.823▲▲	-0.287	
Spearman's rho Correlation: A A p<0.01 A p<0.05: PL OI*: Psoriasis Life Quality			

ing to SPS and BMI groups. Additionally, SQ was not different in obese and non-obese persons. Correlations of PSQI values and demographic and disease-related other factors affecting on SQ are seen in Table 4. No any linear relationships were detected between PSQI values and age, gender, BMI, and SPS values, whereas they were positively correlated with disease duration, PASI, PLQI, DM, HT and thyroid diseases. Strengths of these correlations were weak for disease duration (0.329), PASI (r=0.363), HT (r=0.256) and thyroid diseases (r=0.248), whereas moderate correlations were obtained for PLQI (r=0.433) and DM (r=0.409). There was a significant relationship with PSQI values and pruritus; PSQI was moderately correlated (r=0.424) with the severity of pruritus. Factors showing both positive correlations with PSQI values and have significant predictivity on SQ are seen in Table 5. According to this stepwise analysis, only PASI and DM had meaningful predictive effects on PSQI values, while other parameters did not show any predictivity.

Discussion

PS is one of the five diseases which the World Health Organization (WHO) reported as having an enormous burden on patients' QoL.^[15] PS has physical, social and psychological negative effects on patients' health.^[6, 7] On the other hand, sleep is an essential requirement for daily functioning and health. Jensen et al. stated in their study that PS patients had poor overall SQ and insomnia in the rates of **Table 4.** Correlations of PSQI values and demographic factors,

 disease duration and some other factors affecting on sleep quality

Variables	PSQI* values
Age	0.212
Gender	0.200
BMI**	-0.078
sDisease Duration	0.329▲▲
PASI***	0.363 🛦 🛦
SPS****	-0.081
PLQI*****	0.433▲▲
Hypertension	0.256▲
Diabetes mellitus	0.409▲▲
Thyroid diseases	0.248▲
Alcohol consumption	0.183
Smoking	0.045
sPruritus severity	0.424▲▲

sSpearman's rho Correlation; Pearson Correlation; $\blacktriangle p<0.01$, $\blacklozenge p<0.05$; r<0.2= very weak or no correlation; r=0.2-0.4 weak correaltion; r=0.4-0.6 moderate correlation; r=0.6-0.8 strong correlation, r>0.8 very strong correlation; PSQI*: Pittsburgh Sleep Quality Index; BMI**: Body Mass Index; PASI***: Psoriasis Area Severity Index; SPS****: Self-perception scale; PLQI****: Psoriasis Life Quality Index.

Table 5. Factors showing both positive correlations with PSQI
values and have significant predictivity on SQ

Determinant factors	В	S.E	ß
Constant factor	14.702	2.190	
Diabetes mellitus	4.347	1.153	0.382
PASI	0.099	0.030	0.332

Multiple linear regression analysis (R²=0.17 in first step and 0.28 in the second step in the stepwise model); PASI*: Psoriasis Area Severity Index.

53.9% and 25% compared to 21.9% and 10.5 of controls, respectively. They indicated that these differences were statistically significant, and the itch was strongly associated with all sleep-related outcomes in PS patients.^[16] Bicici et al. also reported that overall SQ was worse in PS than in their controls. Additionally, patients with worse SQ had higher rates of depression and anxiety scores, and pruritus had a significant effect on worsening in SQ.^[17] Melikoğlu stated that 60% of PS patients had poor PSQI values, and their means were significantly different from healthy controls.^[18] Gowda et al.^[7] indicated that PS patients had important sleep disturbance compared to those of healthy controls, whereas Shutty et al.^[6] reported that the of bed SQ in PS was 4.3 times higher than healthy controls. Similarly, in Wong et al. and Thaçi et al.'s studies, sleep disorders were found significantly higher in PS patients compared to the healthy population, and they stated that this situation was related to patients' fatigue, anxiety and poor QoL.^[19, 20]

However, Stinco et al. did not find any difference in SQ between PS patients and healthy controls.^[21]

In accordance with most of aforementioned literature, we found overall poor SQ (PSQI \geq 5) in our subjects in the rate of 78.3%, and there was not any difference according to age or genders. We detected significant difference between the subjects having low (<10) and high (>=10) PASI values, and subjects having higher PASI values had worse SQ. In Stinco et al. and Duffin et al.' studies, they did not find any correlation with PASI and PSQI values.^[21, 22] However, Strober et al.^[23] found a correlative but non predictor relationship between PASI and PSQI. Similar to the last study, our PASI scores showed meaningful and positive correlation with PSQI values. Although strength of this correlation was weak, PASI was found as a predictive factor for SQ. Mean duration of our subjects was 10.58±9.10 years. Similar to PASI, there was a positive but weak correlation between the PSQI and disease duration. It did not meet our expectations, because both sleep disorders have been associated with chronic inflammatory processes,[22] and higher PASI values and long disease duration are usually related to higher disease activity and increased chronic inflammation in PS, respectively.^[10, 22] However, these inconsistencies related to correlations of PASI and disease duration might be resulted from big distances in minimum and maximum values of PASI (min. 1.5/max. 70) and of durations (min. 1/ max. 45 years), compared to the relatively small number of subjects. Because these variables were distributed asymmetrically and taking account of outliners in an asymmetric group analysis may change the interpretation of results depending on the coefficient preferred.^[24] On the other hand, PS leads to many consequences, such as cardio/occlusive vascular diseases, anxiety/depression, inflammatory bowel diseases, uveitis, arthritis, erectile dysfunction, fatty liver, alcoholism, smoking, lymphomas, osteoporosis, Parkinson's disease and obesity, HT, dyslipidemia, DM, atherosclerosis or metabolic syndrome.^[3] Similar to the literature, 48.6% of our subjects was obese. Although high BMI and obesity have been identified as risk factors for poor SQ, the relationship is still conflicting.^[4] Indeed, our PSQI values did not show any difference according to overweight and normal BMI-groups, and also obese and non-obese groups. Thirty-one of our subjects had at least one chronic disease (HT, DM, thyroid diseases). These findings were compiled with the usual literature. Increase in blood pressure leads to changes in SQ, sleep quantity, and sleep fragmentation,^[25] and DM has been described as a risk factor for poor SQ.^[4] On the other hand, although some reports suggest that thyroid disorders can decrease in SQ as lead to OSAHS, some others suggest that there is no direct correlation between the two conditions.[26]

Considering the correlations with PSQI values, we found positive but weak correlations between the PSQI scores, and, HT and thyroid diseases, whereas DM showed positive and moderate correlation. Additionally, DM had predictivity on SQ. Approximately seventeen of our subjects was alcohol user, but the quantity of consumption in most of them was no more than two standard beer, or two glasses of wine, and only at the weekends. Although alcohol is frequently used for becoming tranquilized and as selfmedication for insomnia, it leads to disruptions in sleep architecture and reduction in the total night REM, especially when consumption is chronic and excessive (>4 standard drinks/day).^[27] However, we did not find any correlation between the two conditions, which might be related to the low amount of consumption of our subjects.

Fifty percent of our subjects were a smoker. There is a strong relationship between smoking cessation and poor SQ. On the other hand, some authors reported that positive association between smoking and poor SQ, which is related to stimulation and inhibition of different neurotransmitters in the sleep-regulating ventrolateral preoptic region, whereas others suggest that no or negative relationship.^[28] We did not find any correlation between SQ and smoking.

Another factor related to sleep disorders in PS is pruritus. Although the exact relationship is not known between SQ and pruritus, it has been suggested that pruritus in PS patients may be related to both mechanical stimulation of pruritus and PS-related psychologic factors, such as depression.^[17] Gowda et al.,^[7] Biçici et al.^[17] and Amatya et al.^[29] found that SQ negatively affected by pruritus in PS. We also detected a significant positive relationship between the two conditions, and there was a moderately correlation between the severity of pruritus and poor SQ.

SQ is one of the most important factors affecting QoL, and humans need an awareness of eight hours of nocturnal sleep to have more energy and performance, better cognition, improved memory, alertness, and healthier immunity. In the evaluation of overall QoL in PS patients, usually HRQoL-scales or dermatologic QoL-scale (DQoL) have been used. However, PS is not only life-restrictive condition, but also causes important psychological consequences because it leads to significant visual impairment, and this relation cannot be neglected.^[13] Thus, we preferred to use PQOL scale to detect PS-specific QoL, instead of the other scales.

Indeed, PQOL is rather similar to a psychological scale than being solely skin scale, which measures especially PS-related physic, social, mental and psychological restrictions in different components of everyday life, such as hairdressing, sleeping with partners, sexual relation, go to a restaurant, shake hands and wear a decollete dress. PS patients feel shame and usually hesitate at these activities.^[13, 30] It is suggested that barriers in QoL in PS patients are developed due to essentially mental and psychological restrictions because of poor skin appearance. Body image (BI) is a multidimensional concept, including thoughts, emotions, feelings and behaviors related to physical appearance and attitude to the body. It began to change when a patient suffers from any kind of dermatosis and finally leads to decrease in QoL, accompanying anxiety, depression, social phobias and adpatation disorders.^[30]

Our moderate/severe PS group also had worse PQOL scores than been in the low-PASI group, and the difference is significant, and our findings were consistent with the literature. We also found a positive and moderate correlation between the PLQI and PSQI values, and PLQI showed a predictive effect on SQ.

The importance of outer aspect and attitude to one's body are the key factors of human mentality. Skin appearance is associated with adaptive mental functioning and well-being, thus plays an important role in the Bl, self-assessment, self-perception (SP), self-esteem, and establishing satisfactory relations with others. Because PS lesions are usually visible, they result in negative mental consequences, and subsequently distortion in the Bl. Studies usually suggest a strong relationship between PS lesions and negative SP due to deteriorated health, unfavorable appearance and lack of satisfaction with the appearance of the body, sexual inhibition, and restricted physical performance; however, irrelevant results have also been taken.^[30]

Our mean SPS score was 142.12±23.83. PSQI did not show a significant difference according to SPS groups, and no correlation was detected in the two conditions. Interestingly, although 75.67% of our subjects had moderate and severe disease, SP skills of them were evaluated as inadequate in only 31.08% of them. Thus, we thought that only the severity of skin lesions is not enough to decrease in SP of PS patients and obtained irrelevant results between SQ and SP might be affected by this reason.

Our study showed that SQ was moderately correlated with factors of QoL, pruritus, and DM, whereas it was no or weakly correlated with others, in PS patients. However, only PASI values and DM had a predictive effect on SQ. Broad-based and controlled further studies are needed to criticize our results.

Conclusion

SQ may be affected by certain factors, such as QoL, disease severity, disease duration, accompanying disorders, such as HT, DM, thyroid diseases, and pruritus in PS patients, in which QoL, pruritus, and DM may be more correlated with it. Disease severity and DM have predictive effects on SQ. Controls of disease activation and prevention of the progression in DM may facilitate to keep SQ in PS patients.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry (Approvel no: 2017/622).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.T., V.K., A.S., D.A.; Design – B.T., V.K., A.S., D.A.; Supervision – B.T., V.K.; Materials – B.T., V.K.; Data collection &/or processing – B.T., V.K., A.S., D.A.; Analysis and/ or interpretation – B.T., V.K.; Literature search – B.T., V.K.; Writing – B.T., V.K.; Critical review – B.T., V.K., A.S., D.A.

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