

Self-reported Excessive Sweating among Patients with Musculoskeletal Pain: A link to Vitamin D and Anxiety

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ABSTRACT

Background: To validate a hypothesis that low level of vitamin D and low daily calcium intake may contribute to excessive sweating (ES) through increases anxiety and depression among patients with Musculoskeletal pain (MSP).

Methods: The study involved 26 patients with MSP who experienced ES and age-gender matched controls. The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological symptoms. Vitamin D level was measured and daily calcium intake was estimated.

Results: All subjects with ES had vitamin D deficiency versus controls (53.8% and 0.0%, respectively). Anxiety (69.2% vs. 30.7%) and Depression (57.1% vs. 26.9%) scores (HADS \geq 8) were also more frequent in cases versus controls, respectively. According to diagnostic criteria of Hyperhidrosis, about 58%, of the cases experienced secondary or generalized Hyperhidrosis. While about 42% of the cases experienced abnormal/unusual sweating. Hot weather, exercise, psychological and emotional conditions were the most exacerbate stimuli of ES. Anxiety negatively correlated with vitamin D and daily calcium intake and positively with depression. Logistic regression analysis revealed that vitamin D status was the significant predictors of ES. Every unit increase in serum vitamin D, the odds of having ES are multiplied by 0.160. In another word, the odds of having ES were decreased by 6.25x'

Conclusion: Low level of vitamin D, and psychological symptoms are commonly observed among patients with MSP who experienced ES. vitamin D status was the significant predictors of ES. Further studies are required to confirm if vitamin D supplementation can be effective in improving ES among patients with MSP

INTRODUCTION

Hyperhidrosis (HH) or excessive sweating (ES), is a debilitating pathophysiological condition that occurs at rest, without the usual triggers such as mental, physiological or thermal stimuli [1-3]. It characterized by sweating in excess of what is required for thermoregulation [3].

Hyperhidrosis can be primary (PHH) or secondary (SHH) in nature. PHH usually occurs in otherwise healthy people, and most often focal, affecting symmetrically bilateral the palms, soles, and axillae, or craniofacial region. Generally, the causes are idiopathic.

The pathophysiology of PHH might be due to an overactivity of the autonomic nervous system which stimulate Eccrine sweat glands, by the neurotransmitter acetylcholine [4,5]. While SHH is usually presented most often as generalized excessive sweating that caused by an underlying medical condition including infectious disease, endocrine disorder (thyroid, pituitary, diabetes), neurological disorder, menopause, gout, and psychological symptoms or side effect of certain medication [6,7].

Higher prevalence of anxiety and depression in patients with PHH was observed in the general population which correlate with the degree of sweating and the quality of life [2,8]. PHH is a prominent feature of social anxiety disorder [1,9].

Based on our preliminary data, [10,11] we have noticed that Jordanian patients with vitamin D deficiency experienced excessive sweating or abnormal/unusual sweating that may occur at rest, regardless of temperature.

Previously, we found that vitamin D deficiency and low daily dietary calcium intake is associated with MSP, fatigue and psychological symptoms [10,11].

Thus, vitamin D deficiency and low daily dietary calcium intake may be associated with the occurrence of ES in Jordanian patients with MSP through increasing anxiety and depression.

The aim of this study is to validate this hypothesis, in addition to identify the clinical and demographic features, and predictors of ES among Jordanian patients with MSP.

MATERIAL AND METHODS

Participants and settings

For the purpose of the current study, ES is defined, as sweating that is not triggered by thermal or physical stimulation [12] or abnormal/unusual sweating. This term was explained to all participants at time of questionnaire filling to avoid misinterpretation of the term. Therefore, all participants who participated in the current study experienced ES or abnormal/unusual sweating.

Twenty-six participants who experienced MSP and ES or abnormal/unusual sweating were volunteered to participate in this study. Participants were recruited at physical therapy clinics, neurology clinics, and radiology department at University Teaching Hospital. Subjects also were recruited to the study through advertising the project at university campus.

Twenty-six gender-age matched apparently healthy volunteers with no MSP or ES (control) were recruited from both genders visiting different clinics for checkups or as accompanying persons as well as university campus [13].

The research was conducted according to the declaration of Helsinki and was approved by the Institutional Review Board Committee (IRB) of Jordan University of Science and Technology. Written informed consents were obtained from all participants.

Exclusion criteria included individuals with chronic diseases affecting vitamin D metabolism and those who were on vitamin D supplements for the past two months at time of study [14], or suffering from disease that cause generalized or focal hyperhidrosis or taking drugs that cause ES [6]. Inclusion criteria included participants experienced ES at least weekly, and their ages were <40years.

Participants were instructed to complete a guided self-assessment questionnaire, including demographic data. MSP pain severity was measured using a 0-10 Numerical Rating Scale (NRS) (0, no pain; 10, maximum pain) [13]. Other sweating relevant data included the time, sites, duration of ES and social impact of ES.

Assessment of daily calcium intake

Similar to the measurement strategies used in past studies [13], daily dietary calcium intake was assessed by asking participants to report their daily intake of different types of dairy products.

Participants have answered questions regarding their daily frequency and type of dairy product intake. Intake of dairy products (milk, yogurt, cheddar cheese, cream cheese and labnah, which is a soft cream cheese made by removal of whey from yogurt through cheese cloth) was determined on a daily basis as none, single, two, three or more dairy servings per day. A dairy serving is defined as 1 cup of milk or yogurt (300mg calcium), 2 full tablespoons of labnah (100mg calcium), and a 1-ounce piece of cheese (162mg calcium), and cream cheese (20mg calcium).

Psychopathology questionnaire

Similar to the measurement strategies used in past studies [13], the Hospital Anxiety and Depression Scale (HADS) was used to assess self-reported symptoms of anxiety and depression. [14].

In the HADS, patients had a score between 0 and 21 for either anxiety (HADS-Anxiety) or depression (HADS-Depression). The total score for either anxiety or depression was classified as the following: Normal (0-7); Borderline (8-10); and Abnormal (clinical) anxiety or depression (11-21). A total score for anxiety (SumA) and depression (SumD) calculated by adding together all the values.

LABORATORY ANALYSIS

Serum 25-hydroxyvitamin D (25-OHD) level was determined by the chemiluminescent assay using Roche Modular E170 Analyzer (Roche Diagnostics, Basel, Switzerland). Vitamin D status was divided into four diagnostic categories according to serum 25(OH)D levels as follows, Vitamin D sufficiency (≥ 30 ng/ml), vitamin D insufficiency (20-<30 ng/ml), vitamin D deficiency (10-<20 ng/ml), and severe vitamin D deficiency (<10 ng/ml).

STATISTICAL ANALYSIS

Data were analyzed using the Statistical Package for Social Science (SPSS, version 21.0). Data were presented as frequencies for categorical variables and means \pm standard deviation for continuous variables. Frequencies and percentages were computed for categorical variables, and means \pm standard deviations (SD) were computed for continuous variables. Independent samples t-test was used for two group comparison. Chi-square (X^2) test was performed to investigate the association between psychological symptoms and categorical variables of interest. Pearson's or Spearman's correlation analysis (based on appropriateness) was conducted to examine the relationships between continuous variables. All statistical significance verifications were conducted at the level of $P < 0.05$.

RESULTS

Demographics of participants

Twenty-six (males and females) participants who experienced ES and 26 gender matched healthy controls with no MSP or ES or abnormal sweating were enrolled in this study.

The age of participants was between 18 and 39 years (mean \pm SD: 25.38 \pm 5.5 and 25.27 \pm 5.1, for patients and controls respectively, $p = < 0.938$). Some 76.9%, $n = 20$ of participants belong to the age group of <30 years old. The majority of participants was females (80.8%, $n = 21$).

Table 1: Characteristics of the study population.

Variables	Case N (%)	Control N (%)	P value
Age (years)			
18-29	20(76.9)	20(76.9)	
30-40	6(23.1)	6(23.1)	
Mean \pm SD	25.38 \pm 5.5	25.27 \pm 5.1	0.938
Gender			
Male	5(19.2)	5(19.2)	
Female	21(80.8)	21(80.8)	
Health status			<0.001
Excellent	1(3.8)	8(30.8)	
Very good	15(57.7)	18(69.2)	
Good	8(30.8)	0(0.0)	
Bad	2(7.7)	0(0.0)	
Body mass index (kg/m²)			0.282
Underweight	2(8.0)	4(15.4)	
Normal	11(44)	13(50)	
Overweight	9(36)	9(34.6)	
Obese	3(12)	0(0.0)	
Mean \pm SD	24.69 \pm 5.9	23.07 \pm 3.6	0.24
HADS-Anxiety scale[†]			0.002
Normal (0-7)	8(30.8)	18(69.2)	
Borderline (8-10)	7(26.9)	7(26.9)	
Abnormal (11-21)	11(42.3)	1(3.8)	
Mean \pm SD	10.4 \pm 5.1	5.6 \pm 2.8	<0.001
HADS-Depression scale[‡]			0.01
Normal (0-7)	11(42.3)	19(73.1)	
Borderline (8-10)	8(30.8)	7(26.9)	
Abnormal (11-21)	7(26.9)	0(0.0)	
Mean \pm SD	8.61 \pm 4.7	4.92 \pm 3.0	<0.001
Vitamin D level			<0.001
Normal (30 \geq ng/ml)	0.0(0.0)	7(26.9)	
Insufficient (20-<30 ng/ml)	0.0(0.0)	9(34.6)	
Deficient (<20 ng/ml)	13(50)	5(19.2)	
Severe deficient (<10 ng/ml)	5(19.2)	5(19.2)	
Mean \pm SD	13(50)	5(19.2)	
Mean \pm SD	9.41 \pm 4.07	22.64 \pm 11.58	<0.001
Total Calcium Intake (gm/day)[¥]			<0.001
<299.88	14(53.8)	3(11.5)	
2.99.88-<483.23	10(38.5)	8(30.8)	
≥ 483.23	2(7.7)	15(57.7)	

Data are presented as numbers and percent within parenthesis. [†] HADS-Anxiety= Hospital Anxiety and Depression Scale subscales score for anxiety, [‡]HADS-Depression= Hospital Anxiety and Depression Scale subscales score for depression, [¥] Total Calcium Intake (gm/day) = total daily calcium intake (mg/day)(dairy + supplement). P value < 0.05 was considered statistically significant.

Assessment of body mass index (BMI) showed that BMI was not significantly different between patients and controls, ($p = 0.282$). About 38%, $n = 12$ of participants were either overweight or obese in cases compared to 9 (34.6%) were overweight in the control group (Table 1).

All patients had chronic pain duration (>3 months). Some of 34.6% ($n = 9$) evaluate their pain as moderate, 50% ($n = 13$) as severe and 15.4% ($n = 4$) as very severe pain. The average pain score on NRS was 7.6 \pm 1.02.

ASSESSMENT OF PSYCHOLOGICAL SYMPTOMS FOR STUDY PARTICIPANTS

With respect to the HADS subscales for anxiety and depression, patients with ES had markedly higher psychological

symptoms than controls (Table 1). Clinical anxiety and clinical depression (HADS score ≥ 11) were reported by 69.2%, n=18 and 57.7%, n=15 of the participants in case, respectively, while 30.7%, n=8 of controls had clinical anxiety and none of them had clinical depressive symptoms ($p < 0.001$), (Table 1).

BIOCHEMICAL PARAMETERS AMONG PARTICIPANTS

All of the patients had vitamin D deficiency, 50%, n=13 of them had severe vitamin D deficiency (< 10 ng/ml) compared to 0.0% of the controls, $p < 0.001$ (Table 1).

Some 53.8%. (n=14) of the subjects with ES consumed < 299.88 mg/day calcium compared to 11.5% (n=3) in the controls, which is less than 1/4 the Recommended Dietary Allowance (RDA) (1000-1300 mg depending on life stage group) [15].

CHARACTERISTICS OF EXCESSIVE SWEATING AMONG PARTICIPANTS

Table 2: Characteristics of excessive sweating.	
Parameter	N (%)
Excessive Sweating when temperature is not hot and not exercising	
Yes	15 (57.7%)
No	11 (42.3%)
Time of excessive sweating	
Day time	16(61.5%)
At night	1(3.8%)
Both	9 (34.6%)
Social impact of excessive sweating	
Yes	
Social anxiety	10 (38.5%)
Social embarrassment	12 (53.8%)
Social isolation	2 (7.4%)
Low self esteem	6 (23.1%)
No	
	12 (46.2%)
Excessive Sweating duration	
≥ 3 Months-24months	7(26.9%)
> 24 Months	19(73.1%)
Primary Site of Sweating as a chief complaint	
All body	4(15.4%)
Under arm	22 (84.6%)
Palm	18 (69.2%)
Face	12(46.2%)
Scalp	7(26.9%)
Feet/soles	6(23.1%)
Factors increase Sweating	
Hot weather	23(88.5%)
Walking	21(80.8%)
Exercise	18(69.2%)
Anxiety	17(65.4%)
Stress	13(50%)
Embarrassment	13(50%)
Depression	11(42.3%)
Thinking	8(30.8%)

Data are presented as numbers and percent within parenthesis.

Some 13 patients (53.2%) reported ES when temperature is not hot and not exercising, 61.5% (n=16) reported day time sweating, only one case reported night sweating, while 34.6% (n=9) indicated ES during day and night times. Approximately, 53.8% (n=14) of participants reporting ES indicated some degree of undesirable social effects, and 53.8%, n=12 of the patients addressed social embarrassment, as the main reason for adverse social impact of ES, (Table2).

No significant difference in all measured parameters (vitamin D, psychological symptoms, daily calcium intake, MSP severity) between patients who experienced ES at rest and when temperature is not hot and patients have ES upon stimuli with exception to age (23.46 ± 4.3 and 28.0 ± 6.2 , $p = 0.037$, respectively).

STIMULI, SITES OF EXCESSIVE SWEATING AMONG PARTICIPANTS

Hot weather was the main stimulus for ES among participants (88.5%, n=23). Walking was listed second major trigger for ES (80.8%, n=21), followed by exercise 69.2%, n=18, anxiety 65.4% n=17, stress (50%, n=13), embarrassment (50%, n=13), thinking 30.8%, n=8, depression (42.3%, n=11), and pain 6 (23.1%).



Figure 1 A 28-year-old male experienced excessive sweating in the scalp even when the temperature is not hot or exercising.

The most common sites for ES were the axilla/underarm (84.5%, n=22), palms of hands (69.2%, n=18) (Figure 1), the face (46.2%, n=12), scalp 26.9% n=7 (Figure 2), and feet/soles (23.2%, n=6). Only 4 participants (15.3%) reported to have ES over all the body.



Figure 2 A 21-year-old female experienced excessive sweating day and night in the sole of the foot and in the palm.

Correlation between psychological symptoms and Selected Variables among study population

A correlation analysis was also conducted to evaluate the relationships between psychological symptoms, vitamin D level, total daily calcium intake, age and BMI.

Pearson correlation (1- tailed) revealed that serum vitamin D level was significantly and negatively associated with both HADS-anxiety and HADS-depression (p=0.001 and P=0.004, respectively). HADS anxiety positively and significantly correlated with HADS-depression, P<0.001 (Table 3).

Spearman correlation (1- tailed) revealed that HADS-anxiety and HADS -depression were significantly and negatively associated with total daily calcium intake (p=0.003, p=0.039, respectively) (Table 3).

Binary Logistic Regression for the Predictors of excessive sweating among the study population

Because there is no patient with ES who had insufficient or normal vitamin D and one control subject had Abnormal HADS-Anxiety no one had Abnormal HADS-Depression (≥11-21), logistic regression continuous rather than categories were used to determine variables predictive of ES.

Logistic regression analysis revealed that vitamin D level is the only significant predictors of ES. Every unit increase in serum

vitamin D, the odds of having ES are multiplied by 0.160. In another word, the odds of having ES were decreased by 6.25x' (Table 4).

Table 3: Correlation analysis between psychological symptoms and selected variables among study population (N=52).

	HADS-Anxiety†‡	HADS-Depression
Variables		
Age	0.096 0.238	0.292* 0.018
BMI (Kg/(Height in meter) ² §	-0.146 0.151	0.045 0.375
Serum Vitamin D (ng/ml)	-.417** 0.001	-0.363** 0.004
HADS-Depression†‡	0.58** <0.001	1
T. Ca intake (mg/day)¶	-0.375** 0.003	-0.264* <0.039

Pearson's or Spearman's correlation test were used as appropriate (p-values were one-tailed and considered statistically significant at p-value < 0.05). §BMI=Body weight Index, †HADA = Hospital Anxiety and Depression Scale total score, ¶ T. Ca intake (mg/day) = total daily calcium intake (dairy+ supplement). P value<0.05 was considered statistically significant.

Table 4: Binary logistic regression analysis for predictors of excessive sweating.

Variable	Odds ratio	CI (95%)\$	P value*
Serum vitamin D†	-0.160	0.744- 0.977	0.022
HADS-Anxiety†‡	1.266	0.9461.693	0.166
HADS-Depression	0.678	0.805- 1.693	0.678
T. dietary Ca intake (mg/day) ‡	-0.996	0.947- 1.693	0.086

\$OR (95% CI) = results represented as odds ratio and 95% confidence intervals, †Vitamin D= Serum vitamin D level (ng/ml), ‡Total Calcium Intake (mg/day) = total daily calcium intake (dairy+ supplement) stratified as tertile, *P value <0.05 was considered statistically significant.

DISCUSSION

The aim of this study is to validate a hypothesis that low level of vitamin D and poor daily calcium intake may contribute to ES among Jordanian patients with MSP.

The most notable findings of the current study are that all patients with MSP who experienced ES had vitamin D deficiency and high prevalence of psychological symptoms compared to controls. ES is associated with anxiety, which was negatively correlated with vitamin D level and daily calcium intake, and positively with depression. Serum vitamin D level was a significant predictor of ES.

According to diagnostic criteria of Hyperhidrosis [6], about 58% of patients with MSP experienced secondary or generalized Hyperhidrosis. While about 42% of patients

experienced abnormal/unusual sweating. Hot weather, exercise, psychological and emotional conditions were the most exacerbate stimuli of ES

Interestingly, and to the best of our knowledge, this is the first study to find that vitamin D status, psychological symptom, and low calcium intake to associate with secondary ES or abnormal/unusual sweating among patients with MSP.

It is worth mentioning that patients with Fibromyalgia syndrome, which is a chronic condition characterized by persisting MSP and other frequent symptoms such as anxiety and depression [16], reported to experienced various dermatologic conditions including ES (32%)[17]. in addition to high prevalence of vitamin D deficiency (95%) [18].

Vitamin D is a fat-soluble vitamin; it exerts anatomic, hormonal, neurological, and immunological influences on pain manifestation. Vitamin D deficiency is associated with persisting MSP [11,19-21] that often comorbid with psychiatric disorders across diverse populations world- wide [19,20,22-24].

In the current study, and concordant reports, all patients who experienced MSP and secondary ES or abnormal/unusual sweating had vitamin D deficiency. In addition to significantly high prevalence of anxiety and depression compared to controls. Anxiety was significantly and inversely association with vitamin D status and positively with depression.

Vitamin D status is the only significant predictor of secondary ES or abnormal/unusual sweating among patients with MSP.

Previously and Concordant with our findings, a high prevalence of anxiety, depression was found among patients with primary hyperhidrosis [2,8,25], (American Academy of Dermatology annual meeting. March 2, 2019, <https://www.hcplive.com/view/hyperhidrosis-associated-with-higher-anxiety-depression-add>). A significant correlation was observed between sweating and anxiety [2] and a positive correlations between sweating severity and the prevalence of anxiety and depression among patients with PHH also was observed [8].

In addition to vitamin D, calcium plays a significant role in the central nervous system (CNS) and may have crucial implications in the etiology of many of the neuropsychiatric disorders [19,26]. The current study revealed a significant inverse association between total daily calcium intake, anxiety, and depression among patient with secondary ES or

abnormal/unusual sweating, which is consistent with previous published articles [11,16,19,20,].

Although emotional triggers enhance symptoms, ES is not considered a psychiatric disorder; rather it is a physiological disorder [12]. Hypothalamic centers involved in regulation of sweating appear to be more sensitive to emotional stimuli in patients with hyperhidrosis compared to healthy people [27]. Induction of ES can be caused by heat, humidity, and vigorous exercise [27]. In this study, in addition to psychological factor and emotional factors, hot weather and physical activity were the most common causes of excessive sweating among the population studied. However, 58.7% of patients in our study reported ES even when the temperature is not hot or exercising.

Sweating in excess that is required to regulate body temperature which conducted mainly by eccrine sweat which are distributed over the body surface especially in the axillae, palms of hands, and soles of feet [6,12,27]. While apocrine sweat glands are responsible for focal hyperhidrosis (mainly axillary and urogenital regions), that regulated by mainly by hormonal processes [5,6,28].

In this study both eccrine and apocrine sweat glands apparently involved in the production of excessive sweating since the stimulants for excessive sweating involve factors that stimulates both type of sweat glands including physical, emotional and psychological factors. Patients reported excessive sweating even when the temperature is not hot or exercising.

In this study, the only significant factor between patients that sweat at rest and patients have ES upon stimuli was age. Dramatic decrease in the prevalence of PHH with increasing age was observed [29].

ES negatively affects quality of life. Affected individuals face difficulties on personal, social, and occupational levels [12]. Affected patients suffer of decreased socialization, anxiety, and embarrassment [12]. In this study, 53.8%, n=14 of responders with ES suffered of adverse social consequences including social anxiety, embarrassment, low self-esteem and isolation. Previously, Strutton et al. 2004 [30] reported that approximately one third of individuals with axillary hyperhidrosis sweating is barely tolerable and frequently interferes with daily activities.

Previously, vitamin D supplementation and increased daily dietary intake to patients with MSP resulted in improved MSP severity and comorbid psychological symptoms [13,19,20]. Further studies are required to confirm if vitamin D supplementation can be effective in improving secondary ES or abnormal/unusual sweating among patients with MSP.

One limitation in our study was the reliance on patient reports of excessive sweating and the sample size was relatively small. An overall, the findings of our study demonstrated that vitamin D deficiency (100%), and psychological symptoms (69.2% for anxiety and 57.7% for depression) are common problems in subjects with MSP who experienced Secondary ES or abnormal/unusual sweating. Serum vitamin D level is the significant independent predictor of ES.

The finding will support recommendation to physicians to measure serum vitamin D level for patients with MSP who experienced ES as part of the clinical assessment. Further studies are required to confirm if vitamin D supplementation can be effective in improving secondary excessive sweating or abnormal/unusual sweating among patients with MSP.

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CONFLICTS OF INTEREST

none to be declare.

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