Hot Flashes in Adolescence and Young Adult Females: a Link to Vitamin D and Calcium

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ABSTRACT

Background: Menopause is a stage in life when a woman stops having menstruation and the ovaries produce less estrogen. Hot flashes (HFs) are the classical symptoms for menopausal transition and cessation of menses. Increased anxiety had been reported as a significant risk factor of HFs. Vitamin D deficiency and low daily dietary calcium intake may be associated with the occurrence of hot flashes (HFs) in adolescents and young females that are not related to hormonal changes of menopausal transition. Objective: The aim of this study is to validate this hypothesis. Methods: A case-control study was conducted. Thirty-eight females (38) with HFs aged 18-40 years, and 38 age-matched healthy controls with no HFs were involved. Participants answered questions about HFs symptoms. Psychological symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Serum vitamin D, Follicle Stimulating Hormone, Estradiol, and Prolactin were measured. Results: Vitamin D deficiency, psychological symptoms, and Musculoskeletal pain (MSP) were more prevalent in cases versus controls. About 73.68% of females had HFs on a daily basis, 73.7% of them reported that their HFs associated with excessive sweating. Spearman correlation revealed that number of daily HFs were correlated positively and significantly with anxiety scores ($r^2 = -0.278$, $p=0.045$), and average MSP pain ($r^2 = -0.536$, $p<0.001$). Binary logistic regression showed that, Anxiety score and vitamin D status, (OR=1.33 (1.104-1.7), $p=0.02$, and OR=0.89 (0.79-0.99, $p=0.03$) respectively were the predictors for HFs. Conclusion: This study showed that adolescents and young females may experience HFs that are not related to hormonal changes of menopausal transition. The predictors for HFs were vitamin D deficiency and anxiety.

Keywords: Hot flashes, Adolescence, Vitamin D, Anxiety, Quality of life.

1. BACKGROUND

Menopause is a stage in life when a woman stops having menstruation and the ovaries produce less estrogen. Hot flashes (HFs) are among the most frequent distressing complaints of women during the menopausal transition which begins 4–6 years before cessation of menses, experienced by up to 80% of women during menopausal transition and peaking around the final menstrual period (1, 2). Risk factors of HFs and night sweating include increased body mass index, smoking, anxiety, depression, lower levels of estrogen, higher Follicle-stimulating hormone (FSH) levels, premenstrual syndrome, lower education, and medical treatments, such as hysterectomy, oophorectomy, and breast cancer-related therapies (2).

Although HFs present almost exclusively with the menopausal transition, young females before age of 40 may experience a mild HFs in a condition called primary ovarian insufficiency (POI) (3) and secondary amenorrhea. (4) hyperprolactinemia is a common cause of secondary amenorrhea. Women with hyperprolactinemic amenorrhea are more prone for psychological symptoms (5, 6) and symptoms of menopause including HFs (7). Little attention has been given to HFs in adolescence and young adult females because they are under-reported to healthcare providers.

Based on our preliminary data (8-12) we noticed that adolescents and young Jordanian females with vitamin D deficiency experienced sudden sensation of intense heat often accompanied by sweating. This symptom may occur at any time of the day or night but particularly occurs at night, which disrupted their sleep.

Increased anxiety had been reported as a significant risk factor of HFs (13), and higher anxiety scores were significantly associated with the occurrence,
severity and frequency of HFs in the early transition to menopause (14).

Previously, we found that low serum vitamin D level and low daily calcium intake were more prevalent among patients with MSP (8), psychiatric outpatients (9) subjects who experienced non-cardiac chest pain (10) subjects with overactive bladder (11) subjects with Car-pel Tunnel Syndrome (12), subjects with nightmare and bad dreams (15) and subjects with sleep bruxism (16).

2. OBJECTIVE

Thus, vitamin D deficiency and low daily dietary calcium intake may be associated with the occurrence of HFs in adolescents and young Jordanian females that are not related to hormonal changes of menopausal transition. The aim of this study is to validate this hypothesis.

3. PATIENTS AND METHODS

Participants and setting

This is a case-control study which involved 38 females with monthly menstrual cycles and HFs aged 18-40 years, and 38 age-matched healthy controls with monthly menstrual cycles and no HFs, no musculoskeletal pain (MSP) nor general weakness; the symptoms of vitamin D deficiency.

Females with HFs were recruited from Obstetrics and Gynecology outpatient-clinics at King Abdullah University Hospital, Irbid, Jordan, while the controls were recruited from subjects who visited different clinics for checkups or as accompanying persons or subjects who visited Jordan University of Science and Technology (JUST) campus.

Inclusion criteria

Baseline eligibility included healthy women (age between 18 and 40 years-old), with monthly menstrual cycles and hot flashes, presence of an intact uterus and at least one ovary, absence of pregnancy and lactation, and must not be on oral contraceptives or hormone therapy.

Exclusion criteria

The following subjects were excluded from the study: females with abnormal hormone levels (FSH, Estradiol, and Prolactin), those with chronic diseases that affect vitamin D metabolism including (kidney and liver), diseases and conditions that may damage nerves (include Diabetes Mellitus, stroke, Multiple Sclerosis, and Parkinson’s disease), those who were on vitamin D supplements for the past two months, in addition to females on niacin therapy for the treatment of hyperlipidemia.

Data collection

All data were obtained under the supervision of well-trained research assistants. They were responsible for guiding all participants to fill out the questionnaires, ensuring that all questions were answered, and obtaining consent from participants. Participants were instructed to complete guided self-assessment questionnaires including their demographics, health status, and information regarding their medical, reproductive and menstrual status, in addition to psychological symptoms. Participants with MSP were asked to determine pain sites and pain intensity. Pain intensity was measured using a 0-10 Numerical Rating Scale (NRS) (8).

Characteristics of Hot Flash and quality of life

Participants answered questions about HFs’ symptoms including duration of HFs (months or years), frequencies over the past 24 hours (hrs) and 48hrs, severity (mild: <5min, moderate: up to 15min, severe: up to 20 min and very severe: up to 45 min), in addition to rate the severity of each hot flash using a 0 (not at all) to 10 (extremely) point numeric rating scale NRS (8) if the HFs wake you up at night and how many times. Participants also answered question, if the HFs were associated with sweating. Participants also asked to rate how much the HFs disturbing them on scale from 0-10 and the exacerbating factors for HFs.

Assessment of daily calcium intake

Information regarding participant’s frequency and type of dairy product intake (milk, yogurt, cheddar cheese, cream cheese, and labnah (a soft cream cheese made by removal of whey from yogurt through cheesecloth) were recorded. Intake of dairy products was determined on daily basis as none, single, two, three or more dairy servings per day. A dairy serving was defined as: 1 cup of milk or yogurt (300 mg calcium), 2 full table spoons (2 oz.) of labnah (100 mg calcium), and a 1-ounce piece of cheese (162 mg calcium), and cream cheese (20 mg calcium) (8, 17).

Psychosocial questionnaire

Self-reported symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), which is a simple, reliable, and potentially valid measure commonly utilized to evaluate anxiety and depression disorders in both somatic, psychiatric and primary care patients and in the community settings (18).

The HADS is a 14-item self-rating questionnaire measuring anxiety and depression (seven items each). Each item is rated on a 4-point scale ranging from 0 (not at all) to 3 (very often). Thus, the study subjects were divided into three groups according to the total HADS score: total score from 0–7 indicates normal, 8–10 indicates borderline abnormal, and 11–21 indicates abnormal or clinical case of anxiety or depression.

Hot flashes related daily interference

To assess the psychometric properties of the hot flashes and its impact on daily activities, a Hot Flash Related Daily Interference Scale (HFRDIS) was used (19).

The HFRDIS is a 10-item, self-report questionnaire assessing the impact of HFs on a woman’s life using 0-10 point scale, a 0 (do not interfere) to 10 (completely interfere). A total score is computed by summing items with cut points of mild (0–3.9), moderate (4–6.9), and severe (7–10) interference (19). Women without were asked to mark 0 for each item. In the current study, we used 9-items self-report questionnaire. The question about HFs and sexuality was not included since most of females were single (71.8%, n=28). Thus, the cut points of severe HFs related daily interference was considered to be 7-9 instead of 7-10.
| Variable                  | Total number of participants (n= 76) | Healthy controls (n= 38) | Cases (n= 38) | P-value* |
|---------------------------|--------------------------------------|--------------------------|---------------|----------|
| Age (Years)               | 24 (21-26)                           | 24 (21-26.25)            | 23 (21-25)    | 0.65     |
| Marital status            |                                      |                          |               |          |
| Single                    | 61 (80.3)                            | 35 (92.1)                | 26 (68.4)     | 0.02     |
| Married                   | 15 (19.7)                            | 3 (7.9)                  | 12 (31.6)     |          |
| BMI (Kg/m²)               | 23.33 (20.70-26.21)                  | 22.83 (20.32-25.77)      | 24.23 (21.58-29.48) | 0.10     |
| Serum 25-hydroxyvitamin D (ng/mL) | 14.60 (8.60-24.07)                        | 20.43 (12.50-30.38)       | 9.99 (6.33-19.09) | <0.001   |
| HADS-anxiety score (0-21) |                                      |                          |               |          |
| Normal (0-7)              | 35 (46.1)                            | 29 (76.3)                | 6 (15.8)      |          |
| Borderline (8-10)         | 12 (15.8)                            | 4 (10.5)                 | 8 (21.1)      | <0.001   |
| Abnormal (11-21)          | 29 (38.2)                            | 5 (13.2)                 | 24 (63.2)     | <0.001   |
| HADS-depression score (0-21) | 6.5 (4-10)                             | 4 (2-6)                  | 9.5 (7-11.25) | <0.001   |
| FSH (pmole/L)             |                                      |                          |               |          |
| Estradiol (µg/L)          |                                      |                          |               |          |
| Prolactin (µg/L)          |                                      |                          |               |          |

Table 1: Differences in variables between female participants with hot flashes and healthy controls. * Mann Whitney U test, Chi-square test, or Fisher exact test as appropriate (P < 0.05 was considered statistically significant). Data are presented as frequency (%) or median (25th – 75th percentiles). HFs, Hot flashes; BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale; MSP, Musculoskeletal Pain; FSH, Follicle-stimulating hormone.
Biochemical analysis:

About 10 ml of non-fasting venous blood samples were collected from all participants for measurement of: Follicle Stimulating Hormone (FSH), Estradiol, and Prolactin using electrochemiluminescence immunoassay using cobas 6000 analyzer - Roche Diagnostics. Hormones were measured at the second day of menstruation for all participants with HFs. Vitamin D levels were measured using electrochemiluminescence immunoassay using the Roche Modular E170 Analyzer - Roche Diagnostics. Normal Reference Range: FSH (3.5-12.5 pmole/L, Estradiol (45.4-854 µg/L), Prolactin (4.79-23.3 µg/L), and Vitamin D (ng/mL).

Statistical analysis

Data are presented as frequencies (%) or (median 25th-75th quartiles) as appropriate. Mann Whitney U test, Chi-square test, or Fisher exact test were used for group comparisons to investigate the association between HFs and continuous or categorical variables of interest, respectively. Spearman’s correlation test was used to assess the correlation between continuous variables. Binary logistic regression was used to investigate predictors of HFs adjusting for other confounders. Multiple linear regression analysis was used to investigate predictors of anxiety. All statistical significance verifications were conducted at the level of P < 0.05. Data analysis was performed using the Statistical Package for Social Science (SPSS, version 21.0).

Ethical Approval

The research was approved by Institutional Review Board (IRB) at Jordan University of Science and Technology (33/122/2019).

4. RESULTS

Totally, 38 healthy women with monthly menstrual cycles and no HFs were included in this study. All women had regular menstrual cycle for the past three months with (5-8.25) for the cases and (3-6.75) for the control, p= 0.03. The median age for cases and controls were 23 (21-25) years and 24 (21-26.25) years, respectively, p= 0.65. Majority of the participants were single (68.4%, n=26 for the cases versus 92.1%, n=35 for the controls). Obesity was more prevalent in females with HFs compared with controls although there was no significant difference in BMI between the two groups (p= 0.10) (Table 1).

Vitamin D deficiency (<20ng/ml) was found in 76.3% of females with HFs compared to 47.4% of controls, p=0.001. Most of the participants with HFs had normal FSH, Estradiol, and prolactin hormone levels.

Characteristics of HFs

The study sample included 38 women who experience HFs for the duration of 12 (4-27) months. Some 13.2%, n=5 of participants describe their (HFs) as a feeling of transient sense of warmth, and 73.7%, n=28 as a sudden

| Vitamin D | HADS-Anxiety | HADS-Depression | Average pain Scale | No of HFs in 24 hrs | Intensity of HFs | Average effect of HF on daily quality of life |
|-----------|--------------|-----------------|-------------------|--------------------|-----------------|---------------------------------------------|
|           | 1            | 0.568**<0.001 | 0.278* 0.045      |                    | 0.360* 0.013    |                              |
| HADS-Depression | 0.568**<0.001 | 1               |                    |                    |                 |                              |
| T. Ca. Intake | -0.326* 0.023 | -                  |                    |                    |                 |                              |

| Average pain Scale (NRS) | 0.536<0.001 | 0.413**0.005 | 0.366* 0.012 |
| No of HFs in 24 hrs | 0.278* 0.045 | 0.385**0.009 | 0.366* 0.012 |
| Intensity of HFs | 0.361* 0.013 | 0.385**0.009 | 0.366* 0.012 |
| Average effect of HF daily quality of life | -                  | -                  | -                  |

Table 2: Spearman’s correlation analysis between hot flushes symptoms and selected variables. *Data is presented as r2-values. **Spearman’s correlation is significant at the 0.05 level (1-tailed), HADA-Anxiety = Hospital Anxiety and Depression Scale total score for anxiety, † HADA-Depression= Hospital Anxiety and Depression Scale total score for depression, YBMI, Underweight<18.5, Normal 18.5-24.9, Overweight 25-29.9, Obese≥30, ‡ T. Ca intake (mg/day) = total daily calcium intake (dairy+ supplement), **P value<0.05 was considered statistically significant. BMI (Kg/(Height in meter)2
intense heat. Some 73.7%, n=28 of them reported that their HF's are associated with excessive sweating and 26.3%, n=10 with skin redness. Some 60.5%, n=23 of participants reported that HFs wake them up at night with average 1.83±1.2 times.

Some 73.68%, n=28 of participants had HFs on a daily basis, with an average of 2.3±1.63 and 26.31%, n=10 had HFs with 48 hours (hrs) with average of 1.28±0.7. Some 31.6%, n=12 of HF's last<5 min (mild), 50%, n=19 last up to 15 min (moderate) and 0.5%, n=4 last up to 20 min (severe) and 7.9%, n=3 last up to 45 min (very severe).

On 0-10 scale, participants reported the median intensity of HFs was 5 (5-7) and the median degree of disturbance from HFs was 7.5 (6.88-10).

Exacerbating factors for HFs

The most exacerbating factors for the HFs reported by participants are: Psychological stress (81.6%), before menstrual cycle (68.4%), during menstrual cycle (60.5%), weather/room temperature (65.8%), fatigue/general weakness (63.2%), MSP (31.6%), insomnia (31.6%), smoking (26.3%), and tight clothes (23.7%).

Hot Flashes Related Daily Interference Scale (HFRDIS)

Higher scores for HFRDIS indicate higher interference due to HFs and thus, greater impact on quality of life. HFRDIS showed that HFs had a significant adverse effect on adolescent and young females daily functioning especially for mood, concentration, sleep, and enjoyment of life (19).

In the current study, the adverse effects of HFs on daily functioning was ranged between mild (0-3.9) for work, social activities and relations with others, to moderate (4-6.9) for mood (6.37), concentration (6.0) sleep (5.79), and enjoyment of life (5.29). The average effect of HFs on overall quality of life was 5.32.

Spearman correlation between selected variables (Table 3)

One-tailed correlation analysis was conducted among participants with HF's to evaluate the relationships between vitamin D level, psychological symptoms, total daily calcium intake and some HF's symptoms (number of daily HF's severity), 0-10 NRS for MSP and Overall quality of life.

Spearman's correlation revealed that none of HF's symptoms was correlated with vitamin D levels, anxiety and depression scores. Depression score was negatively correlated with daily dietary calcium intake (r²=-0.3265, p=0.023). Anxiety score was positively correlated with depression score (r²=0.556, p<0.001). Number of HF's during 24hrs were correlated positively and significantly with Anxiety scores (r²=-0.278, p=0.045), and intensity of MSP (r²=-0.536, p<0.001). Overall quality of life correlated positively and significantly with Anxiety scores (r²=0.361, p=0.013), intensity of HF's (r²=0.366, p=0.012), and number of HF's during 24hrs (r²=0.385, p=0.009).

Independent predictor of hot flashes

The results of binary logistic regression (Table 3) showed that, vitamin D status, and anxiety score were significant predictors of HF's. Anxiety score was the strongest predictor of HF's (OR=1.33 (1.04-1.70), p=0.02) followed by vitamin D level (OR=0.89 (0.79-0.99), p=0.03).

5. DISCUSSION

The current study tested the hypothesis that vitamin D and calcium might be associated with the occurrence of HF's in adolescence and young adult Jordanian females.

The most notable finding of the current study was that adolescence and young adult females can experience HF's ranged from mild to very severe that are not related to hormonal changes of menopausal transition. A high prevalence of vitamin D deficiency, MSP, and psychological symptoms were found. Decreased vitamin D levels and increased anxiety scores were the independent predictors for HF's. HF's had adverse impact on Jordanian adolescence and young adult female's daily life.

Vitamin D is a fat-soluble vitamin that exerts critical roles in muscle functions (20) and brain function (21) where its receptors expressed there. An association between vitamin D deficiency, MSP and psychological symptoms was previously reported among patients with MSP (8-12).

In line with these findings, the current study observed high prevalence of vitamin D deficiency (76.3%), MSP (94.7%), anxiety (84.3%) and depression (66.7%) among females with HF's as compared to controls (47.4%, 0.0%, 23.7%, and 18.4% respectively).
Interestingly, the somatic symptoms (HFs, night sweats), psychological symptoms (depression, anxiety and mood swings), decreased cognitive function and the adverse effect of HFs on daily functioning in adolescents and young adult females with normal measured hormones were similar to the HFs symptoms previously reported by women during menopausal transition status (22). Therefore, HFs appears to have an important effect on reporting of somatic and psychological symptoms, independent of hormone levels.

Several reports have linked HFs during stages of the menopausal transition to anxiety (23, 24). Freeman et al study (23) showed that somatic anxiety is a strong predictor for menopausal hot flashes, and may be a potential target in clinical management of HFs during menopausal transition (23). Lermer et al. (24) found anxiety was significantly associated with a higher HFs score (P = 0.04) (24). Therefore, treatment of anxiety may be a potential target in clinical management of HFs during menopausal transition (7). However, there is a negative report (25). Thus the association between anxiety and menopausal status is not consistent.

Anxiety and depression are common and often comorbid with chronic pain across diverse population worldwide. The three conditions have been long recognized to co-exist, exacerbate one another, share biological pathways and neurotransmitters, and respond to similar treatments, independent of hormone levels. The three conditions have been long recognized as bid with chronic pain across diverse population worldwide. The three conditions have been long recognized to co-exist, exacerbate one another, share biological pathways and neurotransmitters, and respond to similar treatments, independent of hormone levels.

Anxiety and depression are common and often comorbid with chronic pain across diverse population worldwide. The three conditions have been long recognized to co-exist, exacerbate one another, share biological pathways and neurotransmitters, and respond to similar treatments, independent of hormone levels.

In the current study a high prevalence of vitamin D deficiency, anxiety, depression and low daily calcium intake were found in adolescent and young females with HFs. Anxiety and vitamin deficiency were significant independent predictors for HFs which are not related to hormonal changes of menopausal transition.

A substantial number of women experience night sweating when approaching the menopause which is primarily due to thermoregulation. In the current study, night sweating also was common (71%) which was not associated with any measured parameters, i.e. vitamin D status, psychological symptoms, total calcium intake, severity of HFs and MSP. Thus night sweating most likely was also due to thermoregulation.

Similar to night sweating, sleep disturbances are also common among women during menopausal transition status. The problem of sleep disturbances is multifactorial. It is strongly associated with HFs as a result of fluctuating hormone levels i.e. decreased estrogen and increased FSH, and psychological symptoms as well as other factors such as stress, poor health and chronic pain (8, 27, 28). In the current study about 84% of participants reported that HFs affects their ability to sleep. This finding is consistent with the existent literatures among women during menopausal transition status.

In the current study, 94.7% had MSP, 84.3% had anxiety, 66.7% had depression, and 66.6% of participants had less than ¼ of recommended amount of daily calcium intake (29). Previously, High prevalence of low dairy calcium intake and association with insomnia, anxiety, depression and MSP in university students from Jordan was reported (17). Participants with moderate to severe insomnia had lower dairy calcium, higher anxiety and depression scores and higher measures of MSP compared to participants with no insomnia (P-values < 0.05).

However, not all women who report menopausal symptoms that reduce their quality of life (30), but several studies have demonstrated an association between menopausal symptoms and lower quality of life (22). In the current study, Quality of life of females are adversely affected by HFs symptoms that are not related to hormonal changes of menopausal transition, with significant adverse effect on daily functioning especially for mood, concentration, sleep, and enjoyment of life.

Regarding factors that exacerbate HFs in adolescents and young females, psychological stress was the main exacerbating factor followed by before menstrual cycle and weather/room temperature. These findings indicate that characteristic of HFs in adolescents and young adult females vary greatly which consistent with previously published report in healthy middle-aged women in the time when first experienced HFs (31).

Interestingly, number of daily HFs were correlated positively and significantly with anxiety scores, and MSP pain severity, also, the adverse effect of HFs on overall quality of life was correlated positively and significantly with anxiety scores, number and severity of daily HFs.

An overall, adolescent and young adult female may experience HFs that are not related to hormonal changes of menopausal transition, with similar characteristic for women during menopausal transition. HFs appeared to have adverse effect on female’s quality of life with significant adverse effect on daily functioning especially for mood, concentration, sleep, and enjoyment of life. Vitamin D levels and anxiety were the independent predictors for HFs in adolescent and young females.

6. CONCLUSION

This study showed that women can experience hot flashes from mild to very severe that are not related to hormonal changes of menopausal transition. A high prevalence of vitamin D deficiency, MSP, and psychological symptoms was found. Vitamin D levels and anxiety were the independent predictors for HFs. HFs symptoms influenced by a range of factors similar to HFs related to menopausal stages, including psychological stress, and before menstrual cycle. HFs have adverse impact on female’s daily life.

- **Ethical Approval:** The research was approved by Institutional Review Board (IRB) at Jordan University of Science and Technology (33/122/2019).
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