

Relation between Sodium Balance and Menstrual Cycle Symptoms in Normal Women

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Objective: To determine whether sodium balance affects expression of menstrual symptoms.

Design: Prospective study of menstrual symptoms during three cycles: a baseline month (usual intake of sodium, 115 mmol/d) followed by 2 months of sodium restriction (intake of sodium, 73.0 mmol/d). Added salt was allowed during the last month. Investigators were aware of the diet sequence.

Setting: Outpatient. Meals were prepared by a metabolic kitchen during the 2 months that the participants received salt-restricted diets.

Participants: 13 healthy menstruant women.

Measurements: Plasma sodium levels, urinary sodium excretion, and plasma renin activity were measured for five time periods during the baseline cycle and the two cycles of salt-restricted diet. Eleven women completed a questionnaire assessing somatic symptoms and sensory cravings at the same time every day during the 3-month study period.

Results: Sodium restriction was associated with a mean decrease (\pm one half of the 95% CI) in plasma sodium levels of 0.9 ± 0.9 mmol/L from a mean of 139.3 mmol/L during the baseline cycle ($P = 0.018$), a decrease in urinary sodium excretion of 40.3 ± 18 mmol/d from a mean of 117 mmol/d during the baseline cycle ($P = 0.001$), and an increase in plasma renin activity of 0.14 ± 0.08 ng/(L · s) from a mean of 0.28 ng/(L · s) during the baseline cycle ($P = 0.008$). During the luteal phase of the sodium restriction cycle, significant decreases in plasma sodium levels of 1.23 ± 0.5 mmol/L (from values of 138.8 mmol/L during the follicular phase) and increases in urinary sodium excretion of 27.2 ± 10 mmol/d (from values of 65.5 mmol/d during the follicular phase) preceded periods when menstrual symptoms were most severe. Ratings of breast tenderness increased sixfold to eightfold in the late luteal phase ($P < 0.001$) and those of swelling or bloating increased twofold to threefold during early menses ($P < 0.001$) compared with nadir symptom ratings during each cycle. Sodium

cravings increased in the luteal phase of all cycles but were not accompanied by increased sodium intake when access to added salt was allowed.

Conclusions: Breast tenderness and bloating did not result from sodium retention in the luteal phase of the menstrual cycle. During normal and sodium-restricted diet cycles, women actually had urinary sodium loss, not retention, during the luteal phase; severity of menstrual symptoms was unchanged.

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Women often have cyclical physical symptoms of bloating, swelling, and breast tenderness. During the luteal phase of the menstrual cycle (1, 2) and pregnancy (3), osmoregulation changes significantly (1, 2) and sodium-retaining hormone secretion (4-7) and salt preference (8) increase. The concurrence of these cyclical changes has indicated that water and sodium retention may cause physical symptoms during the luteal phase (9, 10). If sodium is retained during the menstrual cycle, the mechanisms involved might include increased salt intake or urinary sodium retention, or both, related to the luteal phase. We hypothesized that sodium balance, a product of total sodium intake and sodium excretion, affects expression of somatic symptoms and inferred that a lower sodium intake or sodium balance should alleviate these symptoms. We therefore explored the effects of a decrease in sodium intake on the expression and severity of menstrual symptoms in women studied during three consecutive menstrual cycles.

Methods

Participants

Thirteen healthy menstruant women without the premenstrual syndrome (10-12) (age, 21 to 35 years; weight, 50 to 80 kg; height, 160 to 180 cm) were recruited by a newspaper advertisement that requested volunteers for a "diet and hormone study." Participants were taught how to complete food frequency questionnaires, collect 24-hour urine samples, and complete visual analogue scale questionnaires about the severity of menstrual symptoms (11, 12).

Study Design

Diet

Baseline sodium chloride intake averaged 115 ± 23.5 mmol/d (6.7 ± 1.3 g/d) or 2.6 ± 1.0 g of sodium

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ion (Na^+) per day (from food frequency records analysis, University of Minnesota Nutrition Coordinating Center, Minneapolis, Minnesota). Intake of dietary salt was then reduced by 30% (to 73.0 ± 12.2 mmol/d [4.3 ± 0.6 g/d]; Na^+ intake, 1.6 ± 0.2 g/d) during the next two menstrual cycles to create a moderate salt-deprivation stimulus (13). To determine whether the use of salt depended on cycle phase, women were allowed to add salt to their food during the second month of this diet (salt-access cycle). All meals were prepared by the metabolic kitchen at the Beltsville Human Nutrition Research Center (U.S. Department of Agriculture, Beltsville, Maryland); the same menu was used every week. The use of added salt was determined from the difference in weight of packaged salt before and after each meal (each packet weighed 10 to 13 mmol [0.57 to 0.74 g]).

Cycle Periods

Each cycle was divided into five time periods: I = early follicular phase, days 1 to 4 (menses); II = mid-follicular phase, days 5 to 8; III = late follicular phase (luteinizing hormone surge ± 2 days); IV = mid-luteal phase (days 20 to 25; 7 days after the luteinizing hormone surge); and V = late luteal phase (4 days before menses). Blood specimens to determine plasma renin activity, plasma sodium levels, atrial natriuretic peptide levels, and aldosterone levels (during the 2 months of the salt-restricted diet) and two consecutive 24-hour urine samples to determine total volume, creatinine, and sodium excretion were obtained in the mid-follicular, late-follicular, and mid-luteal phases (time periods II, III, and IV, respectively) of the cycle. Luteinizing hormone levels were measured from day 11 until the luteinizing hormone surge occurred, and progesterone levels were measured 1 week after the luteinizing hormone surge. Levels of all hormones and peptides were measured by established radioimmunoassays. All samples except those of luteinizing hormone, estradiol, and progesterone were run in the same assay to avoid interassay variability. Sodium levels were measured by ion-selective electrodes. Fasting weights were obtained daily during the last 2 months of the study.

Documentation of Menstrual Symptoms

The visual analogue questionnaire was completed by 11 women at the same time every day for 3 months (10, 14) and was used to record ratings on questions assessing somatic symptoms and sensory cravings.

Statistical Analysis

A mean value was generated from the questionnaire results, body weights, and amounts of added salt (during the salt-access cycle) for the days en-

compassing each of the five time periods. Data were analyzed using repeated-measures analysis of variance and paired *t*-tests. Significance was set at a *P* value less than 0.05 for quantitative data and a *P* value less than 0.01 for symptom questionnaire scores (using the Bonferroni adjustment for interdependent questions). All expressions of variability represent the 95% CI. Data are presented as means \pm one half of the 95% CI.

Results

Effects of Salt Condition

Decreasing dietary sodium intake significantly altered extracellular fluid volume and sodium balance. During the first month of the salt-restricted diet (salt-restriction cycle), urinary sodium excretion decreased by 40.3 ± 18 mmol/d from a baseline value of 115 ± 20 mmol/d ($P = 0.001$) (Figure 1, top). Plasma sodium levels decreased by 0.9 ± 0.9 mmol/L from a baseline value of 139.1 ± 0.9 mmol/L ($P = 0.018$) (Figure 1, upper middle), and plasma renin activity increased by 0.14 ± 0.08 ng/(L·s) from a baseline value of 0.25 ± 0.08 ng/(L·s) ($P = 0.008$) (Figure 1, lower middle) during the 2 months of the salt-restricted diet. Levels of atrial natriuretic peptide decreased during period III of the salt-restriction cycle by 6.1 ± 8.1 pg/mL from a mean value of 58.2 ± 13 pg/mL in period III of the baseline cycle ($P = 0.024$).

Effects of Time of Cycle

All women had ovulatory cycles during the study and equivalent estrogen and progesterone levels during each cycle. Body weight did not change significantly between or within cycles (data not shown). Plasma sodium levels were significantly lower in the luteal phase than in the follicular phase; they decreased by 1.8 ± 1.3 mmol/L (from 140.0 ± 0.9 mmol/L) in the baseline cycle and by 1.23 ± 0.5 mmol/L (from 138.8 ± 0.8 mmol/L) in the salt-restriction cycle (Figure 1, upper middle). Retention of urinary sodium was not seen in any cycle period. An increase in urinary sodium excretion of 27 ± 16 mmol/d (from 65 ± 10 mmol/d) was seen in period IV (mid-luteal phase) of the salt-restriction cycle (Figure 1, top). Plasma renin activity increased in the luteal phase of the baseline cycle by 0.17 ± 0.08 ng/(mL·s) from a mean value in the follicular phase of 0.19 ± 0.08 ng/(mL·s), in the luteal phase of the salt-restriction cycle by 0.25 ± 0.17 ng/(mL·s) from a mean value in the follicular phase of 0.28 ± 0.08 ng/(mL·s), and in the luteal phase of the salt-access cycle by 0.19 ± 0.14 ng/(mL·s) from

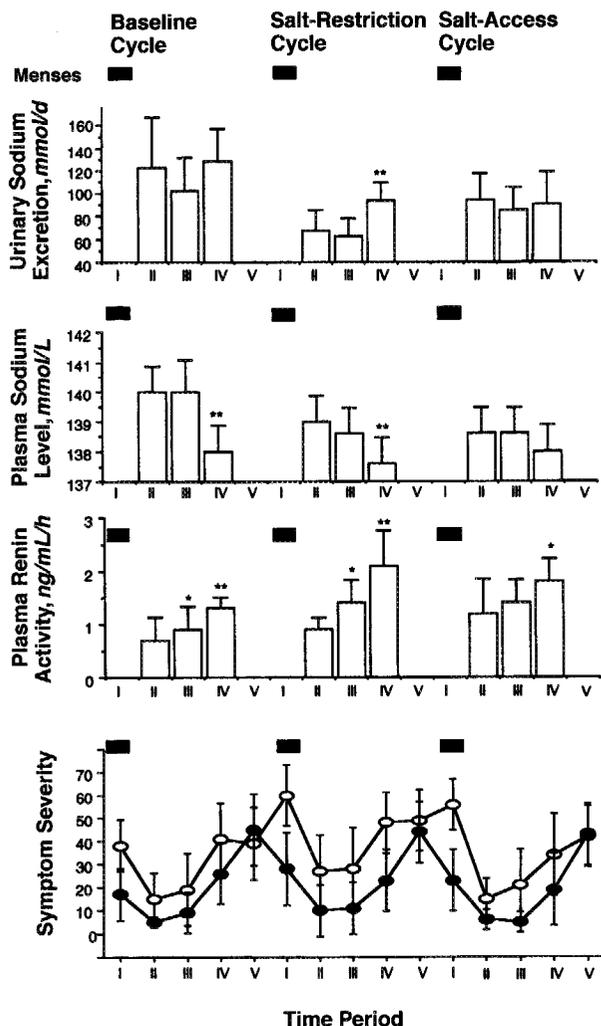


Figure 1. Variables measured during the baseline cycle, the salt-restriction cycle, and the salt-access cycle; during the latter, women were allowed to add salt to their food. The x-axes represent the five time periods studied for each cycle: I = cycle days 1 to 4; II = cycle days 5 to 8; III = luteinizing hormone surge \pm 2 days; IV = mid-luteal phase, days 20 to 25; and V = 4 days before menses. Black rectangles show when menses occurred for each cycle. Variables in the salt-restriction cycle (except for those in the bottom panel) were significantly different from those in the baseline month. For comparisons with values in period II of a given cycle, values marked with an asterisk have a *P* value less than 0.05; those marked with two asterisks have a *P* value less than 0.01. All data are presented as mean \pm one half of the 95% CI. **Top.** Urinary sodium excretion. **Upper middle.** Plasma sodium levels. **Lower middle.** Plasma renin activity. For SI units of $\text{ng}/(\text{L} \cdot \text{s})$, multiply values by 0.2778. **Bottom.** Severity ratings for symptoms of bloating or swelling (white ovals) and breast tenderness (black ovals), measured on a scale of 1 to 100 (a higher value represents a worsening of the symptom). Symptom severity varied with cycle time ($P < 0.001$). Symptoms of bloating or swelling were affected by sodium restriction ($P < 0.001$).

a mean value in the follicular phase of $0.31 \pm 0.17 \text{ ng}/(\text{mL} \cdot \text{s})$ ($P < 0.001$) (Figure 1, lower middle). Aldosterone levels doubled in all cycles during the luteal phase (data not shown). Breast tenderness and bloating were phase dependent during all cycles studied (Figure 1, bottom). Severity ratings of swelling or bloating were higher in period I than in period II by 25 ± 12 points (period II value, 15 ± 11 points) in the baseline cycle, 31 ± 15 points (period II value, 27 ± 15 points) in the salt-restric-

tion cycle, and 40 ± 11 points (period II value, 15 ± 9) in the salt-access cycle ($P < 0.001$) (Figure 1, bottom). These symptoms were also affected by the salt condition: Peak severity ratings were 16 ± 19 points higher during the salt-restricted diet cycles (salt-restriction cycle and salt-access cycle) than during the baseline cycle (peak severity rating, 38 ± 11 points; $P < 0.001$). Breast tenderness was most severe 4 days before menses, during which time ratings increased from the nadir of the follicular phase by 42 ± 16 points (from 5.0 ± 2.2 points) during the baseline cycle, by 35.0 ± 11 points (from 10.0 ± 11.1 points) during the first salt-restriction cycle, and by 39 ± 6 points (from 6.0 ± 4.4 points) during the salt-access cycle ($P < 0.001$). Breast tenderness was not affected by sodium balance. The highest physical comfort ratings coincided with the lowest severity ratings for breast discomfort and bloating (periods II and III).

Compared with nadir ratings in the follicular phase, ratings of thirst and cravings for salt and sweets increased and peaked during the late luteal phase (time period V) ($P = 0.006$ for the baseline cycle, $P < 0.001$ for the salt-restriction cycle, and $P = 0.002$ for the salt-access cycle) (data not shown). In the salt-access cycle (second salt-restricted diet cycle), use of added salt was less than $10 \text{ mmol}/\text{d}$ and did not vary with phase of the cycle ($P > 0.2$; data not shown). Dietary salt condition and time of cycle did not affect appetite.

Discussion

To study the relation between menstrual cycle symptoms and sodium balance in normal women, we changed sodium balance by decreasing intake of sodium by 30% for 2 months. This modest change in sodium balance did not decrease the severity or the cycle-dependent expression of somatic symptoms during the luteal phase or menses. We found no evidence of urinary sodium retention, and, paradoxically, sodium loss was seen during the luteal phase in the first month of the sodium-restricted diet (salt-restriction cycle), despite biochemical evidence of extracellular fluid volume contraction (13). Although the information was not documented, we believe that natriuresis occurred during the luteal phase of the other two cycles (baseline cycle and salt-access cycle), because levels of urinary sodium excretion remained high despite elevated renin activity and aldosterone levels. Progesterone is a competitive antagonist of aldosterone (15), and high salt intake can reverse the progesterone-related increase in renin and aldosterone levels (16, 17). These findings, together with our data, suggest that progesterone enhances natriuresis during the luteal phase in normal women and that the changes in the renin-

aldosterone system during this time are probably secondary to primary natriuresis.

Use of added salt did not increase in the luteal phase of the salt-access cycle, despite elevated salt cravings and sodium-retaining hormones. The combination of increased cravings for salt and sweets with lack of a change in appetite observed in all cycles suggested a nonspecific need for increased sensory taste stimulation in the luteal phase cycle.

Our study has limitations that prevent us from unequivocally stating that the menstrual symptoms studied are unrelated to sodium balance. First, only 13 women were studied. Second, the sodium restriction may not have been severe enough to affect menstrual symptoms or potentiate salt-seeking behavior in the luteal phase (severity of craving salty food was not higher during the 2 months of salt restriction). Third, blood and urine were not collected when symptoms were at their peak (time periods I and V, **Figure 1**), and fluid intake was not monitored. Thus, we cannot conclude that changes in water balance or intercompartmental shifts of water and sodium did not occur, particularly given the lack of weight change during intravascular fluid contraction. Finally, we were not blinded to which diet the women received, and a sequence or carryover effect from the order of the diets may exist.

Given these caveats, our findings may have clinical implications for pathologic conditions that cyclically affect subsets of women. Women with cyclical edema maintain normal osmoregulation and hormonal milieu and gain 2 to 3 kg during the luteal phase (11, 18–20). These findings suggest dysfunctional sodium regulation. If the natriuresis found during the luteal phase in the women we studied reflects the normal physiology in larger cohorts, then it is conceivable that cyclical edema might result from defective natriuresis, volume expansion, or both during the luteal phase. Finally, the finding of predictable symptom occurrence in these normal women emphasizes the difficulty clinicians face when distinguishing normal menstrual symptoms from those of the premenstrual syndrome or cyclical edema. For these latter pathologic conditions, sodium handling may vary and treatment options are clearly different.

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