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The Effect of Dietary Intake on Hot Flashes in Menopausal Women

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Abstract

Objectives—To describe the relation between dietary intake and menopausal hot flashes.

Design—Two studies are reported: a controlled, repeated-measures study and a descriptive study.

Setting—The controlled study was conducted in a general clinical research center of a large Midwestern university. The descriptive study was conducted in a metropolitan community in the Southwest.

Participants—Ten healthy symptomatic postmenopausal women participated in the controlled study and 21 symptomatic women completed the observational study.

Interventions—The controlled study included a 30-hour intensive blood sampling protocol of two sequential experimental phases with an observational phase between them. In the observational phase, each participant served protocol-specific meals and snacks at predetermined times.

Main Outcome Measure—Skin conductance monitoring provided continual assessment while blood glucose levels were analyzed every 30 minutes in the controlled study.

Results—Eating provided a hot flash-free period that averaged 90 minutes in both studies. Also, hot flash frequency increased as time between meals increased.

Conclusions—Our evidence indicates that hot flash frequency is suppressed after eating, while hot flashes are experienced when blood glucose falls between meals. Nursing interventions aimed at maintaining stability in blood glucose level may be effective in reducing menopausal hot flashes.

Keywords

Hot Flashes; Women's Health; Nutrition; Menopause

Menopausal hot flashes (HFs) are experienced by approximately 80% of the 20 million women of menopausal age (45-54) in the United States, making this a significant concern during menopause. The incidence is even greater for women who have their ovaries surgically removed with 95% to 100% of this population experiencing HFs (Bachmann, 1999). Hot flashes can disrupt women's lives and affect work responsibilities, social activities, and sleep (Dormire, 2003; Greendale & Sowers, 1997). The impact of HF on women's lives is revealed in health care utilization data indicating that the majority of women seeking care related to menopausal symptoms do so because of the discomfort associated with HF (Kronenberg, 1994). Although HFs occur widely, the HF physiological trigger mechanism is unknown.

The current standard management for HF is hormone therapy (HT), used by approximately 3 million American women. However, confusion and anxiety about HT have dominated management concerns following the publication of findings regarding increased risk for cardiovascular events and invasive breast cancer in both the Heart and Estrogen Replacement Study II (Grady et al., 2002) and the Women's Health Initiative (Writing Group for the Women's Health Initiative Investigators, 2002). The association of breast cancer and cardiovascular events with HT leaves women in the difficult situation of having to choose between these risks and the distress they endure from HF. If the physiological mechanisms of HF were known, alternative management strategies could be developed and directed toward the underlying cause. Research focused on uncovering the HF mechanism has the potential to redirect treatment strategies.

An emerging model, the Impaired Glucose Delivery Model of Hot Flashes, indicates that the HF is a result of altered blood glucose transport across the blood-brain barrier (BBB; Dormire & Reame, 2003). An experimental design study was conducted in a sample of symptomatic women to explore the relationships proposed in the model. The incidence of objectively identified HF was significantly reduced when blood glucose concentrations were elevated experimentally (Dormire & Reame). HFs were much more likely to occur during the fasting state. Findings related to a nonfasting period phase of this study are reported here. Participants were fed a prescribed diet at prescribed times while blood glucose was monitored every 30 minutes and skin conductance was monitored continuously. In a second observational study, symptomatic menopausal women recorded in a diary all dietary intake and HFs over a 24-hour period. The purpose of this study was to describe the relationship between dietary intake and HF frequency indicated by the results of both studies.

According to the Impaired Glucose Delivery Model, the hot flash is a result of altered blood glucose transport across the blood brain barrier at menopause.

Impaired Glucose Delivery Model of Vasomotor Symptoms

The Impaired Glucose Delivery Model of Vasomotor Symptoms suggests that vasomotor symptoms may be due to changes in glucose delivery to the brain. The regulation of brain glucose comprises complex central and peripheral processes involving glucose supply. In the central component, three processes (neurometabolic, neurovascular, and neurobarrier) together maintain the glucose levels that provide for the metabolic functioning of neurons. These systems are interrelated through coupling processes among levels of neuronal activation, metabolic activation, blood flow, and glucose transport across the BBB (Leybaert, 2005). In addition, peripheral blood flow and blood glucose levels also stimulate the central coupling processes.

Simple activation of neurons from resting states generates both increased glucose consumption in the brain and increased BBB glucose transport (Leybaert, 2005) since only a 2-minute supply of glucose is maintained in the brain (Chih & Roberts, 2003). As glucose is used for brain metabolism, glycolytic breakdown occurs in the astrocytes and the oxidative processes occur in the neurons interconnected via glutamate release (Magistretti, Pellerin, Rothman, & Shulman, 1999). Although glucose metabolism in the brain is compartmentalized, it is connected via neurometabolic coupling. Such coupling further stimulates activation of the subsequent coupling processes as well.

Given the short-term supply of glucose in the brain, neuronal activation stimulates neurobarrier coupling to provide the needed energy to sustain activation. Glucose transporter 1 (GLUT 1) is the carrier protein in the plasma membranes of endothelial cells of brain interstitium whose function is to move glucose molecules into the brain via facilitated diffusion (Pardridge, 1991). Neurobarrier coupling signals increased glucose transport at the BBB by increasing

both the rate of transcription of GLUT 1 messenger RNA (mRNA) and the number of GLUT 1 molecules in the BBB. The end result of increased GLUT 1 availability is increased movement of glucose molecules into the brain. An increase in GLUT 1 at the BBB has been demonstrated to occur within 3 minutes of neuronal activation (Cornford, Nguyen, & Landaw, 2000). Peripheral fluctuations in blood glucose also activate this system. In an effort to maintain the 2-minute glucose supply in the brain, GLUT 1 mRNA responds to glucose concentrations in the blood with downregulation during periods of increased glucose concentrations and with enhanced production in response to glucose decline (Rydzewski, Wozniak, & Raizada, 1991).

Estrogen plays a role in this system by facilitating the production of GLUT 1 when the demand for glucose transport increases, either under conditions of brain activation or low blood glucose levels. In the presence of estradiol, glucose transport at the BBB increases by up to 40% (Shi & Simpkins, 1997). By augmenting GLUT 1 in the cerebral cortex (Cheng, Cohen, Wang, & Bondy, 2001), estrogen enables rapid response to changing glucose needs.

The third coupling system, neurovascular coupling, supports brain glucose levels through vasodilation with resultant increased blood flow. This mechanism serves to adapt glucose and oxygen delivery in response to neuronal metabolic needs (Pellerin & Magistretti, 2003). Through changes in the vascular perfusion, the number of functional GLUT 1 transporters increases by virtue of the increase surface area of perfused capillaries responding to the increased blood flow (Davson, Purvis, & Segal, 1969).

The Impaired Glucose Delivery Model of Vasomotor Symptoms proposes that the HF is the result of an exaggerated response of the neurovascular coupling system as estrogen decline diminishes the ability to increase GLUT 1 as needed. That is, when estrogen levels decrease in menopause, the responsiveness of GLUT 1 production to the demands of increased glucose transport needs (either because of increased neuronal activity or lowered blood glucose levels) is constrained. The HF is seen as a counter-regulatory neurovascular response resulting in vasodilation with resultant increased blood flow to aid delivery of glucose and oxygen delivery to meet the metabolic needs associated with neuronal activation.

Background

Animal model research provided preliminary evidence in support of the model. Hot flash can be induced in rodent models using a variety of stimuli that reduce blood glucose or block the ability of brain cells to use glucose (Bishop & Simpkins, 1995; Namba & Sokoloff, 1984; Nehlig, Porrino, Crane, & Sokoloff, 1985). Conversely, blood glucose elevations preclude HF induction in this model (Simpkins, Katovich, & Millard, 1990). Based on these findings, it is hypothesized that the human female at menopause has diminished ability to respond to fluctuations in blood glucose over the course of the day, which results in HF as a counter-regulatory response.

Two studies in which this relationship was explored (a controlled and a descriptive study) are reported here. In the controlled study, an experimental design study included a sample of symptomatic women. Blood glucose levels were manipulated in a sample of 10 postmenopausal women with a history of HFs. The experimental periods were separated by a 20-hour observation period including 9 hours of scheduled dietary intake. The observational phase of this study explored the relationship of fluctuations in blood glucose and HFs during conditions of eating and between-meal “fasting.”

Related findings from a descriptive study are also reported in this article. This study was designed to provide preliminary evidence to determine if the effect of blood glucose manipulation in controlled conditions on HFs and blood glucose under controlled conditions

was also observed in the natural environment of symptomatic women. In this self-report study, a volunteer sample of symptomatic menopausal women was recruited to record both dietary intake and HFs experienced for a 24-hour period. The purpose of this study was to describe the relationship between dietary intake and HF frequency indicated by the results of both studies.

Controlled Study Methods

Design

A repeated-measures experimental crossover design was used to test the hypotheses of this study. The sample was composed of postmenopausal women withdrawing from HT for at least 1 week until return of daily HFs. The study was conducted in the inpatient unit of a general clinical research center (GCRC) of a large Midwestern university. The protocol provided 30-hour intensive blood sampling, with 3.5-hour experimental phases on two sequential mornings. Each participant was exposed to randomly ordered experimental periods of glucose and normal saline infusion. The experimental periods were separated by an observational period of natural changes in blood glucose and HF frequency associated with eating. The results reported here detail the 9-hour nonfasting observation period in which two protocol specific meals and two snacks were served at specified times. Constant skin conductance assessment was maintained and blood glucose was measured every 30 minutes during this period.

Sample

Approval of the clinical protocol for use with human subjects was obtained and all volunteers provided written informed consent. This study was conducted in a GCRC of a large Midwestern university. Healthy postmenopausal volunteers using HT to manage HFs were recruited via flyers posted on the university hospital bulletin boards and from a university Web site. To participate in the study, volunteers agreed to withdraw from hormone replacement therapy for at least 1 week until return of daily HFs. Postmenopausal women withdrawing from HT were specifically selected to help control the wide variation of hormone levels in the perimenopausal women who experience HFs. In addition, the half-life of conjugated estrogen is 15 hours (www.fda.gov/cder/foi/label/2003/04782s129lbl.pdf). Therefore, after the washout period, we could anticipate stability in the hormone levels of the participants. Each volunteer met strict hormone-level enrollment criteria in order to participate in the study.

Because smoking is a known HF stimulant, women who smoked were excluded from the study. Hyde Riley, Inui, Kleinman, and Connely (2004) note that body mass index (BMI) is not associated with HFs in postmenopausal women. However, because of a lack of consensus regarding BMI, women with BMI greater than 31 kg/m² or less than 20 kg/m² were excluded from this study. Participants were also screened for diabetes prior to admission to the study. The general health of all potential participants was screened via thorough history and physical examination conducted by a nurse practitioner.

Twelve women completed the protocol before the end of the funding period. However, data from two participants were dropped from the final data analysis. In one participant, estradiol concentrations did not confirm postmenopausal status. The remaining participant experienced no HFs during any aspect of the study. The average participant in this study was 48.6 years old (range 38-55 years), well educated with 15.4 years of schooling, 5 years past menopause, and exhibited a BMI of 25.4 (range 20.2-30.7). Six of the study participants were naturally menopausal and four were surgically menopausal. However, to confirm menopause status, blood samples for follicle-stimulating hormone (FSH) and estradiol (E₂) were collected at admission. An FSH value greater than 30 mIU/ml and estradiol level less than 20 pg/ml were used as clinical indicators of postmenopausal status (Reame, 2000). Concentrations of FSH

and estradiol were in the expected ranges for postmenopausal women and all laboratory indexes of general health were within normal limits. The final sample consisted of seven Caucasian, one Hispanic, and two African American women.

Procedure

Participants were admitted to a GCRC for a 30-hour intensive blood sampling protocol that included experimental phases on two sequential mornings and one nonfasting observational phase between them. The variables of interest in this study were HF frequency and plasma blood glucose level. A heparinized catheter was placed in the forearm of the dominant arm for the frequent collection of blood in the protocol. A second indwelling catheter was placed in the antecubital space of the nondominant hand for infusion of fluids during the experimental periods of the study. Continuous skin conductance monitoring provided the objective measure of each HF. In addition, plasma blood glucose level was tested every 30 minutes.

In the observational nonfasting phase reported here, beginning 30 minutes after the experimental period, each participant was served a protocol-specific lunch, afternoon snack, dinner, and evening snack at predetermined times. All foods were weighed and measured before being served and after the participant completed the meal. The caffeine-free diet provided an average caloric intake of 1791 ± 158.0 SD kcal. No foods were served at temperature extremes and no ice was served to avoid stimulating or inadvertently treating HFs. In addition, all food and fluid intake except water was stopped at 2100 hours in preparation for the second experimental period.

Control of other factors known to precipitate HFs was achieved through environmental controls in the protocol. Participants were restricted to bed rest with bathroom privileges; they could also sit in a bedside chair, if desired. Participants rested although they could watch television, read, or work on craft projects. Room temperature was set at 72°C. All participants were dressed similarly in cotton pants, socks, and a cotton T-shirt.

Measures

Skin Conductance—Decreasing skin resistance is an established objective measure of the menopausal HF (Freedman, 2000). Hot flash frequency was measured continuously during the 30-hour time period using the Biolog® skin conductance monitor. Skin conductance monitoring was initiated at admission using standard application procedures (Carpenter, Andrykowski, Freedman, & Munn, 2002; Dormire & Carpenter, 2002). Skin conductance leads were placed approximately 2 inches from each side of the sternal border and 2 inches below the clavicle. A 5-cm circular area was cleaned for 30 seconds with alcohol and allowed to dry prior to placement of the lead.

In this study, HF incidence was objectively measured through continuous monitoring using the Biolog® skin conductance monitor (UFI Model 3991/1 SCL; UFI, Morro Bay, CA). A standard criterion of increase in skin conductance of greater than a 2 μ mhos in less than 30 seconds is considered a valid HF (Freedman, 1989). Also, participants noted perceived HFs by pressing a button on the monitor to event mark on the tracing.

Blood Glucose Level—For each blood glucose sample, 0.5 cc of blood was drawn from a catheter placed in the dominant forearm and flushed with heparinized saline. A Beckman Glucose Analyzer was used to determine the blood glucose level. The 0.5-cc sample of venous blood was centrifuged for 20 seconds and five drops of unhemolyzed plasma was pipetted into the analyzer (Beckman, 1977).

Data Analysis

The Biolog® software program analyzed skin conductance data, using the standard HF identification criteria for skin conductance recording (greater than 2 μ mhos increase in skin conductance in less than 30 seconds). Since HFs are not experienced in a regular, predictable pattern, there were more HF-free 30-minute time frames in the sample than there were HF-positive periods. As a result, blood glucose measures would be inflated if we include all blood glucose measures in the HF-free time frames. Therefore, to provide a standard for comparing 30-minute time frames in which HFs did occur, we calculated HF-free blood glucose by comparing only the immediate blood glucose measurement following the HF period. Time to first HF after eating each snack or meal was also calculated in minutes.

Data for the hypothesis, HF frequency is inversely related to blood glucose levels under the natural conditions of food intake, were analyzed for each 30-minute data point during the observational period. A paired *t* comparison tested the hypothesis that HF frequency would be higher with lower blood glucose than when blood glucose was elevated following dietary intake.

Descriptive Study Methods

Sample

Approval of this study for participation of human subjects was obtained and all volunteers provided written informed consent. Eligibility requirements for this study included the following: women of ages 40 to 55 experiencing HFs daily, not taking HT, and nonsmoker. Flyers were posted in community venues and interested symptomatic women called or e-mailed for additional information and screening. A total of 22 symptomatic postmenopausal women volunteered for this study. One volunteer did not complete and return study materials. Thus, the final analysis includes 21 women who met inclusion criteria and completed all study materials.

The majority of participants were between 50 and 54 years of age ($M = 51.67$, $SD = 4.07$), Caucasian (two African American participants), married (71.44%), and completed undergraduate education (47.62%). Self-report of health information indicated that the participants were generally overweight with an average BMI of 28.35 ($SD = 4.73$, range 25-30), exercised one to three times a week (66.67%), and were not on any particular diet (57.14%).

Procedure

During a volunteer-initiated telephone interview, the study was described, and the caller was screened for inclusion/exclusion criteria. Participants were informed that consent in the study was given or implied through return of completed study materials. If participants remained both interested and eligible, a study packet was mailed to them. The mailing included a cover letter, the diary, a demographic form, the Menopause Guidebook® as a gift for participating, and a stamped and addressed return mail envelope. Contact information was shredded when the research packet was mailed.

Participants were directed to self-select a 24-hour period during which they should chart time and severity of each HF as well as document food intake (a detailed summary of what was eaten and time consumed). The completed diary and demographic data sheet were returned to the research team in the stamped/addressed envelope provided. Confidential data submission procedures were used to minimize individual risk. Participants were asked not to add their personal return address or name on the envelope.

Measures

Demographic Questionnaire—A demographic questionnaire was developed and refined by the principal investigator in the above-described controlled study (Dormire & Reame, 2003). Data collected include characteristics of age, ethnicity, marital status, number of children, highest level of education, and occupation as the demographic variables.

Health Information—A questionnaire was used to assess sample health information including height, weight, smoking history, diabetes, chronic diseases or medical conditions, exercise, particular diet, and medications. Health information also included gynecologic history such as date of last menstrual period, date of hysterectomy, any HF experiences, any instances of waking up with night sweats, and history of medications taken to manage menopausal symptoms or HFs.

Hot Flash Diary—Use of the diary methodology is considered to be the gold standard of HF assessment when sternal skin conductance is not feasible (Barton et al., 1998; Carpenter, 2005; Carpenter et al., 1999). The HF diary provided a detailed evaluation of HFs occurring over a 24-hour period. Participants were asked to provide time of each HF, rate their overall level of HF severity using the score from 0 (*not at all*) to 10 (*extremely severe*), overall rating of how bothered they were by HFs using the score from 0 (*not at all bothered*) to 10 (*extremely bothered*), and providing documentation of their activities during an HF. Hot flash frequencies were calculated as the number of HFs recorded in 1 day. Both mean severity and mean bother ratings were determined by summing individual severity rating and dividing by the number of HFs experienced in the 24-hour time period.

Dietary Intake—As part of the study diary, participants were asked to describe in detail all foods and fluids consumed during the 24-hour research period. Participants were instructed to record time, food and fluid items consumed, and amount of food or fluid as specifically as possible. Participants were instructed to estimate and record amount of food intake; however, the only data used in the current analysis were the timing event of dietary intake.

Data Analysis

Data were coded and recorded on the coding sheet. Before being entered into a data file, data were double checked to minimize error. Data were analyzed using the SPSS Windows release 13.0. As an initial data assessment, descriptive statistics, including means, standard deviations, range of scores, frequencies, and percentage, were calculated to describe the characteristics of the sample. Since each participant was her own control experiencing both dietary intake and between-meal fasting, paired *t* correlations were used to examine the relationship between HFs and blood glucose in the controlled study. Pearson product-moment correlations were used to examine HF frequency differences in the observational study.

Results

In the controlled study, the frequency of objectively recorded HF ranged from 0 to 23, with a mean of 7.6 and a standard deviation of 8.29. Hot flashes were experienced when blood glucose levels averaged 97.3 mg/dl during the observation phase. Mean blood glucose during HF-free periods was 103.3 mg/dl. Irrespective of dietary intake, blood glucose levels were significantly different in the 30-minute time frames in which HFs were experienced and those that were HF free ($t = -2.46$, $df = 56$, $p = .017$).

Dietary intake affected timing of HFs. In the 30-minute period immediately preceding the meal or snack, HF frequency was greater than in the 30-minute period immediately following dietary intake (see Figure 1). In the premeal 30-minute time frame, 14 HFs were recorded, with average

blood glucose levels of 92.04 mg/dl (range 73-117 mg/dl). However, after eating only, two HFs were recorded. Five of the women experienced many HFs during the observation period. In those five women, HFs were experienced both before and after dietary intake. Hot flashes recorded in the other five participants occurred before eating episodes. Corresponding average postmeal blood glucose levels were 107.74 mg/dl (range 92-124 mg/dl). Minutes from eating time to first HF were also calculated. An HF-free period of 89.9 minutes was noted with dietary intake in this sample; the mean blood glucose level at 90 minutes was 93.7.

In the observation study, participants reported HF frequency between 1 and 24 per day ($M = 8.05$, $SD = 5.41$). Pearson's product-moment correlation was used to explore the effect of dietary intake on HF frequency. Only time of dietary intake and time of HFs were used for analysis. In this sample, two effects were noted. First, self-selected eating provided an HF-free period. Similar to the HF-free period noted in the controlled study data, the average time to first HF was 91 minutes in this sample (range 20-258 minutes, $SD = 56$). Conversely, HF frequency increased as length of time between meals increased ($r = .242$, $p = .05$). As time from last food intake increased, the number of HFs experienced also increased.

These findings provide preliminary evidence for development of dietary treatment strategies for hot flashes.

Discussion

In the controlled study, timing and content of dietary intake were specific as part of the protocol for the study, while in the observational study both timing and content of dietary intake were self-selected by the participant. In both the controlled and the observational studies, HF frequency was related to dietary intake. The controlled study provided objective measurement of HFs and blood glucose levels, providing direct evidence of the association between HFs and lower blood glucose levels. However, in the observational study, a lower blood glucose level was assumed in the observational study given expected physiological changes as time from eating increases. Notably, menopausal HFs were most often observed when blood glucose was lower regardless of the study design.

This finding is supported by the physiological premises of the model guiding these studies. Increased glucose needed for neuronal activity stimulates the neurobarrier coupling system. However, given the lower estrogen level of women at menopause, there is a diminished ability to upregulate GLUT 1 molecules as needed to maintain the glucose supply. The system is able to maintain the glucose supply as long as the peripheral blood glucose level is sufficient to saturate the available GLUT 1 molecules. When blood glucose levels decline, the GLUT 1 molecules are not sufficient to maintain neuronal glucose supply. As a secondary response to provide the needed glucose, an exaggerated response of the neurovascular system results in the HF.

Further supporting the model, HF frequency was reduced following dietary intake. In both studies, eating provided on average a 90-minute HF-free period. These data indicate that dietary intake has a potential treatment effect of eating on menopausal HFs. Although these findings provide further support of the model guiding this work, additional study is required.

Eating provided an average 90-minute hot flash-free period

Implications

Confusion and anxiety about HT have dominated menopause management concerns for women following publication of the findings regarding increased risk for cardiovascular events and invasive breast cancer in both the Heart and Estrogen Replacement Study II (Grady et al., 2002) and the Women's Health Initiative (Writing Group for the Women's Health Initiative

Investigators, 2002). Nurses and other health care professionals seek effective alternative therapies for symptomatic menopausal women.

Our clinical evidence indicates that HF frequency is suppressed when blood glucose level is within the elevated normal range, while HFs are experienced when blood glucose falls. Nursing interventions aimed at maintaining stability in blood glucose level may be effective in reducing menopausal HFs. Dietary management strategies yet to be tested will focus on interventions similar to those offered to individuals with diabetes such as small frequent meals and guidance in nutrient selection for meals and snacks. Exercise effects on blood glucose may also be effective in stabilizing blood glucose, however, further research in this area. While additional study is needed, these findings provide preliminary evidence for the development of HF treatment focused on dietary modification as an alternative or supplement to HT.

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FIGURE 1.
Pre- and postmeal hot flash frequency.