Hot flashes ... in January

Background and epidemiology: About 75% of postmenopausal women and about 40% of perimenopausal women experience hot flashes. Hot flashes typically begin 1 or 2 years before a woman's final menstrual period and persist for 6 months to 5 years.[1] These vasomotor episodes are characterized by the sudden onset of an intense warmth that begins in the chest and progresses to the neck and face; the warmth is often accompanied with anxiety, palpitations, profuse sweating and red blotching of the skin. Each episode usually lasts only a few minutes, although the frequency and severity of hot flashes vary greatly. During the peak of the menopausal transition it is not unusual for a woman to experience 8 or more hot flashes a day and for these symptoms to interfere with her ability to work, socialize and sleep.

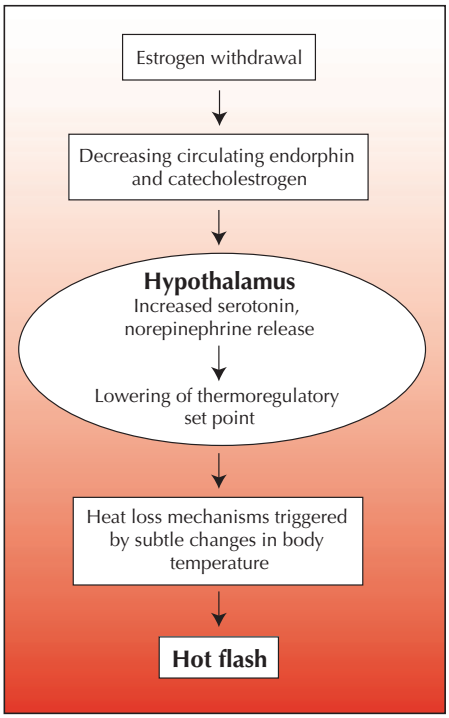
Dysfunction of central thermoregulatory centres in the hypothalamus caused by changes in estrogen levels at the time of menopause has long been postulated to be the cause of hot flashes. Estrogen withdrawal rather than low circulating estrogen levels seems to be the central change that leads to hot flashes. According to one working model of the pathogenesis of hot flashes, estrogen withdrawal leads to decreased levels of endorphin and catecholestrogen (a metabolic by-product of estrogen) and culminates in increased hypothalamic release of norepinephrine and serotonin. Norepinephrine and serotonin lower the set point in the thermoregulatory nucleus; this allows heat loss mechanisms to be triggered by subtle changes in core body temperature. In this model, endorphins play a key role in the regulation of norepinephrine release, and agents that increase estrogen and endorphin levels or that decrease central norepinephrine release would be expected to reduce hot flashes.[1]

Clinical management: Estrogen replacement therapy relieves hot flash symptoms by about 80%–90%.[1] Estrogen also improves vaginal dryness and urine control and reduces the risk of osteoporosis and colon cancer.

However, for many women the benefits of estrogen replacement therapy are offset by the increased risk of venous thromboembolic disease, breast cancer, stroke and coronary artery disease, as shown in the Women's Health Initiative study. Several small trials have shown that certain progestins (e.g., megestrol acetate[2]) are also effective in alleviating hot flash symptoms, by 75%–80%.[1] However, some controversy exists over the possible role of these progestins in accelerating breast cancer recurrence in some patients. Regardless, many women are reluctant to use hormonally active agents that are perceived to be synthetic or "unnatural." It is not always clear what is meant by "natural" hormones, but according to a survey of women customers in a pharmacy, it refers primarily to plant-derived compounds with estrogenic activity.

Phytoestrogens are plant-derived compounds with structural homology and binding affinity to specific estrogen receptors. The most prominent of the phytoestrogens are isoflavones. For dietary purposes and purported estrogenic activity, there are only 4 important ones: formononetin, biochanin, daidzein and genistein; they are found in soy protein, garbanzo beans and other legumes. The binding coefficient of genistein for the alpha and beta estrogen receptors is 5 and 36 respectively (as compared with 100 and 100 for estradiol and 60 and 37 for estrone).[3] The results of several short-term trials are mixed, but overall they suggest that soy protein and isolated isoflavones do not reduce hot flashes substantially[1] and that a very high volume of soy protein (76 mg/d, equivalent to six to eight 85-g servings of silken tofu) would need to be consumed daily in order to achieve even slight symptomatic relief.[3] Black cohosh is a perennial plant native to North America. Results from several studies conducted in Germany in the 1980s indicated that the reduction in hot flashes was 25%–40% better with black cohosh than with placebo.[3] However, this finding was not borne out in a more recent trial of breast cancer survivors.[4]

Newer antidepressants that affect the release and uptake of serotonin and norepinephrine have become the most promising class of medications for nonhormonal treatment of hot flashes. Venlafaxine,[5] fluoxetine and paroxetine have been found to reduce hot flashes significantly (by 50%–60%) when compared with placebo.[1] Gabapentin, a gamma aminobutyric acid analogue, is also showing promise,



A working model of the pathogenesis of hot flashes.[1]

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and randomized controlled trials of its effectiveness are underway.[1] Trials of clonidine have demonstrated a modest, statistically significant reduction in hot flashes, but the benefit was tempered by adverse effects (dry mouth, constipation, drowsiness and insomnia).[1]

Prevention: Although less well studied, behavioural interventions may also decrease hot flashes. Relaxation techniques and exercise programs can mediate their severity. Daily doses of vitamin E (800 IU/d) improve symptoms slightly. Efforts to maintain a lower body core temperature by maintaining good air circulation, sipping cold drinks and lowering the thermostat can also help, as does avoiding alcohol, spicy foods and cigarettes.

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IN THE LITERATURE

Is there sustained renal benefit from previous intensive insulin therapy in people with type 1 diabetes?

Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type I diabetes mellitus on development and progression of diabetic nephropathy. *JAMA* 2003;290:2159-67.

Background: The benefits of intensive insulin therapy for type 1 diabetes mellitus to prevent microvascular complications have been established.[1] However, it is unknown whether these benefits persist when insulin therapy becomes less intensive and begins to approximate that of conventional treatment.

Design: In a randomized controlled trial, 1441 patients with type 1 diabetes were randomly assigned to receive either intensive insulin therapy to achieve normal glycosylated hemoglobin (HbA_{1C}) levels or conventional therapy (1 or 2 daily injections of insulin) without specific goals for glycemic control. Patients were eligible if they had no advanced diabetes complications and normal renal function. Following completion of the trial, a follow-up study of the cohort was begun in which patients who had been receiving the intensive therapy were encouraged to continue it and those in the conventional treatment arm were encouraged to switch to intensive treatment. Of the original 1441 subjects, 1375 agreed to participate in the follow-up study. No treatment intervention was involved, and participants were assessed for renal outcomes over 7–8 years.

Results: After completion of the initial randomized controlled trial, patients in the intensive therapy arm had significantly lower HbA_{1C} levels and a lower incidence of microalbuminuria than those receiving conventional treatment did (Table 1).

Table 1: Outcome measures of previous intensive insulin therapy versus conventional therapy in patients with type 1 diabetes

Outcome	Intensive insulin therapy *n = 676*	Conventional therapy *n = 673*	*p* value
At end of initial study			
Mean HbA_{1c} level, %	7.4	9.1	< 0.001
Microalbuminuria, % of patients	7.4	12.9	< 0.001
At follow-up at 7–8 yr			
Mean HbA_{1c} level, %	8.0	8.2	0.002
New microalbuminuria, % of patients	6.8	15.8	< 0.001
New clinical albuminuria, % of patients	1.4	9.4	< 0.001
Hypertension, % of patients	29.9	40.3	< 0.001
Creatinine > 177 mmol/L, no. of patients	5	19	< 0.004

Note: HbA1c = glycosylated hemoglobin.

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