

Issues in Women's Health

WEIGHT MANAGEMENT DURING MENOPAUSE AND PERIMENOPAUSE: A REVIEW OF THE LITERATURE

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Menopause doesn't have to be a time of uncontrolled weight gain, nor does it have to mean a transition from an active, enjoyable life to one of constant misery, fatigue, anxiety and depression. In this paper we will introduce you to a variety of dietary supplements that have been clinically shown to produce effective weight loss (without ephedrine/ma huang), to significantly increase your energy and vitality and to help you avoid or overcome mood problems that leave you drained, tired and feeling down at the end of the day. The brand name of the commercial product is Estrin-D™.

WHAT IT MEANS TO BE A WOMAN

If you are overweight and a woman, you are probably overweight because you are a woman. This simple idea has apparently escaped the attention of even the most well-respected weight loss researchers in this country, but it is true. Compared to men, women have special weight-loss needs. These needs are typically apparent almost from the day of birth and steadily increase over the woman's life span.

When it comes to weight management, women start life at a disadvantage. This disadvan-

tage grows rapidly, culminating in the dramatic and discouraging effects of menopause on body weight. Women are plagued with weight problems during at least three specific times in life: menarche (the onset of menses), pregnancy and menopause. Men are not subjected to any comparable fat-inducing times in their lives.

The gender differences are apparent early and become more pronounced with each year. When young children, aged 3-8, are matched for age, height, and body weight, the girls already are 152% fatter than the boys (4.9kg vs 3.2kg). By adulthood, women have 29% to 120% more fat than men. In most developed countries, such as the United States, there are significantly more overweight women than men.

The gender difference is a huge problem. By menopause, the consequences of being overweight involve increased risks for serious disease, including heart disease, diabetes, and breast cancer.

So there is something about just being a woman that predisposes you to excess weight gain. And if you haven't had the problem prior to menopause, there is no guarantee you won't fall prey to this condition at or around that time. Obesity affects about 60% of perimenopausal women. According to some experts, excess weight

in women at different times in their lives, including menopause, stems largely from the influences of reproductive hormone concentrations (or lack thereof). It is a fact that sexual hormones are important determinants of body fat distribution and of energy metabolism, especially in females.

PREMENOPAUSE

Before menopause, body fat is distributed differently in women than men. Men tend to carry their fat within their frames, while women tend to carry fat on their frames. Premenopausal women have more fat on their extremities than men, while men tend to accumulate fat in the abdominal area and around the abdominal viscera. Women also have gender-specific, obligatory fat storage in the breasts, thighs and buttocks. The result of these differences in fat distribution is that female fat is more visible and tends to destroy her good looks more readily. Estrogen tends to favor lower body obesity, the pear-shaped kind, while upper body obesity, the apple-shaped kind, is more likely to be a characteristic of men. In summary, we agree with the observation of respected obesity researcher Lovejoy, that “obesity is truly a women’s health issue, both from the perspective of gender differences in the prevalence of obesity and in some of the related health risks.” It seems to us that the bottom line to gender differences is the result of the influence of hormones.

PERIMENOPAUSE AND MENOPAUSE

Menopause is high risk time for weight gain in women. Although the average woman gains 2-5 pounds during menopausal transition, some women are at risk for greater weight gain. There is also a hormone-driven shift in body fat distribution from peripheral to abdominal at menopause, which may increase health risks in older women. We will have much to say about this as we continue.

Many of the changes that occur during “The Change,” can be traced directly to the loss of the female hormone estrogen. What was it that kept fat in the breast, face and arms in the years pre-

ceding menopause? The answer is estrogen. As estrogen production diminishes, these areas of the female body begin to sag (fortunately, there are now certain topical preparations available that help retard these events). Unfortunately, concurrent with the demise of estrogen, the fat mass of the female body begins to take on some of the characteristics of male physiology. As a result, the female form begins to lose some of its native beauty. One of the more prominent effects of the change is on the distribution of body fat. In menopausal and perimenopausal women there is a tendency for weight gain to shift from the lower body to the abdominal region.

How does that happen? To understand the answer to that question, we need to appreciate the activity of certain other hormones on fat cell metabolism. Obesity is, after all, simply the accumulation of fat in cells called adipocytes. The deposition and removal of fat from these cells is totally under the control of two kinds of hormones: catecholamines (adrenaline and noradrenaline) and insulin. These hormones communicate with fat cells by attaching to receptors on the fat cell membrane, thereby triggering either fat storage (insulin) or fat removal (catecholamines).

Although the matter is still somewhat controversial, most experts agree that the shift from lower- to upper-body obesity occurs during menopause. Looking at fat distribution in postmenopausal women, we find that regional differences in the distribution and concentration of catecholamine receptors has changed to favor increased fat storage in the abdominal area. That is, there are now far fewer catecholamine receptors on abdominal fat cells than there are on cells in the lower body.

Now for the really bad news: Not all fat is alike. Recent evidence suggests that adipose tissue is not a single entity but differs in extremely important aspects according to its anatomic location. Body fat distribution, as measured by the ratio of waist girth to hip girth, is associated with diabetes, hypertension and gallbladder disease in women 40 to 59 years, and with menstrual abnormalities in women age 20 to 39 years. Women with relatively more fat around the waist (android)

as compared to hips (gynoid) had higher prevalence rates of these diseases. Since, with menopause, fat tends toward the android kind of distribution, well, the results cannot be good.

However, in the area of human physiology, it seems that nothing is ever black and white, and so we must hasten to add that obesity is not all bad all the time. Obesity may act as a protective factor for osteoporosis in postmenopausal women since it is associated with greater bone mass and relatively higher levels of estrogen during menopause. Indeed, research has shown an association between obesity, bone mineral density and its relationship to sex hormones. Hence, while it may be critical for postmenopausal women to lose much of their excess fat, it would not be wise to enter a weight reduction program that led to hasty weight loss or excessive weight loss. A sensible weight management program will promote balance among all of the factors that influences a woman's health after menopause.

RELATED ISSUES

The menopause transition results in a reduction in resting metabolic rate, physical activity, energy expenditure, fat-free mass, and leads to an increase in fat mass and abdominal adipose tissue accumulation. These changes ultimately predispose women to increased risk of cardiovascular disease. As women near the age of menopause, the tendency to accumulate extracellular fluid increases. This excess fluid is often accompanied by lower metabolic rate, a sedentary lifestyle and a resulting increased difficulty in losing weight and maintaining weight loss.

We often talk about the effects of premenstrual syndrome on mood and binge-eating behavior. In fact, premenstrual women show a 61% greater energy intake, due to a large extent on an increased intake of both sweet and non-sweet, high-fat, high-carbohydrate items. But, the strongest associations between mood and eating are found in menopausal women. Appetite plays a central role in the regulation of energy balance and body weight. Appetite itself is influenced by numerous factors including signals from gastroin-

testinal tract, metabolites of food oxidation such as pyruvate, neuropeptides, hormones such as insulin, the intrinsic factors of food itself such as taste, sight and smell, learned behavior such as eating habits and psychological factors such as mood.

DEALING WITH MENOPAUSAL WEIGHT PROBLEMS

While we cannot always control all of these factors, science is learning more about how some of the above factors influence eating behavior and body weight, and methods are being devised to deal effectively with each one. The most promising target currently is the so-called "hunger hormone," ghrelin. (The dietary materials discussed in the remainder of this paper have all been collected into one product, called Estrin-D™. Several of these ingredients are protected by United States Patents.)

I. CONTROLLING GHRELIN, THE 'HUNGER HORMONE'

Estrin-D contains a group of compounds that have been observed in a clinical study to produce as much weight loss as the famous ephedrine/caffeine/aspirin (ECA) stack. Many of the subjects were women of menopausal age. The publication of the study was closely followed by the appearance of several studies that seem to hold the key for explaining why the compound of the study worked so well. The Study and The Key are discussed below.

The Study: In the summer of 2001 an exciting article appeared in the *Journal of Human Nutrition and Dietetics* revealing the results of an extensive experiment in human obesity. The report contained details of a double-blind clinical study in overweight individuals (32 women, 15 men). Relevant to this research summary is an analysis of the weight change of the subgroup of 15 perimenopausal and menopausal women with a mean age of 47.9 years and a BMI of 26.6. Seven of these women were randomly assigned to

receive the treatment that consisted of capsules containing a unique and patented blend of South American herbs (Yerba Mate [*Ilex paraguarensis*], Guarana [*Paulinia cupana*], and Damiana [*Turnera diffusa*]). Eight of these women, assigned to the control group, took capsules containing a placebo. Each subject took three capsules with a glass of water 15 minutes before main meals. They all were instructed to continue their normal food and exercise habits. Both groups had similar mean weight at the start of the study (day 0 - 74.3 kg). At the end of 45 days, the YGD-treated group lost an average of 3.16 kilos (8 lbs) whereas the placebo group lost only an average of 0.16 kg (0.3 lbs). The difference in weight loss between the 2 groups was statistically significant ($p=0.016$; see table 1).

The problem was coming up with an explanation for this dramatic effect, since an examination of the active ingredients in this herbal compound fails to suggest a reasonable mode of action. Originally, the researchers felt it probably had something to do with gastric emptying, and, in fact, additional research reported by these scien-

tists did uncover a significant delay in gastric emptying time attributable to the compound.

In spite of the apparent reasonableness of the gastric emptying theory, there are reasons to doubt that the theory fully explains the dramatic weight loss observed in that arm of the study. And there was no data to implicate common hormones, such as insulin. The complete answer, we felt, must lie elsewhere. But where? Within months of the publication of the research on the herbal compound, a series of articles appeared in the scientific literature that seemed to hold the key.

The Key: The recent discovery of a substance native to the upper GI tract (the stomach) has suddenly and altogether changed our thinking on how the special herbal compound was able to produce such astonishing success. The original researchers investigating the gastric properties were on the right track, they were perhaps just looking in the wrong area.

The newly discovered substance has been given the name ghrelin (grey-lin). “Ghre” is the root for the word “growth,” and “relin” signifies “releasing substances.” So ghrelin means a substance that releases

growth substances in the body. Technically, it is a 28-amino-acid acylated peptide hormone, widely distributed in the body, but produced predominantly by the stomach.

Ghrelin is universally considered a landmark discovery. Plasma ghrelin levels increase about twofold immediately before each meal and fall to baseline levels within one hour after eating; this suggests that ghrelin plays a physiological role in

Table 1:

Weight Change after Treatment with YGD Combination Versus Placebo

capsules	Age	wt day-0 (kg)	BMI day-0	wt day-45 (kg)	BMI day-45	Wt Diff (kg)
placebo	48	73.4	26.3	72.8	26.1	-0.6
placebo	52	70.1	26.1	70.6	26.2	0.5
placebo	45	75.3	27.3	76.1	27.3	0.8
placebo	57	82.2	28.2	81.4	27.9	-0.8
placebo	59	69.8	26.9	69.8	26.9	0
placebo	46	73.5	27.3	73.1	27.2	-0.4
placebo	55	82.8	30.4	82.4	30.3	-0.4
placebo	44	76.1	27.6	75.7	27.4	-0.4
Placebo group Mean		75.40	27.51	75.24	27.41	-0.16^a
YGD	41	75.5	28	73.2	27.2	-2.3
YGD	40	70.1	25.8	67.9	25	-2.2
YGD	49	76.5	27.4	72.1	25.8	-4.4
YGD	45	70.2	26.4	64.9	24.4	-5.3
YGD	46	72.8	26.4	72.9	26.4	0.1
YGD	44	76.9	27.3	73.7	26.1	-3.2
YGD	48	69.1	26.4	64.3	24.5	-4.8
YGD Group Mean		73.01	26.81	69.86	25.63	-3.16^b

* the difference between a and b after 45 days was statistically significant ($p=0.016$)

meal initiation in humans. In other words, ghrelin levels peak just before meal times, precisely when you least need further inducement to eat. Then, as you eat, and afterwards, ghrelin levels gradually subside and are at their lowest when you don't need to eat any more. For those of us fighting the battle of the bulge, this would appear to be Mother Nature's own little nasty feat of horrendous timing. Here's why. We know that the gastrointestinal tract is the place where all ingested food winds up. And we know likewise that the hypothalamic center in the brain ultimately regulates food intake and growth (the latter through the effects of growth hormone). What has been missing is a substance that would clearly link these two anatomical sites. Very recent research supports the notion that ghrelin makes the connection. Through the activity of ghrelin, the stomach can effectively communicate with weight management centers of the hypothalamus and pituitary gland. Furthermore, ghrelin also links these sites to metabolic influences arising from the liver and muscle cells. It may sound strange to link the stomach to the brain, but that is exactly what ghrelin does.

That the stomach can exert a direct control over the pituitary is a stunning breakthrough in our understanding of appetite and hunger. The actions of ghrelin are directly involved with hypothalamic and pituitary growth factors as well as the regulation of metabolism, energy expenditure and food intake. Ghrelin can forcefully stimulate food intake and weight gain, and can inhibit the body's ability to burn fat. We have all heard about leptin — the hormone that definitely makes laboratory rats leaner, and that may help keep people thin too. Well, ghrelin can completely negate the activity of leptin. Furthermore, ghrelin may actually increase gastric emptying rates, stimulate gastric motility and increase gastric acid secretion.

Put it all together and ghrelin may be the most potent obesity-inducing factor human beings will ever encounter. And we make it ourselves, right in our own stomachs.

Now the involvement of the stomach in this circuit is important because this is one place in the body where dietary manipulation can exert some influence. However, because ghrelin can be pro-

duced by many other tissues in the body, a fair question is: If I reduce ghrelin production in my stomach, how big of an impact is that going to make on weight management? The answer is: a big impact. Consider that a simple gastric bypass operation — but not stapling of the stomach — reduces ghrelin concentration by over 70%. This is an important finding for the additional reason that there is practically no rebound weight gain from gastric bypass surgery. The connection with stomach-manufactured ghrelin is so strong that we would not be surprised to discover that weight loss achieved through effective ghrelin management is also free from the rebound effect seen with virtually all diets.

What is needed is something to counteract the action of ghrelin, something that will prevent the dramatic increase in appetite and hunger caused by this hormone and thereby significantly reduce food consumption at mealtime. We believe that the herbal compound discussed above is the answer. There appears to be a perfect match between the activity and timing of the herbal mixture and the signs of ghrelin reduction. If we are right, the compound either inhibits the production of ghrelin or counteracts its activity (the ability of the herbal mixture to delay gastric emptying is one intriguing action that seems to counteract the action of ghrelin).

According to this vision, taking a couple of capsules of the compound several minutes before a main meal should reduce the level of ghrelin at the exact moment when it would otherwise be at its peak level. Without this encouragement to eat, our appetites are lower and our subsequent food intake is significantly depressed. The act of eating would depress ghrelin levels even further. For one thing, the herbs are clearly offsetting the tendency of ghrelin to accelerate gastric emptying.

Eating slowly and deliberately, chewing food thoroughly, putting the fork down after every bite — these and other behavioral techniques are known to help reduce food intake. Now we know why: The slower we eat, the greater the chance that ghrelin levels will dip. But these measures alone seldom produce the desired degree of weight loss. The implication of the new ghrelin

research is that effective weight control is dependent on our ability to reduce ghrelin levels before eating. Then, and only then, will everything work together for our good.

Also, with ghrelin out of the way, other locally produced hormones, such as leptin (the satiety hormone), are free to more profoundly affect our eating behavior. Furthermore, without ghrelin, perhaps much of the natural stimulus to eat in the first place goes missing.

In studies investigating the association of ghrelin with obesity in humans, it has been observed that ghrelin levels are low in obese individuals, but as they begin to lose weight, ghrelin levels go back up. This suggests a complicated state of affairs in which even ghrelin may be affected by internal factors as yet unknown. Once ghrelin has achieved its purpose — making a person obese — it shuts down, only to be revived if internal sensors in the body signal the brain that you are losing weight. This negative feedback mechanism may explain the plateaus experienced by most dieters. They exercise, cut calories and consume metabolic fat burners and experience immediate success that is quickly blunted by that predictable plateau. Why? Because at the start of the program ghrelin levels are low, but as the diet program begins to succeed, the ghrelin levels quickly rise, which results in a stalemate between your aggressive intervention and your body's equally belligerent, ghrelin-motivated defense of its overweight profile. It may be hard to believe, but it is now a known fact that weight loss produced by diet and exercise will stimulate the production of ghrelin, which will directly oppose efforts to lose weight.

There are still other difficulties involved in ghrelin management. It turns out that ghrelin levels rise with advancing age. Hence, by the time those menopausal years arrive, ghrelin is working overtime to increase your body fat stores. In addition, ghrelin is stimulated by low-protein diets and is decreased by high-fat diets. Other research on diet composition suggests that the typical Mediterranean Diet may be best suited for effective ghrelin management.

To summarize, in this model, obesity can be

largely regulated by inhibiting the production and activity of ghrelin. First, such regulation would prevent further weight gains by reducing food intake. Second, it would open the doors to effective weight loss by removing plateaus and making your diet program continually work for you, and third, reducing the pre-meal ghrelin level will remove the stimulus to eat too much.

The Estrin-D™ Ghrelin Study in Menopausal and Perimenopausal Women

These thoughts on weight management, stemming from the exciting work being done on ghrelin and the incredible results achieved by the herbal compound, demand further investigation. To that end, a recent study was conducted to help determine the extent to which the herbal compound does or does not reduce ghrelin levels during the interval prior to normal mealtimes in menopausal and perimenopausal women.

In the study, female volunteers, either perimenopausal or postmenopausal, fasted overnight and then ate a moderate, early-morning breakfast. Ghrelin levels were taken at set intervals both before this meal and for several hours following the meal. It was reasoned that ghrelin levels would be low immediately following the meal and that they would increase dramatically at some point in time a few hours later as the lunch hour approached. Since individuals probably respond slightly differently, several time points were measured to increase the probability of “catching” the rise in ghrelin. As the appointed meal time approached, a ghrelin measurement was taken and the volunteer was immediately administered a single serving of the patented herbal mixture in a capsule. Fifteen minutes later, ghrelin was measured again, and then again after another fifteen minutes had passed, following which lunch was eaten. A few more measurements were taken at set intervals following lunch.

The researchers found that ghrelin levels were low following breakfast and then steadily increased over the next 3-4 hours preceding lunch. The calculation of most interest to the investiga-

tors was the difference between the ghrelin levels at the time the herbal compound was administered and fifteen minutes later. This difference — which was the most important indicator of the ability of the herbal compound to reduce ghrelin levels — turned out to be statistically significant, although there was much variability in response. The least positive response was a drop in ghrelin of 4.15%, and the greatest drop was 23.61%. One subject experienced a slight (2.34%) increase in ghrelin. Whether or not this increase would have been greater in the absence of the treatment could not be determined, but seemed likely in view of the dramatic response of the other subjects.

Overall, the results of this modest study clearly support the possibility that the herbal compound suppresses ghrelin levels in menopausal and perimenopausal women at precisely the time the levels should have been the highest. To the best knowledge of the investigators, this was the first demonstration of ghrelin suppression by a dietary supplement, OTC compound or prescription drug.

The results suggest that the weight-loss results observed with the herbal compound (and previously hypothesized to be the sole result of a delay in gastric emptying) can almost certainly be attributed at least in part to the ghrelin-suppressing nature of the herbal combination. Eventually, we hope to discover the genetic pathways regulating ghrelin and the compounds that will affect those pathways.

In the final analysis, the newly discovered hormone, ghrelin, is being compared in importance to insulin and leptin. As one scientist put it: “In fact, ghrelin and leptin may be the ‘ying and yang’ of a system that relays peripheral information [e.g. from the stomach] to the brain and directs the body in the appropriate maintenance of energy reserves [body fat] and nutritional intake.” Furthermore, Estrin-D™, prepared especially to help manage the changing weight parameters of menopause, contains the first natural compound ever discovered to clearly regulate this hormone.

II. Dealing With the Difficulties of Mood Fluctuations: Getting Adequate Magnesium,

Vitamin B6 and DHEA.

The story of Estrin-D could very well end here, but there is more. Although pure weight loss is a noble end in itself, a good weight management compound should ideally address related issues such as energy, mood and vitality. Estrin-D, therefore, was designed to improve mood, provide energy and simply make life more enjoyable and exciting.

Of all the essential minerals necessary to maintain life, magnesium is perhaps the most important for preventing and reversing symptoms of neural and neuromuscular dysfunction. Magnesium is a key element in the stabilization of the nerve cell. Without it, the nerve would be in a constant state of excitation, a state known as tetany.

When ingested, most magnesium compounds release free magnesium which is then utilized by the body, or stored away, as needed. Magnesium is the central element in the chlorophyll molecule, just as iron is the central element in the hemoglobin molecule. In fact, hemoglobin and chlorophyll are almost identical substances, except for the magnesium-iron substitution. Thus, it is possible to equate iron and magnesium as the two most fundamental elements in the two most important life cycles on the planet.

In the fluids of the body, magnesium is a necessary part of the transport systems that maintain water and electrolyte concentrations inside and outside of cell membranes, thereby regulating cellular ability to operate properly. Whereas calcium is an activator, as in muscle contraction and nerve excitability, magnesium is an inhibitor, as in nerve and muscle relaxation; it thus counterbalances the action of calcium throughout the nerves and muscles of the body.

Magnesium deficiency produces neuromuscular tetany, vasodilation, convulsions, tremors, depression, apprehensiveness, muscle twitch, confusion, psychotic behavior, nervous tachycardia, disorientation, and increases the incidence and severity of muscle cramps. All of these signs and symptoms are the result of an unstable neural membrane, whether in the brain, the G.I. tract, the muscles or the blood vessels.

The metabolic role of magnesium is quite extensive. It appears to be a crucial cofactor in energy production cycles (oxidative phosphorylation), activating enzymes that convert ATP to ADP. It is also crucial in all mechanisms that depend on the thiamine coenzyme. Additionally, magnesium is necessary for the synthesis and degradation of RNA and DNA molecules, helps regulate temperature, assists in the production of protein by assisting in ribosomal aggregation, helps remove excess ammonia from the body, and promotes the absorption and metabolism of numerous nutrients, including vitamins C, E and B complex, sodium, potassium and phosphorous.

Based on its numerous metabolic functions, magnesium has been used therapeutically to prevent heart attacks and congestive heart failure, to treat prostatitis, polio, tremors, delirium tremens, urinary and kidney stones, high cholesterol, arteriosclerosis, tooth decay, periodontal disease, diarrhea, vomiting, epilepsy, kwashiorkor, nervous system degeneration, diabetes, hypertension, fractures, osteoporosis, rickets, colitis, multiple sclerosis, neuritis, celiac disease, arthritis, nephritis, leg and other muscle cramps, backache, headache and obesity.

Of greater pertinence to this paper, the list of benefits from magnesium supplementation also includes relief from nervousness, depression, neuromuscular disorders, tantrums and pain.

Severe mental depression, convulsions, nervousness, irritability, restlessness, confusion and related symptoms are signs of a need for greater magnesium consumption. Mood swings and depression are very stressful, and this kind of stress depletes the body of magnesium. Urinary levels of magnesium skyrocket during stress. A lifetime of menstruation is another significant source of stress on magnesium levels. Studies have shown that magnesium levels wax and wane during the monthly cycle, reaching a nadir during the ovulatory phase. Supplementation significantly reduces mood changes during the premenstrual phase. After 30 or 40 years of menstruation, it is no wonder that magnesium and mood are stressed-out during menopause. Magnesium is low in a substantial proportion of women con-

suming Western-style diets. This has been shown in many dietary surveys. G.E. Abraham first suggested that in case of magnesium deficiency, supplementation with magnesium would restore cell membrane electrolyte imbalances to normal.

Under normal circumstances, magnesium deficiency is quite rare; however, with advancing age and especially during the years surrounding menopause, magnesium deficiency is much more common and is responsible for a good portion of the mood problems experienced by women of this age.

A very important consideration for most menopausal women is maintaining a balance between magnesium and calcium. With all of the emphasis in the popular and medical press about menopause-associated bone mineral deficiency, menopausal women are prone to consume a relatively large amount of calcium. Since calcium and magnesium compete for the same absorption sites, a high concentration of one of these minerals generally results in poor absorption of the other. Hence, while it is important for menopausal women to obtain the necessary calcium, attention must also be paid to maintaining adequate magnesium levels. The amount of magnesium in Estrin-D™ is based on studies showing that around 200mg of magnesium is required to produce meaningful clinical results, even during normal calcium supplementation.

Another nutrient that seems to be very important for avoiding or overcoming depression and other mood problems at menopause is vitamin B6. An adequate intake of vitamin B6 is required for maintenance of normal intracellular magnesium concentration. Most studies on the effects of vitamin B6 and mood have shown a positive effect, especially when combined with magnesium.

In fact, in a recent ground-breaking study published in the *Journal of Women's Health & Gender-Based Medicine*, a synergistic effect of magnesium and vitamin B6 was observed in the relief of anxiety-related premenstrual symptoms. In this randomized, double-blind, placebo-controlled, crossover design experiment, a combination of 200mg/day of magnesium oxide plus 50mg/day of vitamin B6 was significantly better

than placebo in reducing anxiety-related symptoms such as nervous tension, mood swings, irritability and anxiety.

Magnesium is a logical choice for an anti-anxiety agent because of its ability to counter neuromuscular excitability. Vitamin B6, on the other hand, is required to maintain normal intracellular magnesium concentration because the vitamin plays a critical role in the transport of magnesium across cell membranes. This sets the stage for a synergistic relationship between B6 and magnesium.

It should be noted that the effects of magnesium/B6 are probably going to be particularly manifested in women who are deficient or borderline deficient in one or the other of these nutrients. The women in the above study were about normal for magnesium and were slightly higher than normal in B6, yet the beneficial effects were still observed.

Magnesium and vitamin B6 are central components in an anti-anxiety compound known as Relacore™ (Carter Reed Company™). One particular subgroup of nutrients in that formula in which magnesium and vitamin B6 figure prominently is a robust multivitamin/mineral compound. Vitamin and mineral supplements should be capable of improving psychological status, especially if the patient is deficient. Someday, perhaps, we will have the luxury of doing complete and accurate nutritional work-ups on all subjects involved in anxiety research. Presently, however, the discipline is in its infancy. There have been few excursions into this area, and those that have been done have been more exploratory than definitive. Such is the case with an interesting combination of vitamins and minerals developed in Europe and used to combat stress. Several different groups of scientists have subjected this modest combination of nutrients to the test, using human subjects. The test material contained, in addition to magnesium and vitamin B6, specific amounts of vitamins B1, B2, pantothenic acid, biotin, folic acid, B12, C, and calcium and zinc.

One trial used 307 subjects who were selected on the basis of being constantly exposed to occupational stress. In this study, subjects were

administered the above combination for 1 month and experienced significant improvement in a composite questionnaire measure of fitness, activity and mood. In another 60-day trial study using the same combination, 67% of the subjects reported less depression and 82% reported less fatigue. More recently, this same combination of nutrients was administered to 80 volunteers in an intense double-blind, placebo-controlled trial. The vitamin/mineral combination produced statistically significant and dramatic reductions in anxiety and insomnia as determined by the battery of measurement tools.

Let's look at one more study with this same mixture of nutrients. In this double-blind, placebo-controlled, two-center study, the mixture was administered to 300 high-stress subjects for 30 days. The degree of improvement in anxiety and related psychological parameters was statistically significant for all psychometric instruments used.

Although the results reported in these studies cannot be attributed solely to magnesium and B6, the results are directly in line with the results of the studies confined to these two critical ingredients.

DHEA

Our understanding of relationships between body weight, aging and adrenal hormones has improved dramatically in the last few years. Central to this relationship is the gradual waning of the secretion of dehydroepiandrosterone (DHEA) as we get older. Since this hormone is an important precursor to several of the so-called 'hormones of youth,' the result of the loss can be devastating. In fact, lowered DHEA levels are associated with several disorders, including obesity and chronic fatigue syndrome, as well as by certain psychological disorders such as major depression. Simply replacing lost DHEA levels would appear to be a reasonable procedure for the treatment of obesity and mood disorders. Unfortunately, the situation is not that easy. Consuming DHEA orally poses certain problems. For example, it is not the absolute oral serving size that is important, but rather the level of DHEA in the blood. Individuals vary widely in

blood DHEA levels, depending on age, gender, degree of acute or chronic stress, and other health-related factors. Hence, the amount of DHEA in Estrin-D™ is carefully metered to provide important benefits to the consumer but not high enough to warrant concern over the likelihood of abuse, overuse or side effects.

During the last 40 years or so, dozens of animal experiments have demonstrated that DHEA is a hormone with wide-ranging functions, including immunoenhancing, antidiabetic, antiobesity, breast-cancer preventing, neurotropic, memory-enhancing, and antiaging effects. DHEA has been studied in older men, older and postmenopausal women, and in people with chronic fatigue syndrome/mood disorders. USC researchers analyzed steroid hormone levels in 699 depressed women, aged 50-90, and found that only DHEA sulfate levels were significantly and inversely associated with depressed mood. Estrogen is considered one of the main sex hormones related to depressed mood. Women experience depression two to three times more often than men. Estrogen replacement therapy has been shown to improve mood in estrogen deficient women. DHEA could also affect mood by conversion (aromatization) to estrogen or by a direct action of the central nervous system.

DHEA administration at the rate of 50mg/day resulted in impressive improvement in well-being, depression scores and sexual interest in women with adrenal insufficiency and very low endogenous DHEA levels.

On another tack, we are just beginning to understand the role of the immune system during stress. It is apparent that low-grade infection that tends to compromise the immune system leads to other symptoms that at first do not seem related, such as chronic heart disease and obesity. However, as of this writing, a whole school of medicine is emerging that deals specifically with the myriad connections between the immune system and the symptoms of heart disease, diabetes, arthritis, obesity, etc. Hence, it is interesting that small amounts of DHEA (50mg/day) for just 3 weeks has been shown to increase several aspects of immune function. A higher dose (200mg/day)

produced significant symptomatic improvement in female lupus patients. In older men, 50 mg/day for 20 weeks produced significant stimulatory effects on the immune function. The improvement in immune function occurs more slowly in older than in younger patients.

Human aging affects, and is affected by, adrenal cortical function. Aging is usually accompanied by increases in fat mass and a decline in lean body mass, with decreased muscle strength. These changes are normally accompanied by a progressive shift from an anabolic (building up) to a catabolic (tearing down) state and a decline in the health of the immune system. The ratio of cortisol/DHEA exhibits an interesting U-shaped curve when plotted against age. Early in life the brain is exposed to relatively high levels of DHEA(S), extending into later childhood (adrenarch-puberty) and early adulthood, but to very high levels of cortisol during infancy and old age. As we age, stress-induced cortisol excess plays an ever-increasing role in the development of cognitive impairment, mood changes, hippocampal neuronal loss, among other problems already discussed. Among the methods employed to counter these tendencies has been the administration of DHEA in varying amounts for varying periods of time. At the extreme high end, upwards of 1,600mg/day has been used. At this level DHEA can lower HDL (the good fat) and possibly affect other aspects of physiology in a counterproductive manner. Hence, researchers and physicians have moved away from the idea of megadosing and instead concentrate on just trying to reestablish normal serum levels of DHEA. This approach has produced significant success. Good results are achieved with daily servings as low as 25-100 mg, without any degree of serious adverse reaction.

As a final note to this section, it should be clear that the inclusion of magnesium, vitamin B6 and DHEA in a weight-loss compound designed from menopausal and perimenopausal women should contribute significantly to eliminating mood problems that would otherwise spell certain diet failure — a failure that has frustrated countless women in the past.

III. Energy, Energy, Energy: The Benefits of Natural Methylxanthines

Menopause is marked by not only by bouts of depression but by frequent feelings of lethargy. The fatigue that attends this time of life can be debilitating, robbing the woman of the pleasures and joy that she should be enjoying after a lifetime of work and stress. Fortunately, there is a class of medicinal plants that contain substances renowned throughout history for their stimulating and energizing properties. Plants that contain methylxanthines have been accepted for centuries as mediators of energy. (Note: the terms xanthine, methylxanthine and trimethylxanthine used throughout this paper get more specific as the length of the term increases; the longer is a subset of the shorter. The shortest term, xanthine, is thus the most inclusive, and the longest term, trimethylxanthine, the most specific). In Africa and South America, long distance runners achieved these ends by chewing the medicinal parts of plants containing methylxanthines to help their bodies turn stored fat into the fuel they needed to keep up the pace. In modern times, these xanthines have been extracted and synthesized to produce more compact and easily accessible compounds for maintaining high energy levels. The unique Estrin-D™ formula combines several sources of xanthines in perhaps the most powerful form ever. It is meant to be used by people wanting and needing a high level of energy production, and for weight management.

A good deal of the research on the ergogenic effects of xanthines has shown that xanthines exert their energy-promoting properties in two ways. First, they energize the central nervous system through a fairly direct process. This results in the immediate increase in mental clarity often observed following the consumption of even moderate amounts of xanthines. Second, and most important for meeting the exaggerated needs of menopausal women, xanthines stimulate lipolysis in fat cells.

Lipolysis is the process whereby stored body fat is converted into forms the body uses for short term and long term energy production.

Technically speaking, lipolysis is the process whereby stored triglycerides are broken down into free fatty acids and then mobilized into the blood stream where they circulate and are taken up and metabolized by all other cells of the body to produce ATP, the energy currency of the cell.

Recently, the armed forces of the United States and Canada have become seriously interested in the possible application of methylxanthines as a method for increasing the performance of soldiers under acute and chronic stress. As any menopausal woman can tell you, when people are exposed to several stressors, mental and physical performance are substantially degraded. The military was the first to recognize the serious lack of procedures for counteracting this problem. Astute students of military history, however, would have noticed that plant materials containing xanthines have often been used by military personnel to ward off sleepiness while on guard duty and to maintain vigilance under combat situations lasting for several days without relief.

In one of the most rigorous experimental investigations of the possible role of trimethylxanthine to offset severe acute stress, researchers at the U.S. Army Research Institute of Environmental Medicine, in conjunction with scientists from Tufts University and Pennington Biomedical Research Laboratory, examined whether moderate doses of trimethylxanthine would reduce adverse effects of sleep deprivation and exposure to severe, multifactor, environmental and operational stress on mental performance. In this study, US Navy Sea-Air-Land (SEAL) trainees received either placebo or trimethylxanthine capsules after 3 days of sleep deprivation and continuous exposure to other stressors, including running, lifting, paddling, swimming, calisthenics and other rigors inflicted during the appropriately named “Hell Week” period of training.

As might be expected, sleep loss and exposure to other severe stressors resulted in a profound deterioration in all aspects of cognitive function assessed. Measured against placebo, the trimethylxanthine-treated group experienced a significant improvement in visual vigilance, reaction time, self-reported fatigue and sleepiness,

with the greatest effects on vigilance, reaction time and alertness. Interestingly, marksmanship, a task that could be affected by shakiness or jitteriness, was not adversely affected by trimethylxanthine. The effects of the trimethylxanthine peaked at a little over an hour but persisted for up to 8 hours following administration. Of the doses used, the higher doses (200 or 300mg) yielded the best results. The researchers concluded that even under the most adverse conditions, these moderate doses of trimethylxanthine can improve cognitive function, including vigilance, learning, memory and mood state. What makes this study so valuable are the extreme conditions under which the trial was conducted. SEAL candidates are already some of the toughest, most stress-resistant people on the planet. After weeks of intense, difficult training designed to identify individuals who can withstand the adverse effects of extreme stress, candidates must face the rigors of Hell Week, during which they engage in continuous 24-hour activities, physical and mental challenges, environmental stress (especially cold-induced stress), and constant psychological pressure.

Other studies have yielded similar results. For example, in a study carried out under the Defence R&D of Canada, a group of civilian and military personnel were enlisted in a trial to examine the duration of trimethylxanthine's ergogenic effect and whether it differs between users and non-users of the substance. A user was defined as someone who habitually already consumed methylxanthines during the normal course of his life. In this trial, patients were required to ride to exhaustion on a stationary bicycle, following consumption of trimethylxanthine. In the end, the compound allowed the subjects to exercise for about 1/2 hour longer and the non-users benefited slightly more than the users (about 5 minutes). Not only the duration, but the magnitude of response was greater.

As mentioned above, xanthines exert two primary actions that can account for the observed enhancement of mental and physical performance. Methylxanthines as a group are universally recognized for their ability to augment central nervous system function. This probably accounts for much

of the immediate effect on mental clarity, learning, vigilance, etc. However, the quick effect on the nervous system would only be expected to last for a few minutes in the absence of added fuel in the form of glucose and, indirectly, from increased free fatty acid concentration throughout the rest of the body.

It has been repeatedly demonstrated that ingestion of xanthines enhances fat metabolism. This is achieved by altering the effectiveness of the fat cell's ability to release stored fats, and by increasing the muscle cell's ability to take advantage of the increasing supply of fat-derived fuel. A consequence of increased fat utilization by the muscle cell is a net increase in the amount of glycogen spared. Because glycogen is spared, quick glucose uptake by the brain is feasible. (Glucose is the main fuel of the brain. If glycogen stores are depleted, fuel reserves for the brain disappear, which can result in mental confusion — that xanthines produce mental clarity argues in favor of glycogen sparing under increased metabolic conditions.)

In other words, ingestion of xanthines prior to periods of exercise or stress enhances the mobilization of fatty acids that are then used as the major energy source during endurance, exercise or chronic stress. This leaves the glycogen (quick energy) available for use when needed.

Xanthines achieve their lipolytic effect first by increasing the activity of an enzyme known as hormone sensitive lipase, also by stimulating fat cell receptors that signal lipolysis, and by inhibiting enzymes that inhibit lipolysis. All of these properties have been recognized by researchers as possibly instrumental in increasing endurance, performance time and delaying fatigue.

Parenthetically mentioned above was the importance of glycogen in brain functioning. But there is also an important role played by glycogen in increasing stamina. Stamina requires an optimum use of stored glycogen in muscle and liver. Glycogen storage capacity in the body is severely limited. Therefore the chief causes of fatigue during prolonged work or stress are hypoglycemia (low blood sugar) and depletion of stored glycogen.

The increase in fatty acid availability as a result of ingestion of xanthines reduces the rate of glycogen depletion and improves endurance. Consuming xanthines prior to exercise performance or stressful circumstances would have the net effect of helping to maximize the amount of circulating free fatty acids available for use at the appropriate moment and sparing the sensitive glycogen stores from rapid depletion.

In a very real sense, xanthines should be viewed collectively as a “lipolytic food.” As part of the diet of anyone in need of acute energy surplus, a lipolytic food would stimulate lipolysis and/or fat oxidation at rest, under stress or during exercise. In one study, the administration of trimethylxanthine 60 minutes prior to exercise resulted in an increase in free fatty acid concentration, increased lipid metabolism and decreased muscle glycogen utilization. The rate of fat utilization for energy correlated with an increase in the concentration of free fatty acids. Glycerol concentration was actually elevated following exercise, suggesting that xanthines enhance lipolytic activity in body fat stores.

To summarize the cellular level chemistry, xanthines significantly influence an entire series of biochemical processes that results in an increase in the ability of the cell to release cellular fuel.

To summarize the physiological effects, xanthines act as a lipolytic food, 1) increasing the concentration of serum free fatty acids which becomes the main source of energy for skeletal muscle, and 2) sparing glycogen which is therefore available for energy production during the latter stages of exercise.

To summarize the net behavioral advantages, ingestion of xanthines leads to improved performance, both mentally and physically.

THE METHYLXANTHINES OF ESTRIN-D™ IN MENOPAUSE

The usefulness of xanthines is not restricted to any particular sex or age group. Indeed, it has been shown that the elderly experience a decreased ability to mobilize fat in response to

exercise. In this age group, research has found that xanthines augment fat mobilization as they do in the young, but to a lesser degree. In other words, the elderly and menopausal need all the help they can get and xanthines should be a great aid.

The Metabolic Study on Estrin-D™

To confirm the ability of the methylxanthines found in Estrin-D to enhance metabolic rate, a study was undertaken to measure metabolic rate at rest with and without the methylxanthines contained in Estrin-D. Several female volunteers were tested using indirect calorimetry. The results showed that almost all subjects experienced a significant increase in their resting metabolic rate (RMR) from baseline 30 minutes after ingestion of capsules containing key methylxanthines that occur in Estrin-D. The mean change was about a 10.2% increase from baseline and was statistically significant ($p=0.27$). This is a tough test because methylxanthines will typically work best when the body is moving. That they will improve metabolic rate under resting conditions is all the more impressive.

The majority of perimenopausal and menopausal women experience weight change and body composition change regardless of their weight status when the first symptoms of menopause appear. Simultaneously, the majority of these women experience a decrease in physical activity inherent to the progression in their work career or by the fact that they carry extra weight. Stimulation of energy expenditure and stamina by methylxanthine ingestion is of great interest since we know that methylxanthines are quite safe.

The use of xanthines as ergogenic aids has received considerable attention in recent decades, following on the heels of several centuries of use for improving the performance of tribal runners, trained athletes, military personnel and the population at large: from the habit of chewing gooroo nut on hundred mile long runs through the jungle to the increasing needs of marathon athletes; from ancient herbal decoctions to modern drugs; from the enhancement of exercise to the enhancement of weight loss — throughout history, xanthines

have dramatically improved the lifestyles of millions.

The term “lipolytic food” describes the primary healthful role of xanthines. In this capacity, ingestion of xanthines allows the body to meet unusual (or even usual) energy demands, whether inflicted by environmental contingencies or arising from any form of athletic endeavor.

Research summarized here extends the knowledge base of methylxanthines and confirms their ability to improve metabolism. This is reassuring knowledge for menopausal women seeking solutions for their overweight and fatigue problems.

CONCLUSIONS

As stated at the outset, the purpose of this report has been to explain the benefits to menopausal and perimenopausal women of a group of dietary supplements currently available commercially in the form of Estrin-D™. It has been demonstrated that these substances help women deal with the serious demands of that time of life.

First, we have shown that Estrin-D components produce weight loss in women of perimenopausal and menopausal age. Reviewed herein were two extremely important studies. The first reported weight loss to be as good as that obtained by the powerful ephedrine-containing agents (but without ephedrine), and attributed the success to observed and reported delays in gastric emptying. The second demonstrated that the Estrin-D compounds significantly inhibited the “hunger hormone,” ghrelin. The difficult physiology of fat

distribution caused by menopause is defeated to one extent or another by the combination of delayed gastric emptying and ghrelin inhibition.

Second, we demonstrated that components of Estrin-D are well-documented mood enhancers in women, even during the tough premenstrual phase of the monthly cycle.

Third, we have shown that Estrin-D constituents have a profound effect on the physiology of energy production in people under extreme kinds of stress. A separate paper is reviewed proving that the effectiveness of these compounds in raising resting metabolic rate.

Taken together, the weight of the evidence in favor of the role Estrin-D as an extremely valuable tool for menopausal and perimenopausal women is substantial.

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