

Idiopathic orthostatic edema as a cryptic cause of the inability to lose weight despite dieting

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The clinician is frequently consulted by patients, mostly women, complaining that they are unable to lose weight, despite dieting. Subsequently the physician evaluates the patient for hypothyroidism, Cushing's syndrome or diabetes, but in the large majority of cases these metabolic diagnoses are excluded. Edema could also explain the weight gain, but except in rare cases, hepatic, renal, cardiac or lymphatic causes cannot be found.

Idiopathic orthostatic edema is a condition associated with fluid retention which could also lead to weight gain. (Streeten, 1978). It is considered, however, a rare condition. The diagnosis is confirmed by demonstrating an abnormal retention of fluid in the erect position following a water loading challenge. (Streeten et al, 1960).

A study was designed to determine if patients failing to lose weight despite appropriate dieting might actually have a problem of fluid retention similar to idiopathic edema. Furthermore, the study would determine if any of the therapies effective for women with classic idiopathic orthostatic edema might help these women with recalcitrant weight problems.

Only patients complaining of the inability to lose weight despite dieting were included in the study. Each patient registered was asked to consume their normal foods for the next two weeks, but to keep a careful log. The number of calories consumed was then evaluated. The patient was included in the study only if the total number calories consumed in two weeks was at least 10% lower than the number obtained as follows: $14 \times [1000 + 100a + 0.33(1000 + 100a)]$ where a = number of inches above 60. This number was felt to be a fair estimate of the number of calories consumed on a daily basis in each woman.

The objective was to recruit 200 patients for the study; this required interviewing 277 patients. The majority of the 77 women excluded were eliminated because of underestimating the number of calories ingested. A small number was excluded for endocrine abnormalities (4 patients with hypothyroidism) and one patient with proteinuria. Otherwise, there were no patients with abnormalities in their serum T4, T3 uptake or TSH or their 24-hour urine for free

cortisol or abnormalities in serum fasting glucose, electrolytes or liver function tests or urinalysis. There were 12 patients not included because they did not want to participate in the study; 11 patients were excluded because of side effects to the drugs during the first two weeks.

Water load tests were performed on all patients. The patient would drink 1500 cc water over 30 minutes, then urinate and discard; measure the urinary output over 4 hours (the first day supine for four hours; the next day erect for four hours after repeating the same instructions).

The patients were randomized into four treatment groups: 1) first and last digit of their social security number were even - hydrochlorothiazide (HCT) 50 mg/day; 2) first and last digit of their social security number odd - spironolactone 200 mg/day in divided doses; 3) first digit even and last digit odd - dextroamphetamine sulfate 10 mg spansule twice daily and 4) first digit odd, last digit even - captopril 25 mg 2 times per day. To make the groups have 50 women in each one, once 50 were achieved by one group then the patient would be assigned to another group, especially the group with opposite social security numbers, i.e. HCT group where first and last digit were assigned to spironolactone group where first and last digits were odd.

Each therapy would be evaluated after six months comparing each patient's baseline morning weight right before treatment to the p.m. weight after treatment. If a patient dropped out of the study because of side effects or other reasons they would be replaced by the very next patient appropriate for the study regardless of their social security number.

The patients were advised to eat 10% less per day of the number calculated to be their average daily consumption of calories. One day each week with the day progressing by one each week (i.e. first week Sunday - next week Monday, etc.) the patients were to calculate their calories consumed.

After six months those patients not losing a reasonable amount of weight were to be offered the treatment during the first six months having the best results of the four treatments. These patients also had to log their calories ingested one day each week.

All patients in the study were women. This allowed less variables and was easier to accrue the patients since our practice is almost exclusively gynecologic endocrinology.

The results showed a dramatic response to dextroamphetamine sulfate, but not to any of the other therapies as seen in Table 1.

Table 1

Number of patients losing weight according to treatment during first six months.

| % of Baseline Wt. Lost | Treatment | | | |
|------------------------|-----------|--------|----------|--------|
| | HCT | SPNLT | DEX | CAP |
| >10% | 3 (6%) | 4 (8%) | 34 (68%) | 2 (4%) |
| >15% | 1 (2%) | 1 (2%) | 26 (52%) | 0 |
| >20% | 0 | 0 | 14 (28%) | 0 |
| >25% | 0 | 0 | 10 (20%) | 0 |
| >30% | 0 | 0 | 5 (10%) | 0 |

Legend

HCT = Hydrochlorothiazide
 SPNLT = Spironolactone
 DEX = Dextroamphetamine
 CAP = Captopril

The 141 women from the groups treated with non-amphetamine therapy were now offered treatment with dextroamphetamine for the next six months. A total of 132 accepted therapy. The results showed that 90 (69%) lost at least 10% of their initial baseline weights; 59 (44%) lost over 15%; 40 (30%) lost at least 20%; and 19 (15%) lost at least 25% and 9 (7%) lost at least 30%.

Table 2 demonstrates the response of the 182 patients treated with amphetamine according to whether their orthostatic water retention during their water load testing was under 55%, or under 75% or 75% or greater. The best results as far as numbers losing weight and the amount of weight lost were seen in the patients who retained the most fluid in the erect position.

Table 2

Response to amphetamine therapy correlated with water load test results (n=182).

Water load test results in erect position

| # of Women Losing At Least | 55% to | | | ≥ 75% |
|----------------------------|--------|-----|--|-------|
| | 55% | 74% | | |
| 10% | 52 | 68 | | 4 |
| 15% | 39 | 45 | | 1 |
| 20% | 29 | 25 | | 0 |
| 25% | 19 | 10 | | 0 |
| 30% | 9 | 5 | | 0 |
| <hr/> | | | | |
| Women < Losing < 10% | 2 | 9 | | 47 |

The classic definition of idiopathic edema requires that the patient retain at least 55% of the ingested water load in four hours. Using this definition 58 of the 200 women (29%) in the study fulfilled the criteria to be considered as having idiopathic orthostatic edema; 52 lost at least 10% of their baseline weight, 2 failed to lose sufficient weight and 4 were in the group of 18 who refused dextroamphetamine therapy.

Normal people will excrete 75% or more of the ingested water load in four hours in both the supine and erect position. Therefore, the response to amphetamine was correlated with women excreting under 75% of the water load in the erect position. On this

basis 144 (72%) would have abnormal orthostatic water retention including 120 amphetamine responders, 11 non-responders and 13 from the group of 18 that refused amphetamine therapy. Thus, only 58 of the 182 women (32%) treated with dextroamphetamine failed to lose weight and 47 of these failures (81%) were in the group having 75% or greater excretion of the water load. In contrast only 11 of 131 women (8%) failed to lose at least 10% of their initial weight when the water load excretion was under 75%.

The number of patients in the first six month study who were calculated to have probably still consumed less than 90% of their calculated average calories needed for weight maintenance were as follows: hydrochlorothiazide - 6; spironolactone - 12; dextroamphetamine - 9; captopril - 7. There were 26 women of the 132 women treated by amphetamine only during the second six month study who ingested less than 90% of their calculated average calories, but 19 also ingested an insufficient number of calories during the first six months on non-amphetamine therapy.

The etiology for the inability to lose weight by a group of women who appeared to be dieting appropriately was hypothesized to be possibly on a fluid retention basis. A comparison was made between a standard diuretic (hydrochlorothiazide) versus 3 other therapies where there has been evidence of their efficacy in the treatment of the condition idiopathic orthostatic edema (spironolactone

(Streeten et al, 1960), dextroamphetamine sulfate (Greenough et al, 1962), and captopril (Docci, et al, 1983)). A placebo control was not possible because these highly motivated patients were desperately seeking help and they would not have agreed to a placebo. However, there was a genuine attempt made to be equally encouraging about all 4 therapies.

By far the best response was seen by the patients taking amphetamine and though this drug is also known to be an appetite suppressor, the mechanism of action in these cases did not appear to be on the basis of caloric restriction.

Only a significant minority of these patients (36%) appeared to have classic idiopathic orthostatic edema. However, by relaxing the degree of water retention to at least 26% instead of 46% then the majority of these patients (72%) did demonstrate orthostatic fluid retention. Whether the patients in the group who excrete more than 55%, but less than 75%, of the ingested water load have a milder form of idiopathic orthostatic edema remains to be proven, the fact remains that this modified water load test can predict those patients likely to lose weight with amphetamine

therapy. Close questioning of these patients did reveal many similar signs and symptoms attributed to idiopathic edema, e.g. pedal edema by end of the day, abdominal distention by end of day, nocturia and decreased urination when standing.

In contrast to its effect on appetite suppression where a tolerance develops to the drug requiring constant increments, tolerance does not seem to occur when used for fluid retention. Side effects were minimal at this dosage and only a few were not able to continue therapy because of side effects which included palpitations (n=2), insomnia (n=1), paranoia (n=5) and depression (n=3).

Unfortunately, amphetamines at higher doses may be addicting and have the potential for abuse. Many governmental agencies have therefore limited the use of amphetamines. Hopefully, these studies will encourage researching a drug possibly having its action on capillary permeability, but without these potential problems with amphetamines. Until that drug is found, if amphetamines are to be employed for recalcitrant overweight problems we support governmental regulation of these drugs and we emphasize that our data supports that the patients most likely to respond are those who are already dieting appropriately and appear to have some degree of orthostatic fluid retention and need to have all other medical reasons for decreased ability to excrete a free water load excluded by appropriate clinical and laboratory studies.

The response to amphetamines without restriction of calories does not prove that the dextroamphetamine definitely worked by inhibiting fluid retention. Some other metabolic effect may have been responsible. The failure to respond to hydrochlorothiazide is more supportive than non-supportive of the fluid retention hypothesis since the classic idiopathic orthostatic edema responds to amphetamines, but not to standard diuretics. Further support for orthostatic fluid retention as the etiology for the overweight problem rests with the fact that 29% of this group showed severe orthostatic water retention and 72% mild compared to a group of 50 women (unpublished data) seen for infertility without any problem in weight control who showed no one with over 45% fluid retention and only 12% with over 25% orthostatic water retention.

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