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Mastalgia and total body water

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Summary

Total body water (TBW) was measured early and late in a menstrual cycle in 56 women, 39 of whom had breast pain. The remainder were asymptomatic controls. Most women did not conform to the traditional view that there is a premenstrual increase in TBW. In some TBW decreased, while in others there was no change from the early cycle measurement. No TBW pattern correlated with any syndromes of breast pain or with any psychoneurotic profile.

Introduction

Mastalgia causes distress, particularly since the patient often assumes that it is associated with cancer. Sleeplessness and irritability are often ascribed to it, and surgeons may be asked to provide treatment. At the Cardiff breast clinic, some 50 new patients are seen every month, and in about five of these breast pain is the sole complaint. Many clinicians think of mastalgia as part of the premenstrual syndrome, but accounts of the syndrome, although they describe the sensations of breast distension, do not highlight breast pain as a major component.[1] Dysmenorrhoea has been distinguished as a different clinical entity from the premenstrual syndrome.[2] Other symptoms of the premenstrual syndrome are rarely present in premenopausal women presenting with mastalgia, yet 30% of our patients complain of dysmenorrhoea. Mastalgia has been defined as premenstrual breast pain associated with breast nodularity severe enough to demand active treatment,[3] but we have seen patients in whom the symptom occurs other than premenstrually and even after the menopause.

While weight and water fluctuations during a menstrual cycle occur in women with and without premenstrual symptoms, these increases are not invariably associated with the premenstruum.[4 5] Furthermore, cyclical symptoms are not necessarily correlated with an increase in total body water (TBW).[6 7] For example, a decrease in TBW has been reported as accompanying depression found premenstrually and at other times.[8]

We have tried to clarify the role of body water in the aetiology of cyclical mastalgia by comparing body weights and TBW volumes during one menstrual cycle in patients with mastalgia and in symptom-free age-matched controls. We set out to show what changes in body weight and TBW occurred during the menstrual cycle and whether these changes were the same for patients and controls and for patients whose symptoms were always premenstrual and those who had mastalgia at other times. We also sought a correlation between mastalgia and cyclical changes in weight or water and any psychoneurotic traits, as shown by a questionnaire.

Methods

Informed consent was obtained from patients and controls. Tritiated water (200 μCi) was used to measure TBW, and the dose and method were approved by the Medical Research Council Isotopes Advisory Panel. Whole-body irradiation with this dose was 22 mrads, and tissue irradiation amounted to 40 mrads.[9] Body weight and TBW were measured on the 5th and 25th days of a single cycle in those women who had 28-day cycles and on equivalent days in women with longer or shorter cycles. The women were asked to wear the same clothes for each visit and to fast between 9 am and 12 noon, the times between which the measurements were made.

The method was based on that of Haxhe.[10] Height and weight were measured, and 5 ml of blood was taken into a heparinised tube and used as a background reference. Tritiated water (200 μCi) (Radiochemical Centre, catalogue number TRS 1P) was drunk from a phial, followed with 50 ml of deionised water to wash the phial. Three hours later a further 5-ml blood sample was taken into a heparinised tube. If not counted immediately plasma samples were stored in airtight plastic containers at −40 C. Urine was not collected since the specific activity of body water is not altered by its excretion.[11] Counting was done on an Intertechnique SL-30 liquid scintillation counter; 0·3-ml plasma samples were measured in pairs together with a pair of samples to which had been added an internal standard to determine the efficiency of counting. Results were obtained on punched paper tape and processed by an Intertechnique Multi-8 computer. Values for the TBW and standard deviations of the counting error were obtained.

Clinical information was documented on a proforma by a consultant surgeon on the first two occasions the patient was seen. Controls were not examined, but a history proforma was completed. The 48-item Middlesex Hospital questionnaire was used to assess psychoneurosis.[12] The forms were filled in at home, without help, and the scoring was carried out by one of us (PEP). The scores obtained were evaluated by comparison with specific groups.[13] Statistical analysis was performed by Sumlock 340 Statistician to compare control and patient values by means of Student's *t* test.

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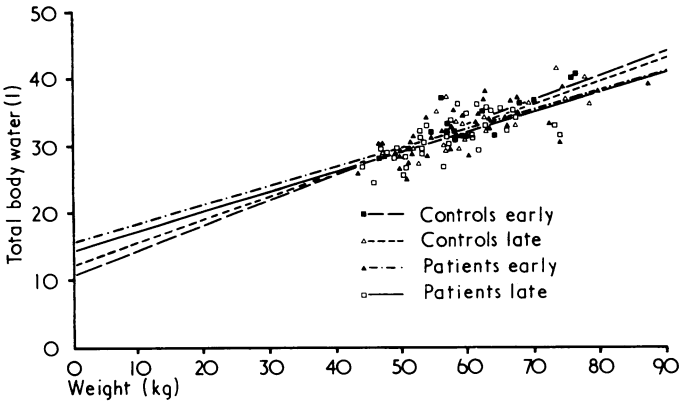
Results

Satisfactory measurements were obtained in 39 patients and 17 controls. Table I shows that the physical and physiological characteristics of the two groups were comparable. In most women there was a significant correlation between changes in body weight and water balance (see fig), correlation coefficients being 0·7 for all subjects on all occasions.

TABLE I—*Details of women studied. Results are means ± 1SD*

	No	Age (years)	Height (cm)	Weight (kg)	Cycle length (days)
Controls ..	17	33·2 ± 6·3	160·6 ± 5·3	61·2 ± 8·0	29·4 ± 5·4
Patients ..	39	35·9 ± 8·8	159·7 ± 5·8	59·0 ± 9·6	26·9 ± 2·2



Correlation between changes in body weight and water balance (r=0·7 for all women on all occasions).

The overall pattern of the change in the ratio of TBW to body weight between the early and the late measurements, calculated assuming ±1 SD error in counting plasma and 1 kg in measuring weight, was not significantly different in the two groups (χ^2 test; table II). There was no statistical difference for either controls or patients between the weights and TBW volumes on the fifth day of the menstrual cycle and those on the 25th day (table III).

Table IV shows that there was no statistical difference in the change in the TBW:body weight ratio between patients and controls or patients with pain at a particular time or site and other patients with symptoms at different times or sites. The difference in the TBW:body weight ratio between the 5th and 25th days in the controls was also compared with the values for patients without psychoneurosis and for those with one or more of the psychoneurotic traits—general anxiety, phobia, obsession, somatic anxiety, and depression. No trait was accompanied by a significant premenstrual trend in the TBW:body weight ratio (table V).

TABLE II—*Patterns of change in TBW: body weight ratio between 5th and 25th days of cycle*

	Controls	Patients	Total
Increased	3 (18%)	4 (10%)	7 (12·5%)
Decreased	2 (12%)	5 (13%)	7 (12·5%)
Unchanged	12 (70%)	30 (77%)	42 (75%)
Total	17 (100%)	39 (100%)	56 (100%)

TABLE III—*Mean (±1SD) body weights and TBW early and late in cycle*

	5th Day		25th Day	
	Weight (kg)	Body water (l)	Weight (kg)	Body water (l)
Patients ..	58·9 ± 7·9	32·33 ± 3·75	59·0 ± 9·55	32·03 ± 3·77
Controls ..	61·1 ± 8·1	33·76 ± 3·71	61·3 ± 7·9	33·44 ± 3·63

Discussion

The method of using tritium to measure total body water is reproducible and gives results comparable to those obtained by non-radioactive methods.[14] We tested the reproducibility of tritium assay in our hands by comparing different methods and by repeat counting of samples.[15] Further evidence on reproducibility was provided by the fact that values for volume of water per unit body weight were not statistically different in a group of 15 women in whom measurements were made in different cycles. Since correlation coefficients of changes of water with weight were not significantly different ($P > 0·05$) any changes observed in body weight may be regarded as changes in body water. This correlation was found by Bruce and Russell[6] and by Hill *et al.*[16]

Cyclical mastalgia, adenosis, and cystic disease of the breast have been regarded as a spectrum of abnormal response of the gland to pituitary and ovarian hormones.[1] This hypothesis has provided the basis for prescribing various hormones to attempt to relieve symptoms.[17] Other than the description by patients of the feeling of distension in their breasts, and Ingleby's discovery of a close correlation between subjective impressions of volume change and volumes measured in asymptomatic women,[18] no theory to justify the use of diuretics for premenstrual mastalgia has been proposed. Nevertheless, these agents are often prescribed for this condition.[3] Their inadequacy in both mastalgia and the premenstrual syndrome has been reported.[19] Bruce and Russell[6] in a careful metabolic study of premenstrual tension concluded that the association between it and water retention was tenuous.

Our study of TBW showed no association between water retention and mastalgia. A difference between breast pain as a

TABLE IV—*Comparison between mean (±1SD) changes in TBW:body weight ratio between 5th and 25th days of cycle in various groups*

Group	No in group	Change in ratio	Group	No in group	Change in ratio	Significance
Controls	17	−0·5 ±3·02 *v*	Premenstrual pain	27	−0·06 ±3·48	NS
			Other pain	12	−1·09 ±3·46	NS
			Bilateral pain	16	−0·62 ±2·61	NS
			Unilateral pain	23	−0·4 ±4·07	NS
Premenstrual pain ..	27	−0·06 ±3·48 *v*	Other pain	12	−1·09 ±3·46	NS
Bilateral pain	16	−0·62 ±2·61 *v*	Unilateral pain	23	−0·4 ±4·07	NS

TABLE V—*Comparison between mean (±1SD) changes in TBW:body weight ratio between 5th and 25th days of cycle in patients grouped according to psychoneurotic traits*

Group	No in group	Change in ratio	Group	No in group	Change in ratio	Significance
Controls	17	−0·65 ±3·02 *v*	"Normal"	7	−0·04 ±3·18	NS
			General anxiety	17	−0·95 ±3·19	NS
			Phobia	6	−1·67 ±4·00	NS
			Obsession	8	−0·61 ±1·98	NS
			Somatic anxiety	13	−0·55 ±4·99	NS
			Depression	6	−2·91 ±4·29	NS

solitary symptom and premenstrual tension as a syndrome is suggested by the fact that in our study of the former significant reductions in TBW during the premenstruum occurred in only five out of 39 patients, only one of whom had a depressive personality trait, while Herzberg found a significant decrease premenstrually in 11 nuns with severe premenstrual tension. Possibly diuretics taken in the premenstruum might induce depression.[8] In our study no single psychoneurotic trait or cluster of traits was characterised by either an increase or a decrease in total body water.

Conclusions—Although there may be some cases of cyclical mastalgia in which an increase in premenstrual water contributes to the symptom, the prescription of diuretics for most patients with this condition has no rational basis. The need for a simple means of recognising those, if any, likely to be helped by diuretics is apparent and other methods of treating the condition should be evaluated.

We are grateful to Mr M Baum and Mr P M Bolton for referring patients. We also thank the hospital staff who volunteered as controls, in particular Miss Joyce Wells, teaching department, Cardiff Maternity Hospital, who encouraged her colleagues to participate. Mr Mostyn Kearle constructed the computer program and Mr Robert Newcombe gave statistical advice. The work was done while one of us (PEP) was in receipt of a grant from the Medical Research Council.

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Regulation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase activity in type II hyperlipoproteinaemia

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Summary

The regulation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase activity in leucocytes was studied in a family with familial type II hyperlipoproteinaemia (WHO classification). The propositus was heterozygous and 16 other members of the family were studied. Leucocytes were isolated by a relatively quick and simple procedure and used for enzyme estimations. The results suggest that measurement of the regulation of this enzyme in leucocytes may be helpful in the diagnosis and management of the condition.

Introduction

Familial type II hyperlipoproteinaemia (WHO classification), an inherited metabolic disorder, is characterised by the accumulation of low-density lipoproteins transporting cholesterol in the blood. Homozygous patients have raised cholesterol levels (over 13·0 mmol/l; 502 mg/100 ml), xanthomata and vascular disease appearing at an early age. Heterozygotes also have an increased incidence of premature vascular disease, which is quantitatively more important because of the frequency of the heterozygous state.

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An important rate-determining step in cholesterol biosynthesis is catalysed by 3-hydroxy-3-methylglutaryl coenzyme-A reductase (EC 1.1.1.34; HMG CoA reductase). Although most studies have used rat and mouse liver systems, available evidence indicates that this is also true in man. Thus Williams and Avigan[1] reported the stimulation of acetate incorporation into cholesterol in human fibroblasts and leucocytes in culture when the medium contained delipidated instead of whole serum, and suggested that this was due to induction of HMG CoA reductase. Fogelman *et al*[2] supported this hypothesis and suggested that the greater induction of HMG CoA reductase that they observed on transferring leucocytes from patients with heterozygous type II hyperlipoproteinaemia to medium containing a low lipid concentration was due to a defective sterol-binding "repressor" in the cell. Brown *et al*,[3 4] using fibroblasts from a homozygous patient, found defective inhibition of HMG CoA reductase activity in cells incubated with low-density lipoproteins and reported an intermediate pattern in heterozygotes. Their evidence suggested a defective binding of low-density lipoproteins to the cell membrane of fibroblasts in affected people.

We report the finding of defective regulation of HMG CoA reductase activity in leucocytes from a patient with familial heterozygous type II hyperlipoproteinaemia and present a study of this enzyme in the patient's family, showing the value of measuring the enzyme in identifying those affected.

Materials and methods

The propositus (subject II 7; see table) was investigated and treated as an inpatient. Members of his family were visited individually. Fasting venous blood samples were taken into tubes containing disodium edetate (final concentration 2 mmol/l) for cholesterol and triglyceride measurement, lipoprotein electrophoresis, and the isola-