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The Effect of a Low-fat Diet on Hormone Levels in Healthy Pre- and Postmenopausal Women: Relevance for Breast Cancer

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It has been postulated that differences in the levels of circulating hormones may be the explanation for the epidemiological link between per capita dietary fat intake and the incidence of breast cancer. We have investigated this possible relationship in 19 postmenopausal, and 18 premenopausal women who completed a 4-week period on a diet aiming to reduce fat intake to around 20% of total kilocalories. 7-day dietary records revealed a significant decrease in dietary fat intake in both the pre- and postmenopausal groups (from 37.2% of calories from fat to 23.2% and from 37.9 to 24.3%, respectively). There was a minor increase in the level of sex hormone-binding globulin, and a small decrease in prolactin in the postmenopausal group, which were of borderline significance. There were no significant changes in total oestradiol (E2), or non-protein-bound (free) E2 concentrations. In the premenopausal group there were no significant changes in any of the hormone levels investigated.
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INTRODUCTION

THERE ARE marked international variations in the incidence of breast cancer [1]. This, combined with the increases in breast cancer incidence in populations migrating from countries with a low incidence of breast cancer to those with a high incidence [2, 3] suggest that environmental factors may influence the incidence of the disease. One such factor is dietary fat consumption, and there is a good correlation between average per capita fat intake and breast cancer incidence worldwide [4, 5]. Animal studies have confirmed the relationship between dietary fat intake and mammary tumorigenesis, and have also demonstrated that tumour formation may be hormonally dependent [6].

In man, there is a wealth of evidence to implicate oestrogens in the aetiology and pathogenesis of breast cancer. Recent interest has concentrated on the proportion of non-protein-bound (free) oestradiol (E2), and several studies have demonstrated an increase in the levels of free E2 in patients with breast cancer [7–9]. There are also differences in the levels of non-protein-bound E2 between British and Japanese women [10], and this may partly explain the differences in breast cancer rates between the two countries.

Several dietary intervention studies have found that investigating the effects of a low-fat diet in both pre- and postmenopausal women include the suppression of plasma oestrogen levels [11–13]. It is possible, therefore, that the relationship between dietary fat intake and breast cancer may be dependent on changes in oestrogenic stimuli to the breast. In the current study we have measured plasma E2 levels, the fractional binding of E2, and prolactin levels in closely monitored groups of pre- and postmenopausal volunteers before and during their adherence to a low-fat diet for a period of 4 weeks.

POPULATION AND METHODS

73 women were interviewed regarding participation in a study involving "dietary modification, and its possible effects on

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circulating levels of hormones". The following groups were excluded from the study: perimenopausal women [i.e. women whose menstruation had become irregular but were < 2 years since last menstrual period (LMP)], women taking exogenous hormones, women on special diets, or women with irregular menstrual cycles. 20 postmenopausal women, and 21 premenopausal women agreed to participate in the study. Subsequently, one postmenopausal woman dropped out because she was already on an extremely low fat diet (< 15% kcals from fat). 3 premenopausal women dropped out, 2 because of menstrual irregularities, and 1 because she became pregnant. Thus, 19 postmenopausal, and 18 premenopausal women completed the study period of 4 weeks.

The study plan was different for pre- and postmenopausal groups, and is summarised in Table 1. The purpose of the study was explained to each postmenopausal subject without being specific about the type of diet involved. A brief medical history and the subject's weight were noted. Each subject completed a detailed 7-day dietary diary and then made a second visit, when the intervention diet was explained in full. The aim was to reduce fat consumption to 20% of kilocalories, without reducing the total caloric intake using a number of 5 g fat exchanges, depending on the subject's original calorie intake. Weekly visits were made when blood samples were taken and further dietary advice was available. Dietary compliance was checked with a further 7-day dietary diary during the fourth week of diet, after which the subject was again weighed.

The protocol for premenopausal subjects differed as follows. Each attended their initial interview between days 4 and 7 of their menstrual cycle. Their 7-day dietary diary was complemented with a menstrual record. Blood samples were taken at weekly intervals, and the diet was commenced at the start of the following menstrual cycle.

In order to avoid the effects of any diurnal variations in hormone levels, blood samples were collected at the same time of day on each visit.

Hormone analysis

E2 [14], prolactin (Prl) [15] and sex hormone-binding globulin (SHBG) [16], were assayed by previously described methods. Free E2 was assayed by an ultrafiltration process, using the Amicon MPS 1 microseparation system, with YMT membranes (Amicon Ltd., Stonehouse, UK). The concentration of free E2 was calculated from the total E2 concentration and the percentage free E2. The within-assay coefficients of variation were < 10% for all analytes.

The 7-day dietary records were coded [17] and recorded on a computer database at the Royal Marsden Hospital. Total energy intake, together with the dietary fat intake were obtained in this way for each subject during the baseline and dietary intervention periods.

Table 1. Study plan for post- and premenopausal subjects

Postmenopausal											
Weeks on diet	Base	Base	1	2	3	4					
Bloods	X	X	X	X	X	X					
7-Day dietary record	X-------X				X-------X						
Premenopausal											
Day of cycle	4-7	11-14	18-21	25-28	4-7	11-14	18-21	25-28	4-7		
Weeks on diet					Start	1	2	3	4		
Bloods	X	X	X	X	X	X	X	X	X		
7-Day dietary record	X-------X							X-------X			

Table 2. Dietary changes as assessed by 7-day dietary records in post- and premenopausal subjects

	Calorie intake (kcal/24 h)	Fat intake	% Calories from fat (g/24 h)	Body Weight
Postmenopausal				
Base	1624 (372)	67.5 (20.1)	37.9 (5.3)	64.1 (8.9)
Diet	1367 (397)	37.3 (15.5)	24.3 (9.6)	62.7 (8.4)
P^*	0.003	0.0001	0.0001	0.001
Premenopausal				
Base	1768 (356)	72.0 (24.1)	37.2 (5.2)	61.8 (7.1)
Diet	1403 (356)	35.8 (14.1)	23.2 (6.1)	61.3 (7.3)
P^*	0.0001	0.0001	0.0001	N.S.

Values are expressed as mean (S.D.).
N.S. = Not significant.
*Paired *t*-test

All the hormone concentrations were log-transformed prior to statistical comparison. The mean baseline concentrations were compared with the mean concentrations during the intervention period, for each individual subject, using paired *t*-tests, as described by Matthews *et al.* [18]. The differences in hormone levels from the baseline values (Δ values) were also calculated. As these values were normally distributed, statistical comparisons were made using arithmetic error estimates.

RESULTS

The results of dietary compliance are shown in Table 2. Significant reductions were achieved in both the total amount of fat ingested, as well as the percentage of calories derived from fat. This was true of both pre- and postmenopausal groups. However, despite efforts to ensure that the diet remained isocaloric, there was also a significant drop in the energy intake for both groups (by a mean 16 and 21% for the post- and premenopausal groups, respectively). This was associated with weight loss in both groups over the 4-week intervention period, although this was only significant in the postmenopausal group. Dietary compliance was variable, with 2 subjects failing even to achieve a reduction in fat intake to 30% calories from fat.

The dietary compliance questionnaire was completed by 71% of subjects. Whilst 80% of the respondants found the fat exchanges easy or relatively easy to understand, practical problems in complying with the dietary advice were experienced in compliance, particularly when eating out or catering for a family. Poor palatability of a low fat diet was also noted as a difficulty. The majority of respondants (81%) stated that they would be prepared to stay on the diet long-term if there was an incentive, e.g. proof of benefit from the diet.

The mean changes in hormone levels from baseline throughout the dietary intervention period are shown graphically in Fig. 1. In the postmenopausal group levels of E2, per cent free E2 and concentration of free E2 were lowered during the diet, but this did not reach statistical significance. There was also a decrease in the level of prolactin (Prl) during the intervention period, and an increase in the levels of sex hormone-binding globulin (SHBG), but these changes were also of borderline significance ($0.05 < P < 0.10$).

The premenopausal group also showed non-significant

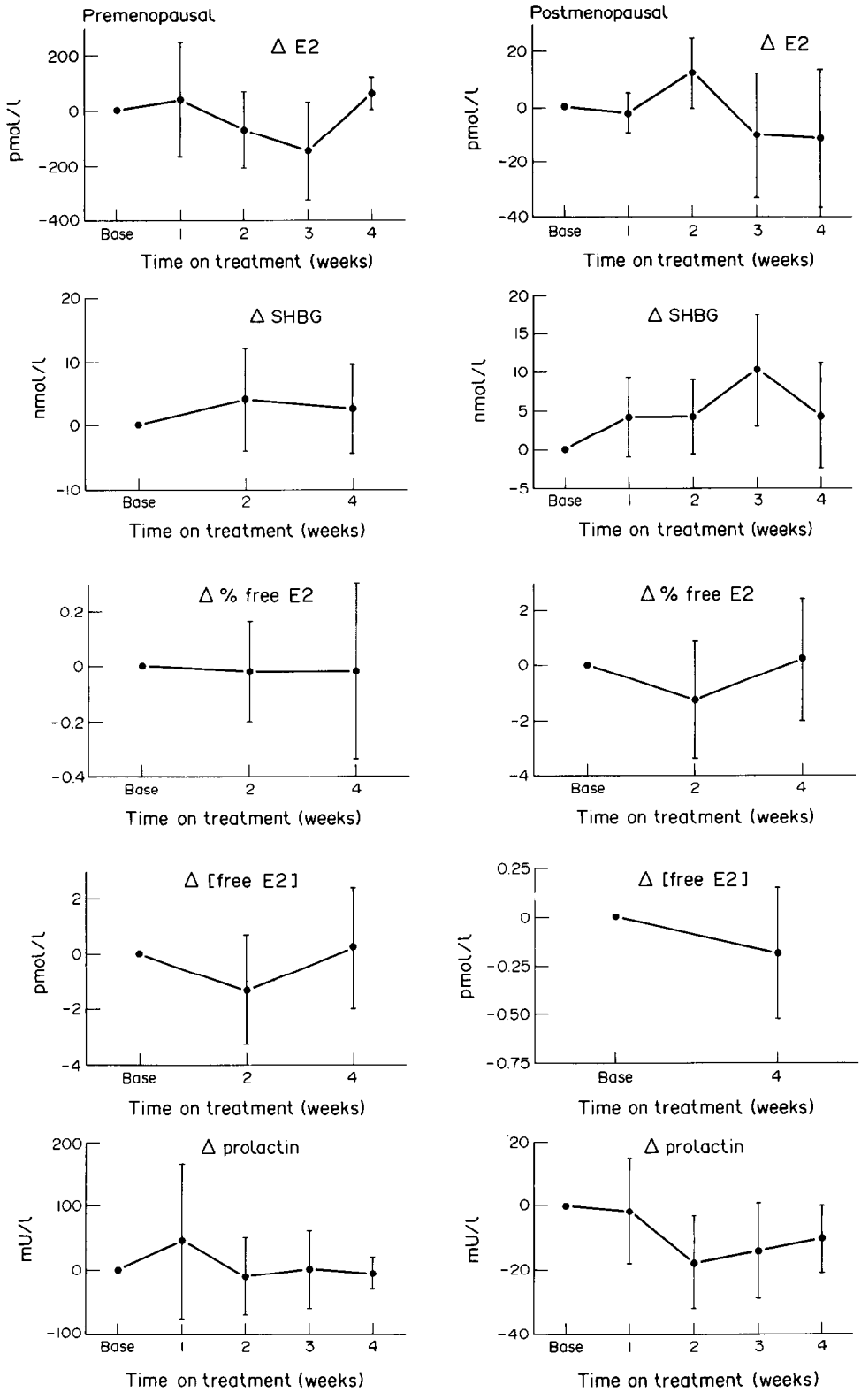

Fig. 1. Mean changes in hormone levels in pre- and postmenopausal volunteers on a low-fat diet. Error bars show 95% confidence intervals.

decreases in the levels of total E2, percentage free E2 and concentration of free E2. There was no difference in the levels of Prl or SHBG. Since compliance was variable, separate analysis of those subjects achieving a reduction to 20% or less of calories from fat was undertaken, but this did not reveal any significant differences from the overall results.

DISCUSSION

The reduction in percentage energy intake as fat from 38 to 24% achieved by the volunteers compares favourably with the results obtained by Rose *et al.* [11], but is not as good as the results of Ingram *et al.* [12], or Prentice *et al.* [13]. We have not confirmed the statistically significant changes in the levels of

oestrogens shown in these studies, although the changes in the current study were in the same direction. This may be due to the short period of intervention in our study: Rose *et al.* [11] did not demonstrate a significant lowering of oestrogen levels until after 3 months of dietary intervention, and the intervention period of the other studies was at least 2 months. It may be that any changes in levels of circulating oestrogens take longer than 4 weeks to manifest themselves.

At recruitment, our volunteers were required to complete 4 weeks on the diet to be assessable and they were asked to stay on the diet thereafter if they could. The small number of volunteers who continued made endocrine analysis of the post-4-week period of very limited value. The practical problems with the diet appeared to be the main reason for this lack of persistance.

The postmenopausal women in our study showed a 7% increase in the levels of SHBG. This was of borderline significance, and was not accompanied by a corresponding significant decrease in the levels of free E2. It may be that this change is related to the significant weight loss rather than to the decrease in dietary fat intake *per se* in this group [24]. In the premenopausal group, there was no significant change in SHBG levels or weight during the dietary intervention.

In the postmenopausal group, Prl was lowered by about 9% during the diet period. Again this was only of borderline significance. It has been postulated that prolactin plays a role in the aetiology of breast cancer [19]. The evidence that Prl levels are lowered by a low fat diet is mixed [20–23].

We have, therefore, shown small, statistically non-significant changes in the levels of circulating hormones over a 4-week dietary intervention period. The relatively small number of subjects studied and the highly variable nature of some of the parameters probably contributed to our inability to confirm some previous data. All the changes demonstrated (with the exception of premenopausal SHBG and Prl levels, which were unchanged), were in the direction that might be expected to be associated with a reduction in the levels of oestrogens and Prl, and an increase in the level of SHBG. If breast cancer develops as a result of cumulative exposure to hormones [25], then it is possible that such small changes, if sustained over a long period of time, could have an effect on risk. It is also possible that any changes in hormone levels brought about by a change to a low fat diet take time to develop, and further work is necessary to determine the effects of a long-term lowering of fat intake on circulating hormones. However, if a low-fat diet is to be studied over an extended period of time, the subjects need to be highly motivated.

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