Investigation of serum sex hormone levels in postmenopausal patients with multiple benign breast lesions detected by mammography

Gy Liszka¹, I Számel², I Pete³, Á Petrányi¹, N Udvarhelyi⁴ and B Budai²

¹Mammographical Screening Center, ²Clinical Research Department, ³Department of Gynaecology and ⁴Department of Molecular Pathology of the National Institute of Oncology, H-1122 Budapest, Ráth Gy u 7-9, Hungary

Abstract
The mammographic appearance of the female breast is influenced by physiological changes related to normal ageing (menopause), endocrine dysfunction, or the combined effects of these factors. During the period from 1 October 1995 to 30 November 1996, mammographic screening was performed on 2356 females from a Budapest district and multiple benign breast lesions (MBBL) were diagnosed in 211 (8.94%) subjects. The hormonal background of this lesion was explored by measuring serum sex hormone levels (oestradiol (E2), progesterone, testosterone, prolactin, FSH and LH) on 40 subjects randomly selected from both Group A (women with involutional changes only) and Group B (patients with MBBL). Serum E2 levels were considerably, but not statistically significantly higher in patients with MBBL (102.2±40.2 vs 50.8±18.7 pmol/l), whereas the elevations of serum progesterone (2.29±0.4 vs 0.901±0.5 nmol/l, P =0.0325) and LH (64.3±9.4 vs 48.9±13.9 IU/l, P =0.0194) levels were statistically significant.

In patients with MBBL, parallel histological studies revealed persistent lobules with cell atypia. Consequently, MBBL with distinct radiomorphological features may result from endocrine dysfunction associated with the postmenopausal period. In such cases, cell atypia is more commonly diagnosed by histology. Accordingly, MBBL can be considered as a precancerous lesion. The changes in hormone levels observed suggest that endocrine dysfunction is accompanied by a slight impairment of negative feedback regulation, and regular clinical and laboratory screening of the risk population is recommended.

Introduction
Mammographic screening programme models designed to estimate the incidence of breast cancer in the 50- to 65-year-old female population of individual regions of Hungary started in May 1995 under sponsorship from the World Bank. A computerised database has been generated during this period from data accumulated on the family history of neoplastic disease, identified risk factors, performed operations and details of hormone replacement therapy. Supplementary investigations (including ultrasonography, cytology, cone biopsy, hormone level measurement and genetic testing in cases with a positive family history) have been performed on patients with mammographic abnormalities. Processing and analysis of compiled data focused our attention on a highly characteristic radiomorphological feature, the so-called ‘post-menopausal mastopathy’, that is, a benign lesion comprised of numerous small, 2-5 mm rounded foci. In our publication we called this radiomorphological feature multiple benign breast lesion (MBBL). In the literature, such lesions are thought to result from hormonal dysfunction and histologically persistent and atypical lobules with fibrosis (Wellings et al. 1976, Powell 1992). This paper discusses the hormonal background of these radio-morphological changes generally observed in post-menopausal women.
Patients and methods

During the period from 1st October 1995 to 30th November 1996, mammography screening was performed at the National Institute of Oncology, on 2356 symptom-free females from the 50- to 65-year-old population of a certain district. None of the patients was perimenopausal. Out of the 2356 patients 983 were included in our examination. From the 983 women 772 patients had physiological involution of their mammary tissue (Group A), and 211 subjects suffered from MBBL (Group B). From both groups 40 women were randomly selected for our investigation. We aimed to create two homo-geneous groups. The inclusion criteria were as follows: (a) age between 55-59 years, with a minimum of 5 years after physiological menopause; (b) the years of their births were even numbers, the months were odd numbers; (c) age at first menstruation was between 12-15 years (Group A: 13.54±1.38 years and Group B: 13.55±1.51 years (means±S .D .)); (d) age at first parturition was between 20 and 25 years (Group A: 22.68±3.15 years and Group B: 22.61±2.04 years (means±S .D .); the number of deliveries was 1.71±0.70 and 1.65±0.64 in Group A and B respectively); (e) there was no family history of breast carcinoma or other malignancy; (f) none of the women was given any hormone replacement therapy (HRT). The women were asked to sign an informed consent form before starting the study.

Radiography was performed with a General Electric CGR SA Sonographe 600 T Seix HF mammography unit, using 3M mammography films. None of the lesions detected in Groups A or B are considered indications for performing a breast biopsy.

The hormonal status of 40 patients randomly selected from each group was evaluated in order to investigate potential endocrine mechanisms leading to the development of breast lesions. Blood samples were taken in the morning before a meal, centrifuged and the sera were stored at −20 °C until assay. Serum sex hormone levels were measured. Oestradiol (E2), progesterone, testosterone, and prolactin concentrations were determined by RIA. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured by IRMA method. Commercially available kits were used (E2: Orion Diagnostica, Turku, Finland; progesterone, FSH and LH: Isotope Institute Ltd, Budapest, Hungary; prolactin: OSSKI, Budapest, Hungary; testosterone: Biodata, Rome, Italy).

Results

Evaluation of the mammographic appearance of the breast in the 2356 study subjects revealed physiological changes (attributed to physiological involution) in 772 patients (32.7%); these subjects were assigned to Group A. A mammary lesion of characteristic radiomorphological appearance (MBBL) was observed in 211 patients (8.94%) assigned to Group B. MBBL is manifested by numerous oval, 2-5 mm foci dispersed in 25-50% of mammary tissue volume, together with common involu-tional changes. Characteristic involutional changes comprised histo-logical features previously well documented in the litera-ture (Powell 1992). In accordance with the literature (Wellings et al. 1976, Powell 1992), focal radiological changes corresponding to persistent lobules were observed histologically in MBBL. In the MBBL group the mass body index (MBI) proved to be quite normal compared with group A as calculated by the Mann-Whitney test ($P=0.0187$).

Comparative investigations on the hormonal status of subjects with involutional changes or MBBL revealed significant differences (Table 1). Although serum E2 levels were remarkably higher in MBBL patients than in females with involutional changes, the absolute values were within the normal range. Progesterone levels were significantly higher and exceeded the upper limit of the normal range in the MBBL group (2.29±0.4 vs 0.901±0.5 nmol/l; $P=0.0325$). Among the gonadotrophins, MBBL patients had significantly higher LH levels than controls with involutional changes only (36.2±4.8 vs 17.2±3.6 IU/l; $P=0.0194$). It must be emphasised, however, that this elevation should not be considered as abnormal, since LH levels remained within the normal range. No significant

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\text{Sex hormone} & \text{Normal range} & \text{Group A} & \text{Group B} \\
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\text{E2 (pmol/l)} & 20-150 & 50.8±18.7 & 102.2±40.2 \\
\text{Progesterone (nmol/l)} & 0.3-1.38 & 0.901±0.5 & 2.29±0.4* \\
\text{Testosterone (nmol/l)} & <3.47 & 1.28±0.3 & 1.04±0.2 \\
\text{FSH (IU/l)} & 30-135 & 48.9±13.9 & 64.3±9.4 \\
\text{LH (IU/l)} & 13-80 & 17.2±3.6 & 36.2±4.8** \\
\text{Prolactin (mIU/l)} & 163-488 & 250±11 & 338±90.1 \\
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* $P=0.0325$, ** $P=0.0194$ compared with Group A
differences have been observed between the serum concentrations of other hormones investigated.

Discussion

Benign disease of the breast is thought to originate from endocrine dysfunction. Our observations support this hypothesis: serum E2 levels were higher in MBBL patients than in involutional controls (102.2±40.2 vs 50.8±18.7 pmol/l). A permanent insufficiency of progesterone production and a relative dominance of E2 are some of the pre-requisites for the development of benign breast disorders (such as mammary dystrophy or dysplasia) (Fournier et al. 1983). In contrast, Rolland et al. (1981) have detected reduced E2 as well as progesterone levels in patients with fibrocystic breast disease. Accordingly, in patients with fibrocystic disease, a tendency for relative oestrogen preponderance can be observed together with reduced progesterone levels. Colin et al. (1978) have found both reduced serum E2 and progesterone levels in patients with mastodynia.

At the menopause, dramatic changes in endocrine functions occur. Ovulation ceases and progesterone synthesis decreases due to the absence of the corpus luteum, leading to the relative dominance of oestrogens. Naturally, the rate of oestrogen production is also reduced and decreases progressively with age (Sas & Szontágh 1981).

During the postmenopausal period, the major source of oestrogens comes from the conversion of circulating androstenedione into oestrone and then into oestradiol, mainly in the adipose tissue but also in the liver, muscle and in normal and cancerous glandular breast tissue. As discovered by Sitter (1982) and Santen et al. (1986) adrenal steroids are converted into oestrone through aromatisation, which is then transformed into E2 by the enzyme 17β-hydroxylase. Consequently, the mechanism androstenedione→oestrone→E2 is presumably the sole and only biochemical pathway available for the biosynthesis of steroid hormones in postmenopausal women. A similar biochemical pathway for progesterone biosynthesis would be cholesterol→pregnenolone→progesterone (James et al. 1986).

According to our findings, MBBL comprises persisting lobules with (occasionally) abnormal hormone levels in the serum. Changes in serum sex steroid levels in our patients are summarised as follows: (1) E2 levels were considerably but not statistically significantly higher in patients with MBBL compared with normal females; (2) progesterone levels of patients with MBBL were statistically significantly higher than in controls; (3) although progesterone excess should have decreased LH levels, these were statistically significantly higher in MBBL patients than in controls with involutional changes only.

This study was not designed to measure hormone levels in breast tissue itself. Therefore, one can speculate that the excessive quantity of progesterone present in serum does not provide sufficient protection, that is, it does not exert an anti-oestrogenic effect at all. Moreover, progesterone excess can create a hormonal milieu that favours in situ steroidogenesis in breast tissue. The end product of the biochemical pathway 17α-hydroxyprogesterone→androstenedione→oestrone→E2 is a physio-logically active oestrogen, a hormone of aetiologic significance in breast cancer (Castagnetta et al. 1996).

In conclusion, our findings on sex hormone levels obtained in postmenopausal women with mammographically demonstrated MBBL suggest the following: (1) postmenopausal MBBL probably results from an endocrine dysfunction, as evidenced by the relatively high progesterone and LH levels; (2) high progesterone levels can facilitate the development of breast dysplasia or cancer through the accumulation of E2 (from the biochemical pathway detailed above) or – as described elsewhere (Brinton et al. 1988, Pike et al. 1993, Toniole et al. 1995) – by a direct action of progesterone on the breast tissue; (3) MBBL induced by endocrine changes and characterised by distinct mammographical and histological features should be considered as a precancerous lesion. This is proven by the fact that, in agreement with the opinion of others (Wellings et al. 1976), cell atypia of variable degree has been found in persisting ducts; (4) the hypothesis is that MBBL induced by endocrine dys-function is a potential risk factor for development of breast cancer. The pattern likewise demonstrated histopathological evidence for periductal and perilobular fibrosis and showed more nodular and focal lesions of the terminal lobular units with increasing grades of atypia (Powell 1992). Persistent mammary lobules after the menopause with atypia form a continuum between normal lobules and carcinoma in situ (Wellings et al. 1976).

Therefore, remarkable elevation of certain sex hormone levels (progesterone, LH) in MBBL suggests an aetiologic role of the hormonal milieu in the development of this lesion, similar to the fibrocystic breast diseases (Számél et al. 1994, 1996). Accordingly, these patients should be considered as a high risk population for breast cancer.

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