Endocrine Function in the Elderly

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Many different changes in endocrine function with age have been described. To give just some of many possible examples, there are increases in the levels of growth hormone in women, rises in thyroid stimulating hormone, modest decreases in triiodothyronine, and increased sensitivity of response to antidiuretic hormone (1). Levels of norepinephrine rise (2) and there are altered circadian patterns for cortisol, norepinephrine, and growth hormone (3). There are falls in renin and aldosterone levels (4) and a rise in parathyroid hormone levels, although this seems to be entirely due to decreased renal excretion (5). Pancreatic polypeptide and gastrin show rises with age, although other gut hormones do not appear to change (6).

However, these and many other described changes are generally small and of doubtful importance in a practical sense. They are certainly dwarfed by the important and major changes in sex hormones and gonadotropins, and this chapter will therefore concentrate on this area.

Changes in sex hormones and trophic hormones occur in both sexes with aging. Obviously the changes are far more dramatic in women in relation to the abrupt cessation of estrogen secretion by the ovary at the time of menopause. However, although there is no abrupt change in testicular function with age, there is a gradual diminution of Leydig cell function so that testosterone levels fall progressively. Gonadotropins rise in both sexes in response to these falls in sex hormone production.

ESTROGENS IN POSTMENOPAUSAL WOMEN

Within a few months of menopause, levels of the most potent estrogen, estradiol, fall markedly, whereas those of estrone fall only a little so that it then becomes the main estrogen (7). The ovary loses its ability to convert androstenedione to estrone and testosterone to estradiol. The greatly reduced production of estradiol now relies on peripheral conversion of its plasma precursors estrone, androstenedione, and, to a smaller extent, testosterone, as there is no direct secretion by the ovaries or adrenals (8). Similarly, the production of estrone is almost entirely by peripheral conversion of circulating androstenedione in adipose tissue. Androstenedione is in turn secreted mainly by the adrenals, although ovarian secretion does continue at about half its premenopausal level (8). As adipocytes are the site of these peripheral
conversions, estrogen production, particularly that of the more potent estradiol, is more efficient in obese postmenopausal women (9). This explains the protective effect of obesity against postmenopausal osteoporosis that has been shown in many studies.

ANDROGENS IN POSTMENOPAUSAL WOMEN

The postmenopausal ovary continues to produce the androgens androstenedione and testosterone, although at somewhat reduced rates (8), while adrenal secretion of these two hormones and of dihydroepiandrosterone continues unchanged (10). As conversion of androgens to estrogens in the ovary no longer takes place, the net result is that total androgen levels are somewhat higher.

GONADOTROPINS AFTER MENOPAUSE

Levels of luteinizing hormone (LH) and of follicle-stimulating hormone (FSH) reach a maximum some 2 to 3 years after menopause (7) and remain elevated throughout later life by approximately four- and sixfold, respectively (11). Administration of estrogens to postmenopausal women causes LH and FSH to fall, indicating that the feedback loop is still intact and that the elevations can be regarded as secondary to the changes in the sex steroid hormones (11).

SEX HORMONE AND GONADOTROPIN CHANGES IN MEN

Although there are no abrupt changes in men comparable to menopause in women, androgens do fall somewhat with age (12) so that the main androgen, testosterone, as well as α-dihydrotestosterone have lower blood levels in elderly men. There do not seem to be any corresponding changes in estrogen levels; estrone, the most important estrogen in men, shows no age relationship (13). The position regarding gonadotropins is less clear-cut, with some workers finding no change with age, whereas others report some increase in LH beyond the age of 60 years (13).

CONSEQUENCES OF MENOPAUSE

The physical consequences of menopause such as atrophic changes in the genital tract, breast, skin, and other organs and tissues influenced by estrogens are well recognized. No less important, however, are the many metabolic consequences of estrogen withdrawal, not all of which are so well appreciated. Osteoporosis is perhaps the most serious and obvious of such changes, but there are various other changes that we should examine.
Biochemical Changes Following Menopause

Many biochemical analyses show age changes that could confound or obscure changes due to menopause itself. However, studies of women in the age groups during which natural menopause is experienced allow us to compare age-matched groups of women who are premenopausal or postmenopausal and so to allow fully for age effect. McPherson and colleagues were among the first to look systematically for such menopausal effects (14). They found that 7 of the 17 analyses they studied showed significant changes attributable to menopause itself.

Links to Bone Metabolism

McPherson et al. found a group of changes that can be linked to postmenopausal osteoporosis. Serum alkaline phosphatase and calcium showed significant elevations and there was also a nonsignificant rise in serum inorganic phosphate. Similarly, Crilly and colleagues (15) found a significant rise in both serum alkaline phosphatase and the urinary excretion of hydroxyproline. Taken together, these findings point strongly to linkage to the phase of rapid postmenopausal bone loss consequent upon estrogen withdrawal and preventable by estrogen administration. Thus, extra calcium and phosphate are released from bone into the bloodstream by the increased osteoclastic activity. This also gives increased collagen removal by destruction of bone matrix, leading to increased excretion of its degradation product, hydroxyproline. As osteoblastic activity is highly geared to osteoclastic activity, the rise in alkaline phosphatase is also readily explicable. It is of interest that the rises in phosphate and calcium persist into old age, where women have significantly higher values than men (16).

Estrogen also appears to have other effects that are relevant to bone physiology. Osteomalacia is widely recognized as being far more likely to affect old women rather than men. This may be due to differences in vitamin D metabolism between the sexes, for elderly women have significantly lower values of serum 25-hydroxycholecalciferol than men even when differences in age, dietary intake of vitamin D, and sunlight exposure are fully allowed for (17). Furthermore, the difference is quite substantial: women have values about 70% of those of men when other factors are balanced.

Urea and Electrolytes

McPherson and his colleagues also found significant elevations of blood urea and of serum bicarbonate and sodium after menopause. The changes reduced the differences between men and women in each case, although significant but small sex differences remained. This would suggest that sex hormones have important influences on renal function.

They also found that serum iron and serum aspartate aminotransferase rose
significantly postmenopausally, again having the effect of bringing values closer to those for men. The change in serum iron could perhaps be ascribed to the cessation of menstrual iron loss, but there is no obvious explanation for the change in aspartate aminotransferase.

**Uric Acid**

Others have shown a significant postmenopausal elevation of serum uric acid (18), confirming the nonspecific trend found by McPherson and colleagues (14). Again, this brings female values closer to those for males and is paralleled by a rising incidence of acute gout in older women.

**CONCLUSION**

By far the most impressive hormonal changes occurring with aging are the changes in sex hormones and gonadotropins after menopause. Reduced estrogens in older women set in motion many physiological changes, some of which appear to be seriously deleterious (most particularly those underlying the development of postmenopausal osteoporosis, which is perhaps better regarded as an integral part of normal aging than as a disease).

Other hormonal changes appear to be relatively minor in nature in comparison with these and, although they may be of academic interest, do not seem to have major practical importance.

**REFERENCES**

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DISCUSSION

Dr. Meredith: Are you aware of any longitudinal studies looking at the rather complicated endocrine changes after the menopause?

Dr. Hodkinson: There are several such studies going on but none has yet come up with any clear answers. Such studies are certainly needed. In particular, we need to come up with better predictors of postmenopausal osteoporosis.

Dr. Guesry: You have dealt with only half the population. What about men? Do you think there is any need to treat elderly men with growth hormone and testosterone, as has already been suggested, or do you think this is unnecessary?

Dr. Hodkinson: I suspect this is unnecessary, but it depends on what the aim is. If we are talking about bone disease, the problem of osteoporosis is predominantly a female one. On any kind of cost-benefit equation we shall not do well if we start treating men with testosterone to prevent osteoporosis. However, this is certainly not the case for hormonal treatment in women. Osteoporosis in older women is an immense problem. If we could only predict those who are destined to suffer most severely, the cost-benefit equation would be highly favorable.

Dr. Nestel: What is your bottom line advice on hormone replacement in postmenopausal women? When one reads about this subject it appears that, as well as getting relief from menopausal symptoms, women on estrogens have half the coronary thrombosis mortality of those not receiving estrogens, quite apart from the beneficial effects on osteoporosis.

Dr. Hodkinson: I don’t think it is yet possible to give definitive advice. However, we have to decide why we are giving hormone replacement therapy (HRT). Treatment is often given for the rather nebulous entity that is considered to be the menopausal syndrome. However, many of the symptoms ascribed to this have been shown to be more common before the menopause—headaches, for example. If replacement therapy is given with a view to preventing bone disease or vascular disease, we are talking about long-term treatment and I believe this to be quite onerous for the women who receive it. There is also the financial aspect to consider, apart from any possible risk of long-term replacement therapy (although I believe these have been exaggerated). My view is that we can afford to be very positive about HRT but we need to be highly selective in applying it.

Dr. Nestel: What do you mean by selective?

Dr. Hodkinson: We need to be able to identify groups of people whose risk is greater than average.

Dr. Nestel: So for the possible prevention of coronary heart disease, you would select only those women who have other risk factors for the condition?
Dr. Hodkinson: Yes, broadly. But one is looking at the osteoporosis problem as well. You need to combine the two: if you have high risk of either bone disease or ischemic heart disease the benefits of treatment of both are going to be very much better.

Dr. Chandra: Since the workshop is on nutrition, I wonder if you can speculate on the role of nutritional factors in modulating the hormonal changes you have described. Referring back to Dr. Guesry's question about HRT in males, we know that nutritional factors modulate testosterone levels so if we accept that in the elderly the frequency of nutritional deficiencies increases, then this may in part explain the lower testosterone levels. Testosterone is a very sensitive index of zinc intake, so even if only 20% of the population has marginal zinc deficiency in this age group, this could account for some of the differences in hormone levels. Is there any information to suggest that decline in estrogen output might be related to diet and nutrition rather than to primary gonadal failure?

Dr. Hodkinson: Decline in estrogen is a biologically programmed event. I don't think we can implicate diet in this. I accept that there are nutrients that may have an effect on the production of individual steroid hormones, but we are not talking about one estrogen. There is a plethora of estrogens and to determine whether zinc deficiency affects estrogen production you would have to measure them all—a daunting task and unlikely to yield a clear result unless there is a major effect. However, I think there is little doubt that there are interactions between hormonal status and dietary factors. Osteoporosis and osteomalacia are relevant examples. I am sure there are interactions in both directions.

Dr. Ballard-Barbash: Our National Cancer Institute has unearthed a number of studies that have examined the effect of dietary factors on estrogen metabolism. It has been postulated that several of these, including fat, alcohol, and fiber, have effects on estrogens. Early findings have confirmed effects on estrogen metabolism in several instances.

Dr. Durnin: It has been reported that exercise affects endocrine function in elderly men. Do you have any information on this?

Dr. Meredith: This also occurs in young men. Lower testosterone levels regularly occur in runners, and this is true for older men as well.