The Aging Male

ISSN: 1368-5538 (Print) 1473-0790 (Online) Journal homepage: www.tandfonline.com/journals/itam20

Estradiol in elderly men

A. Vermeulen, J. M. Kaufman, S. Goemaere & I. Van Pottelberg

To cite this article: A. Vermeulen, J. M. Kaufman, S. Goemaere & I. Van Pottelberg (2002) Estradiol in elderly men, The Aging Male, 5:2, 98-102, DOI: 10.1080/tam.5.2.98.102

To link to this article: https://doi.org/10.1080/tam.5.2.98.102

The Aging Male 2002;5:98–102

Estradiol in elderly men

A. Vermeulen, J. M. Kaufman, S. Goemaere and I. van Pottelberg

Medical Clinic, Section of Endocrinology, University Hospital, Gent, Belgium

Key words: AGING MALE, SEX HORMONES, TESTOSTERONE, ESTROGENS, ESTRADIOL, AROMATASE, BODY FAT, OBESITY

ABSTRACT

The role of estrogens in male physiology has become more evident, as a consequence of the discovery of human models of estrogen deficiency such as estrogen resistance or aromatase deficiency.

In males, testosterone is the major source of plasma estradiol, the main biologically active estrogen, only 20% of which is secreted by the testes. Plasma estrone, 5% of which is converted to plasma estradiol, originates from tissue aromatization of, mainly adrenal, androstenedione. The plasma concentration of estradiol in males is 2–3 ng/dl and its production rate in blood is 25–40 μg/24 h; both of these values are significantly higher than in postmenopausal women. Plasma levels of estradiol do not necessarily reflect tissue-level activity as peripherally formed estradiol is partially metabolized in situ; thus, not all enters the general circulation, with a fraction remaining only locally active.

Of the factors influencing plasma estradiol levels, plasma testosterone is a major determinant. However, the age-associated decrease in testosterone levels is scarcely reflected in plasma estradiol levels, as a result of increasing aromatase activity with age and the age-associated increase in fat mass. Free and bioavailable estradiol levels do decrease modestly with age as does the ratio of free testosterone to free estradiol, the latter testifying to the age-associated increased aromatization of testosterone. Estradiol levels are highly significantly positively related to body fat mass and more specifically to subcutaneous abdominal fat, but not to visceral (omental) fat. Indeed, aromatase activity in omental fat is only one-tenth of the activity in gluteal fat.

Estrogens in males play an important role in the regulation of the gonadotropin feedback, several brain functions, bone maturation, regulation of bone resorption and in lipid metabolism. Moreover, they affect skin metabolism and are an important factor determining sex interest in man.

INTRODUCTION

Whereas testosterone is the major sex hormone in males, recently, several authors have emphasized the role of estrogens in male physiology. Indeed, remarkable progress in our understanding of the role of estrogen physiology has been made, as a consequence of the discovery of human models of estrogen deficiency such as estrogen resistance and aromatase deficiency.

Estradiol, the major biologically active estrogen, is a metabolite of testosterone. Hence, the biological effects of testosterone are the result of the combined action of testosterone (and dihydrotestosterone) and of estradiol.

ORIGIN OF ESTROGENS IN THE MALE

About 20% of estradiol is secreted by the Leydig cells[1–4], whereas 80% is formed in peripheral tissues from androgens, in man, mainly from testosterone[5]. Estrone, on the other hand, originates from aromatization of (mainly adrenal)

Correspondence: Professor A. Vermeulen, Medical Clinic, Section of Endocrinology, University Hospital, 185 de Pintelaan, 9000 Gent, Belgium

ORIGINAL ARTICLE

Received 8–4–02
Accepted 3–5–02

androstenedione, with 20% being secreted directly by the adrenals.

The blood transfer constant of plasma testosterone to plasma estradiol, i.e. the fraction of the blood production rate of testosterone that is converted to estradiol is approximately 0.3–0.4% and of androstenedione to estrone approximately 1.4%, approximately 5% of the latter is then converted to estradiol[6]. As the mean estradiol concentration in men is about 2–3 ng/dl, whereas the metabolic clearance rate is approximately 1600 l/24 h, it follows that the blood production rate of estradiol is about 30–40 μg/24 h. This includes a secretion rate of approximately 5–10 μg/day from the Leydig cells, 20 μg/day originating from peripheral conversion of plasma testosterone and about 5 μg/day from androstenedione. In patients with aromatase deficiency a daily dose of 25 μg of estradiol, administered transdermally, appeared to suffice for effective mineralization[7]. The mean concentration of estrone in males is 3–6 ng/dl[8], and its blood production rate approximately 50–70 μg/24 h.

These conversions occur, under the influence of an aromatase, mainly in fat and muscle tissue, although many other tissues, for example, the brain, liver, Sertoli and Leydig cells, and osteoblasts[9–11], show aromatase activity. The aromatase activity increases with age[12] and obesity.

The total quantity of estradiol which is formed in the organism may, however, be significantly higher than the blood production rate, as part of the peripherally formed estradiol is further metabolized *in situ* (to estrone, estriol or 2-hydroxyestradiol) and, hence, does not enter the peripheral circulation. This locally formed estradiol may be only locally active and, hence, plasma estradiol levels do not necessarily reflect the activity at tissue level.

WHICH FACTORS DETERMINE ESTRADIOL LEVELS?

Testosterone being the major precursor of estradiol in males, it is not surprising that we observed a highly significant correlation between estradiol and testosterone levels ($r = 0.56$, $p < 0.01$) as well as between free testosterone and free estradiol ($r = 0.53$, $p < 0.01$), notwithstanding the fact that testosterone levels decrease with age, whereas aromatase activity increases. This indicates the importance of testosterone as a precursor of estradiol.

Regarding the influence of age on plasma estradiol levels, in the Gent Aging Male Study, involving 419 men aged 24–79 years, our group did not observe any significant decrease of plasma estradiol levels with age, the mean concentration being 84.0 ± 22.4 (SD) pmol/l in young males (24–31 years), 81.5 ± 23.1 pmol/l in middle-aged men (37–46 years, $n = 46$) and 88.1 ± 24.6 pmol/l in elderly men (70–79 years, $n = 283$). This confirms the data of Gray and co-workers[13], Khosla and colleagues[14], and Belanger and associates[15].

As fat mass was significantly higher in the elderly compared with young men, an eventual age-associated decrease in estradiol could be obscured by this increased fat mass which increases aromatization. However, after adjusting for fat mass, the correlation coefficient of estradiol with age was only −0.0035!

As to bioactive, non-sex hormone binding globulin (SHBG)-bound estradiol, as a consequence of the age-associated increase in SHBG-binding capacity, the mean bioavailable estradiol levels decreased modestly but significantly with age, from 46.5 ± 15.7 pmol/l in the young, 40.3 ± 11.1 in the middle-aged and 37.5 ± 10.8 pmol/l in the elderly. Similar results were obtained by Khosla and associates[14]. As the mean testosterone and free testosterone levels decreased from 20.2 ± 5.0 and 0.46 ± 0.11 nmol/l, respectively, in the youngest group, to 19.0 ± 5.2 and 0.25 ± 0.07 nmol/l, respectively, in the elderly, the ratio of free testosterone : free estradiol decreased from 323 ± 82 in the young, to 282 ± 82 in the middle-aged and to 197 ± 55 in the elderly, indicating an age-associated increase in aromatase activity, partly attributable to the aging process itself[16] and partly related to the age-associated increase in fat mass. Confirming data of Khosla and associates[14], we found that this ratio was highly significantly negatively correlated with body mass index (BMI; $r = -0.51$, $p < 0.01$), with procentual fat ($r = -0.55$) as well as with insulin levels ($r = -0.58$; $n = 59$, age 79–89 years, mean 73 years).

It should be noted, however, that other authors[17–19] have reported an age-associated decrease of total estradiol levels.

We studied the role of fat mass and fat distribution on sex hormone levels, in a subgroup of 59 elderly men (79–89 years).

Abdominal fat appeared to be a more important determinant of total testosterone and free testosterone levels than gluteal fat (abdominal fat $r = -0.56$ and -0.37, respectively; gluteal fat $r = -0.42$ and 0.26, respectively). Both estradiol and bioavailable estradiol were significantly correlated with total fat mass ($r = 0.43$ and 0.55, respectively, $p < 0.01$); hence, free estradiol levels were significantly higher (2.54 ± 0.63 pmol/l) in the obese patients than in non-obese controls of similar age (1.57 ± 0.43 pmol/l).

The abdominal/gluteal fat ratio was significantly negatively correlated with testosterone ($r = -0.45$), free testosterone ($r = -0.29$), SHBG ($r = -0.51$) and non-significantly with age ($r = 0.18$), but positively associated with insulin levels ($r = 0.43$, $p < 0.001$). This illustrates the role of abdominal fat in the insulin resistance and metabolic effects of obesity.

The role of fat distribution on estrogen levels, was defined by measuring abdominal subcutaneous and visceral fat by computerized tomography scan in a group ($n = 40$) of obese men 30–60 years old. Free estradiol was significantly correlated with subcutaneous abdominal fat ($r = 0.71$, $p < 0.001$) (Figure 1) but not with visceral fat ($r = 0.30$, not significant)[20]. Thus, it is interesting to note that aromatase activity in omental fat has been reported to be only one-tenth of that in gluteal fat[21], whereas Kirchner and colleagues[22] reported that, in women, lower-body fat is the major site of aromatization of androgens.

After weight loss (mean loss 8.0 ± 6.1 kg, decrease of BMI from 34.11 ± 2.65 to 30.31 ± 2.47), total estradiol as well as free estradiol decreased significantly (estradiol from 81.3 ± 18.4 to 63.2 ± 19.8 pmol/l; free estradiol from 2.54 ± 0.63 to 1.94 ± 0.59 pmol/l, $p < 0.001$) notwithstanding an increase in total testosterone levels ($p < 0.01$) by 10% (from 12.8 ± 3.6 to 11.9 ± 3.5 nmol/l) and free testosterone levels increasing non-significantly. In all subjects, the decrease concerned more visceral fat than subcutaneous abdominal fat, as shown by the increase in the ratio of subcutaneous over visceral fat from 1.85 ± 0.96 to 2.52 ± 1.16 ($p < 0.01$) confirming the higher turnover rate and lipolytic activity in visceral fat. After correction for BMI, the ratio of abdominal over subcutaneous visceral fat correlated negatively with age ($r = 0.66$, $p < 0.01$), i.e. visceral fat increased more with age than subcutaneous fat.

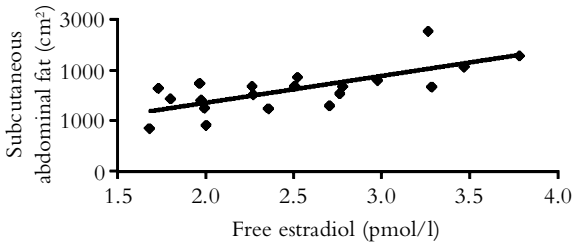

Figure 1 Correlation between free estradiol and subcutaneous abdominal fat (Σ L_1–L_5). $r = 0.71$

It is remarkable that all fat parameters (total, abdominal and gluteal) were negatively correlated with luteinizing hormone (LH) levels, suggesting that the decreased free testosterone levels in obese men have a central origin, the decrease in total testosterone levels being essentially the consequence of the decrease in SHBG levels.

ROLE OF ESTROGENS IN MALES

As estradiol concentration in men is higher than in postmenopausal women and comparable to estradiol levels in the early follicular phase, it can be expected that these estrogens have important physiological functions. Estrogen receptors are found in the brain, liver, osteoblasts, fibroblasts, fat cells, Leydig cells and Sertoli cells.

Estradiol formed in the hypothalamus and the pituitary, is an important determinant of the LH feedback in the human male, decreasing both LH-pulse frequency and amplitude[23]. This is clearly shown by the increase in LH-pulse frequency and pulse amplitude after administration of an aromatase inhibitor such as testolactone or anastrozol. Moreover, estrogens act also on the central nervous system and it has been reported that estradiol is an important factor determining sex interest in men (but not sexual orientation).

Estradiol plays an important role in bone maturation and in the peak of bone mass reached at adulthood[24]. This is best evidenced in subjects with aromatase or estrogen receptor deficiency, characterized by tall stature with linear growth continuing into adulthood, delayed bone age with lack of epiphyseal fusion, eunuchoid habitus and osteoporosis[25], whereas estrogen supplementation

results in the achievement of normal bone mineral density and bone mass of both trabecular and cortical bone[26]. Barrett-Connor and co-workers[27] reported a clear association between estradiol levels and vertebral fractures in elderly men, whereas Khosla and colleagues[14] demonstrated that estradiol plays a significant role in bone loss in elderly men, regulating bone resorption; men with estradiol levels above 115 pmol had little or no bone loss. Unphysiological high doses of estrogens administered prepubertally, however, result in a premature closing of the epiphyseal plates[28].

Estrogens also affect skin and lipid metabolism, whereas the role of estradiol in prostatic disease is still controversial[29]; however, it seems to act synergistically with dihydrotestosterone and stimulates the development of prostatic hyperplasia[30].

CONCLUSION

The majority of the estrogens in the male originate from peripheral conversion of androgens. This results in a plasma estradiol concentration which is higher in males than in postmenopausal women.

Whereas aromatase is found in many tissues, the majority of circulating estrogens are formed in fat and, to a lesser extent, in muscle tissue. The aromatase activity in fat tissue is much higher in gluteal than in abdominal fat and estradiol levels are related to subcutaneous fat mass but not to visceral fat.

The role of estrogens in the physiology of man appears to be more important than was generally believed until some years ago.

References

1. MacDonald PC, Madden JD, Brenner PF, *et al*. Origin of estrogen in normal men and in women with testicular feminisation. *J Clin Endocrinol Metab* 1979;40:905–11
2. Baird DT, Galbraith A, Fraser IS, Newsam JHE. The concentration of oestrone and of oestradiol-17β in spermatic vein blood in men. *J Endocrinol* 1973;53:286–8
3. Saez JM, Morera AM, Dazard A, Bertrand J. Adrenal and testicular contribution to plasma oestrogens. *J Endocrinol* 1972;55:41–4
4. Weinstein BL, Kelch BP, Jenner MR, Kaplan SR, Grumbach MM. Secretion of unconjugated androgens and estrogens by the normal and abnormal human testes before and after hCG. *J Clin Invest* 1974;52:1–7
5. Baird DT, Horton R, Longcope C, Tait JF. Steroid dynamics under steady state conditions. *Rec Prog Horm Res* 1969;25:611–44
6. Longcope C, Kato T, Horton R. Conversion of androgens to estrogens in normal adult men and women. *J Clin Invest* 1969;42:2191–200
7. Rochira V, Faustini-Fustini M, Ballestrieri A, Carani C. Estrogen replacement therapy in a man with congenital aromatase deficiency: effect of different doses of transdermal estradiol on bone mineral density and hormonal parameters. *J Clin Endocrinol Metab* 2000;85:1841–5
8. Nankin HR, Pinto R, Fan DF, Troen P. Daytime levels of testosterone, LH, estrone, estradiol and LHRH in man. *J Clin Endocrinol Metab* 1975;41: 271–8
9. Sasano H, Usuki M, Sawai T, Nagura H, Matsunaga G, Kashimoto O, *et al*. Aromatase in human bone tissue. *J Bone Miner Res* 1997;12: 1416–23
10. Longcope C, Pratt JH, Schneider JH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue *in vivo*. *J Clin Endocrinol Metab* 1978;46: 146–52
11. Ryan KJ, Naftolin F, Reddy V, Flores F, Petro Z. Estrogen formation in the brain. *Am J Obstet Gynecol* 1972;114:454–60
12. Hemsell DI, Grodin JM, Brenner P, Siiteri PK, MacDonald PC. Plasma precursors of estrogens. II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. *J Clin Endocrinol Metab* 1974;38:476–9
13. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease and sex hormone levels in middle aged men: results of the Massachusetts male aging study. *J Clin Endocrinol Metab* 1991;73:2016–25
14. Khosla S, Melton LG III, Atkinson EJ, O'Fallon WM. Relationship of sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab* 2001; 86:3555–61
15. Belanger A, Candas B, Dupont A, Diamond P, Gomez JL, Labrie F. Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. *J Clin Endocrinol Metab* 1994;79:1086–90
16. Siiteri PK, MacDonald PC. Role of extraglandular estrogens in human endocrinology. In Greep RO, Astwood EB, eds. *Handbook of Physiology*. Section

7: Endocrinology. Female reproductive system. Part 1. Washington DC: American Physiology Society, 1975;2:491–508
17. Madden B, Rochira V, Fabbi M, Zerelli L, Carani C. Sex steroids in aging males. Presented at *'Estrogens 2001'*. Modena, Italy, May 2001
18. van den Beld AW, de Jong FH, Grobbee DE, Pols HAP, Lamberts SWJ. Measures of bioavailable serum testosterone and estradiol and their relationship to muscle strength, bone density and body composition in elderly men. *J Clin Endocrinol Metab* 2000;85:3276–81
19. Leifke E, Gorenoi V, Wichters C, von zur Mühlen A, von Büren E, Brabant G. Age related changes of sex hormones, insulin-like-growth factor I and sex hormone binding globulin levels in men: cross sectional data from a healthy cohort. *Clin Endocrinol* 2000;53:689–95
20. Vermeulen A, Goemaere S, Kaufman JM. Sex hormones, body composition and aging. *Aging Male* 1999;2:8–11
21. Killinger DW, Perel E, Danilesen D, Kharlip L, Lindsay WRV. Influence of adipose tissue distribution on the biological activity of androgens. *Ann NY Acad Sci* 1990;5:191–211
22. Kirchner MA, Samoljik E, Drejka M, Szmal E, Schneider GH, Ertel N. Androgen-estrogen metabolism in women with upper body versus lower body obesity. *J Clin Endocrinol Metab* 1990; 70:473–7
23. Hayes FJ, Seminara SB, Decruz S, Boepple PAZ, Crowley WF Jr. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feed back. *J Clin Endocrinol Metab* 2000;85:3027–35
24. Turner T, Riggs BI, Spelsberg TC. Skeletal effects of estrogens. *Endocr Rev* 1994;15:275–300
25. Faustini-Fustini M, Rochira V, Carani C. Oestrogen deficiency in men: where are we today. *Eur J Endocrinol* 1999;140:111–24
26. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, *et al.* Effect of testosterone and estradiol in males with aromatase deficiency. *N Engl J Med* 1997;337:91–5
27. Barrett-Connor E, Mueller JE, von Mühler DG, Laughlin GA, Schneider DL, Sarton DJ. Low levels of estradiol are associated with vertebral fractures in older men but not in women. The Rancho Bernardo Study. *J Clin Endocrinol Metab* 2000;85: 219–23
28. Cutler JB Jr. The role of estrogen in bone growth and maturation during childhood and adolescence. *J Steroid Biochem Mol Biol* 1997;61:141–4
29. Bonkhoff H, Fixemer T, Hunsicker J, Remberger K. Estrogen receptor expression, prostatic cancer and premature prostatic disease. *Am J Pathol* 1999;155:641–7
30. Moore RJ, Gazak JM, Wilson JD. Regulation of cytoplasmic dihydrotestosterone binding in dog prostate by 17β oestradiol. *J Clin Invest* 1979;63: 351–7