Obesity, Androgens, Estrogens, and Cancer Risk

M. A. Kirschner, G. Schneider, N. H. Ertel, and E. Worten

Abstract

Obesity is associated with increased incidence of cancers arising from tissues responsive to estrogenic stimulation, including endometrium, breast, and prostate. We thus wished to explore estrogen production and its origin in obesity in an attempt to provide a possible hormonal link to explain increased cancer risk.

Studies of the hormonal milieu of obese men and women revealed several abnormalities of sex hormone production and metabolism. (a) Androstenedione production rates are elevated and serve as prehormones of both testosterone and estrogens. (b) Extragonadal aromatization of androgens to form estrogens (androstenedione to estrone and testosterone to estradiol) is elevated, resulting in (c) increased production rates of estrogens. The obese person is thus chronically exposed to hyper-estrogenemia. In addition, obesity is associated with other alterations of sex hormone metabolism such as decreased levels of sex hormone-binding globulin and increased metabolic clearance rates of several hormones.

After weight loss to ideal body weight, there appears to be normalization of androgen and estrogen production rates, as well as circulating hormone levels; however, metabolic abnormalities such as increased aromatization of androgens to estrogens and accelerated metabolic clearance rates of androstenedione remain abnormal.

Introduction

Obesity has been associated with increased incidence rates of carcinoma of the endometrium, prostate, and colon (3, 8, 18, 34-38, 56, 57). Further, studies from DeWaard (9), Choi (6), and others (5, 7, 41, 45, 57) suggested an association between obesity and increased breast cancer incidence. Indeed, some of the worldwide differences in breast cancer incidence rates may relate to life style, diet, and/or obesity (3, 5, 9). Since 3 of 4 of these obesity-related cancers arise from tissues that normally represent target organs of hormone action, it is most attractive to speculate that obesity results in abnormal hormone production, end organ hyperstimulation, and subsequent neoplasms (26, 57).

Obesity has been associated with a variety of alterations in hormone production, metabolism, and action. This subject has been reviewed extensively by Glass et al. (15) and Kirschner et al. (26). Of those cancers known to be associated with obesity, it appears that the sex hormones, notably estrogens, play a stimulatory role in growth of the normal tissue of origin. Thus, in the current report, we shall consider the relationship between obesity and sex hormone metabolism, focusing on androgen production, peripheral aromatization of androgens to estrogens, and estrogen production. The studies to date demonstrate that obesity is associated with alterations of sex hormone production and metabolism, lending support for a possible hormonal link between obesity and cancer.

Androgen Production in Obesity

Testosterone. Although there is no a priori reason to suspect hypogonadism in normal obese men, several groups found low plasma testosterone concentrations in this population (1, 16, 29, 30, 52, 53, 58). Schneider et al. (53) reported that plasma testosterone averaged 350 ng/dl versus a mean of 520 ng/dl in nonobese adult men. This finding was explained when metabolic clearance rates of testosterone were observed to be elevated in proportion to the degree of obesity. Testosterone production rates, as well as free "unbound testosterone," were found to be normal in obese men, confirming normal Leydig cell function. Studies from several laboratories indicated that obesity is associated with diminished levels of SHBG (1, 16, 29, 53). Whether this represents decreased production or accelerated clearance of this particular ß-globulin is uncertain at present. Earlier studies by Vermeulen (62) demonstrated that the metabolic clearance rate of testosterone was inversely related to SHBG. The following sequence could thus be used to explain the testosterone findings in obese men. Obesity results in lower levels of SHBG, leading to accelerated clearance of testosterone and lower plasma testosterone concentrations for a given degree of testosterone production. In effect, androgen production and actions are normal and the pituitary-gonadal axis appears to be intact in obese men (15, 53, 59), but metabolism and mechanisms of testosterone distribution are altered.

In obese women, there appears to be an increased incidence of menstrual disturbances and hirsutism, suggesting possible abnormalities of androgen production (12, 17, 42, 48). Indeed, Hosseinian et al. (21) reported elevated "free androgens" in obese amenorrheic (nonhirsute) women. The great majority of obese women, however, have normal menstrual function and none of the clinical features commonly associated with excessive androgens (25, 54). In fact, when serum testosterone was measured in a group of normally menstruating nonhirsute obese women, we observed lower than expected total plasma testosterone concentrations in proportion to the degree of obesity (27). As described for men (above), lower plasma testosterone was explained by decreased levels of SHBG. Thus, it seemed reasonable to assume that low SHBG in both obese men and women resulted in accelerated clearance and lower plasma testosterone concentrations. More recent data from our laboratory (50), however, suggest that testosterone production rates are indeed increased in obese normally men-

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3 The abbreviation used is: SHBG, sex hormone-binding globulin.

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struating nonhirsute women despite the relatively low total plasma testosterone and even normal ‘free testosterone’ measurements. The elevated testosterone production rates could not be normalized by correction for excessive body surface.

**Peripheral Aromatization of Testosterone.** Although aromatization of testosterone to estrogens in the peripheral (extragonadal) circulation represents a minor pathway in its overall metabolism, occurring to the extent of 0.2 to 0.4% (2), the magnitude of testosterone production in men makes this pathway of metabolism the major source of circulating estradiol in normal men. Schneider et al. (53) demonstrated that obesity was associated with a 2- to 3-fold increase in aromatization of testosterone to estradiol. This pathway of peripheral metabolism of testosterone accounted in large part for the elevated estradiol production rates observed in obese men. These data are confirmed by Kley et al. (30) and Zumoff et al. (65) who reported increased plasma estrogen levels in obese men.

In women, testosterone production is small (250 μg/day). The peripheral conversion of testosterone to estradiol is the same magnitude as described above, making this pathway an insignificant source of the total circulating estradiol. Although no formal studies of peripheral aromatization of testosterone to estradiol have been performed in young obese women, it seems reasonable to speculate that there is increased peripheral aromatization of testosterone to estradiol, and if testosterone production is elevated in this population, extragonadal aromatization to estradiol may become a significant component of the total estradiol produced.

**Androstenediol.** This C₁₉ steroid represents a major metab-

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<th>GIRLS</th>
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**Chart 1.** Estrogen production at various ages. Schematic representation of the role of extragonadal aromatization in the daily production rates of estrogens in various age groups. In premenarchal girls, all the estrogens produced arise via extragonadal aromatization of androstenedione. In women of reproductive age, ovarian estrogen secretion is superimposed on extragonadal sources which account for approximately 40% of basal estrogen output. In the postmenopausal state, all estrogens rise via extragonadal metabolism of androgens. In men, approximately 80% of estrogens rise from extragonadal metabolism of androgens.

<table>
<thead>
<tr>
<th>Plasma androstenedione (ng/dl)</th>
<th>Metabolic clearance rate of androstenedione (liter/day)</th>
<th>Androstenedione production rate (mg/day)</th>
<th>Conversion of androstenedione to estrone (%)</th>
<th>μg/day</th>
<th>% from androstenedione</th>
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<td>3140</td>
<td>3.52</td>
<td>2.52</td>
<td>154</td>
<td>89</td>
<td>65</td>
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<tr>
<td>Normal women 121</td>
<td>2140</td>
<td>2.27</td>
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* NS, not significant.
In obese men, Schneider et al. (53) and Kley et al. (28) observed increased conversion rates of androstenedione to estrone, ranging from 1.6 to 5.4%. These findings supported earlier observations of MacDonald et al. (34), MacDonald and Siiteri (36), Schneider et al. (53), and Longcope (32), who observed increased peripheral aromatization of androstenedione in postmenopausal women. In young obese women, Edman et al. (10) demonstrated increased peripheral metabolism of androstenedione to estrone, and in our recent studies (Table 1), the mean aromatization of androstenedione to estrone in obese women was 2.52% versus 1.52% in nonobese controls. The magnitude of androstenedione production and extragonadal conversion to estrone in young women of reproductive age is demonstrated in Chart 2. Thus, data from the varying age and sex groups studied clearly demonstrate that peripheral aromatization of androstenedione is elevated in obesity, leading to increased estrone formation.

 Estrone Production in Obesity

In men, Schneider et al. (53) demonstrated that obesity was associated with increased urinary production rates of both estrone and estradiol proportional to excessive body weight. The source of increased estrogens in obese men appeared to be related to increased aromatization of their respective androgenic precursors (testosterone to estradiol and androstenedione to estradiol). Data from other laboratories confirm these findings (30, 59).

As discussed above, earlier studies established that postmenopausal women with obesity exhibited increased urinary estrone production rates, arising from increased extragonadal aromatization of androstenedione. Current data from our laboratory obtained in 83 young women ages 20 to 40 with varying degrees of obesity have corroborated the earlier study of Edman et al. (10) demonstrating increased urinary estrone production rates in this age group. In our studies, urinary estrone production rates, performed on Days 5 to 8 of the menstrual cycle, averaged 154 μg/day in the obese women versus 104 μg/day in nonobese control subjects of similar age. As noted in Table 1, the increment of estrone production is explained entirely from increased peripheral aromatization of circulating androstenedione.

Although estrogen production rates have not been formally assessed in children or adolescents, it has been commonly observed that obesity in children is associated with early onset of pubertal changes (13, 14). It seems entirely reasonable to assume that childhood obesity is similarly associated with accelerated conversion of prehormones to estrogens. It is intriguing to speculate on whether increased peripheral aromatization of circulating prehormones to form excessive estrogens may be a triggering mechanism leading to accelerated pubertal changes.

From studies of peripheral aromatization and estrogen formation in men, postmenopausal women, young women of reproductive age, and extrapolating data for children, it appears that obesity is associated with lifelong increased estrogen production, as portrayed in Chart 3. Superimposed upon this increased estrogen level arising from extragonadal sources is the normal estrogen output secreted by the functioning ovary and minimal estrogen secretion from the testes. Following menopause, the extragonadal pathway becomes the sole source of estrogens.

 Estrogens and Cancer Risk

From the data surveyed to date, it seems entirely reasonable to postulate that obesity is associated with hyperestrogenism, possibly leading to excessive chronic stimulation of estrogen-responsive target organs. Stimulation of target organs could lead to hyperplasia and subsequently neoplasia. Further, estrogens may serve as promoters of neoplastic transformations occurring within these stimulated target organs.

Although a direct link between endogenous and exogenous hyperestrogenism and carcinoma of the endometrium appears to be reasonably well established (4, 7, 18, 34–38, 40, 47, 56, 57, 64), the same relationship to breast cancer cannot be confidently stated at present (6, 7, 39, 41). Available data linking exogenous estrogen usage and breast cancer are suggestive but uncertain. Oral contraceptive use in young women has not been associated with increased risk of breast cancer (11, 22, 45, 63); but use of these agents by women approaching menopause seems to increase breast cancer risk (11, 22). The relationship of menopausal estrogen usage and breast cancer risk is unclear. Although there is some suggestion that exogenous estrogens in this age group may increase breast cancer risk, the risk ratios are small and more data are needed (20, 23, 41, 49).
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DeWaard (9) suggested that obesity is related to an increased incidence of postmenopausal breast cancer. Paffenbarger et al. (45) suggested that weight gain during reproductive life may also influence postmenopausal breast cancer risk. Since the postmenopausal period is associated with falling endogenous estrogen production, obesity at this time of life would seem to have little effect upon the initiation of breast cancer, unless perhaps estrogens were artificially elevated by exogenous sources, as described above. It was thus of considerable importance to establish that obesity occurring in young women (of reproductive age) results in hyperestrogenism. If tumor induction is associated with a prolonged latent or pre-detection period, then it is the obesity occurring in younger women and its associated hyperestrogenism which may account for the breast cancer later in life.

The relationship of obesity, extraglandular estrogen production, and carcinoma of the prostate is uncertain. Estrogen receptors have been found in both normal and neoplastic prostatic tissue (43). The potential modulating role of estrogens and estrogen receptors on the growth of normal and neoplastic prostatic tissue represents an area of great potential.

Effect of Weight Loss on Hormone Production and Metabolism

The effect of weight loss on production and metabolism of sex hormones has been examined by a number of groups. Perel and Killinger (46) and Takaki et al. (60) reported no change in urinary estriol production or in androstenedione conversion to estrone in subjects studied before and after significant weight loss. These findings seemed reasonable, since adipocytes and/or supporting stroma which represent the likely sites of most of these hormonal alterations (33, 44, 46, 51) are not appreciably altered by weight reduction. Schneider et al. (52), however, reported prompt return of depressed serum testosterone levels to normal in a group of obese men undergoing supplemental starvation and suggested that SHBG abnormalities could be reversed after 1 to 2 weeks of dieting. Similarly, Stanik et al. (56) reported restoration of plasma testosterone levels, as well as decreased plasma estrogen levels, in obese men after 10 weeks of weight loss. In our ongoing studies, sex hormone production and metabolism were studied in young women both before and after major weight loss with stabilization of weight and return of normal menstrual function. Studies to date suggest that hormone production rates tend to be restored toward normal levels; however, several aspects of peripheral metabolism of androgens-estrogens such as metabolic clearance rates of androstenedione and aromatization of androstenedione to estrone remain elevated. These data suggest that adrenal and/or gonadal secretion of the sex hormones and their precursors can be altered by restoration of body weight to more ideal levels. Metabolic alterations may not be reversed by shrinkage of hyperplastic fat tissue. These findings present some hope that correction of the obese state may have some beneficial effect on the abnormal hormonal milieu despite metabolic alterations that may be fixed.

References

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