Relationship of Obesity to Blood Estrogens

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Abstract

It has become conventional wisdom that estrogenic stimulation of breast tissue has something to do with the causation of breast cancer and that the reason obesity is a risk factor for breast cancer is that obese women are hyperestrogenized. However, it has been very difficult to demonstrate that excessive exogenous estrogen increases the incidence of breast cancer, that endogenous estrogen excess is present in breast cancer, or that obese women are hyperestrogenized. We have examined the last question by measuring 24-hr mean plasma estrone and estradiol levels in the midfollicular phase in 18 healthy, regularly cycling, very obese (53 to 218% above ideal weight) women and 16 regularly cycling, age matched, non-obese control women. Unlike obese men, the obese women showed no significant elevation of either estrone or estradiol. Their average estrone level was 72 compared with 64 pg/ml in controls; their average estradiol level was 65 compared with 57 pg/ml in controls. In the combined group (obese plus nonobese), there was a significant correlation of percentage of deviation from ideal weight with plasma estrone (y = 63 + 0.12x; p < 0.05) but not with estradiol. This correlation sup-

The facts that the normal female breast is responsive to estrogenic stimulation, that the growth of breast cancer may be accelerated by increased endogenous estrogen (as in pregnancy) or by administration of exogenous estrogen, and that breast cancer may regress when endogenous estrogen is decreased (by oophorectomy) or antagonized (by antiestro-

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anatomical findings of Sommers (42) and Grattarola (17) and
the hormonal data of Kodama et al. (28), Bulbrook et al. (5),
and Cowan et al. (9), but has been put in doubt by the hormonal
data of England et al. (14), Swain et al. (43), and Malarkey et al.
(32).

A later version of this variant is the "estrogen window hypo-
thesis" of Korenman (30), which proposes that an increased
duration of either of the 2 normal periods of anovulation
and therefore low progesterone/estrogen ratio (i.e., the
"windows"), namely, the few years just after menarche and
the few years just before menopause, increases the risk of
developing breast cancer. This hypothesis has been weakened
by several items of epidemiological evidence, as summarized
by me (47) and by Henderson et al. (21).

Both versions are weakened by the fact that no clear-cut
antiestrogenic effect of progesterone can be demonstrated in
the breast; indeed, it has been reported by Poel (38) that
progesterone is cocarcinogenic for the rodent breast.

The special variants of the "estrogen hypothesis" aside,
trying to ascertain whether there is an overall increase in
estrogenicity in a particular group of women, such as those
with breast cancer or those with obesity, brings us up against
one of the central problems of endocrinology, namely, how to
measure the level of hormonicity for any given hormone.
Conceptually, the answer seems simple: one must measure the
concentration of the final effector at the effector site. This,
however, is of little help in practical terms since the final
effector may not be known, and the effector site may not be
accessible. At the practical level, 2 major approaches have
been suggested: measurement of the production rate of a
hormonal effector or its precursor; or measurement of the
concentration of the effector in an accessible body fluid, nor-
really blood. Although the latter approach seems more direct,
"cleaner," and biochemically more logical, studies of produc-
tion rate, which include all studies of urinary metabolite excre-
tion and all radioactive tracer studies of precursor-to-product
conversions, have been used extensively, on the basis of the
tacit assumption that increases or decreases in production rate
are mirrored, at least qualitatively if not quantitatively, by cor-
responding increases or decreases in effector concentration.

At this point, I want to emphasize that, unless the effector is
synthesized within the target tissue, that tissue can have no
way of "seeing" increased synthesis elsewhere in the body
except through an increased concentration in body fluids (e.g.,
blood). In other words, increased synthesis of a particular
effector (e.g., an estrogen) is biologically irrelevant to a distant
tissue unless it produces an increase in concentration of the
effector in the fluids bathing that tissue.

Are there in fact instances in which changes in the rate of
production of a hormonal effector are not mirrored by corre-
sponding changes in its blood level? There are, with respect to
cortisol in dysthyroidism. Hyperthyroidism markedly increases
and hypothyroidism markedly decreases the rate of cortisol
production (19), but neither condition alters the prevailing
blood levels of cortisol. Clinically, both hyperthyroid and hy-
pothyroid patients are euadrenal, which confirms the primacy
of blood concentration over production rate as a measure of
hormonicity.

This brings us to the present issue. The putatively increased
risk of development of breast cancer in obese women has been
more or less tacitly ascribed to increased estrogenicity in these
women. What is the evidence?

Several groups have reported increased rates of conversion
of Δ4-androstenedione to estrone in obese women (13, 18); it
has also been reported that this conversion is increased in
obese men (26). The increased conversion is generally attrib-
uted to an increased mass of adipose tissue, the presumed
locus of the conversion, and this concept is supported by
reports of a linear correlation between measures of the mass
of adipose tissue and measures of the rate of conversion (13).
The conversion is mediated by aromatase, which is the reason
why aromatase inhibitors have achieved the current high level
of interest in connection with breast cancer.

Is their increased conversion of Δ4-androstenedione to es-
trone biologically relevant to increased estrogenicity in obese
women and thus to an increased risk for breast cancer? As I
have suggested above, there are 2 ways in which the increased
conversion could be relevant, either by taking place within the
breast and thereby raising the local intramammary concentra-
tion of effector estrogens or, if it takes place distantly in s.c.
and omental adipose tissue, by raising the blood levels of
effector estrogens. The first possibility has not been studied
and cannot be ruled out. What about the second?

I have found reports from 6 laboratories concerning blood
estrogen levels in postmenopausal obese women (2, 4, 10, 22,
23, 33, 36, 37, 45), and 2 reports concerning levels in pre-
menopausal obese women (24, 29). My group has recently
published the results of a third study in premenopausal obese
women reporting data on 24-hr mean plasma estrone and
estradiol levels (48). Four of the groups that studied postmen-
opausal obese women (2, 4, 36, 37) found no significant elevation
of blood estrone or estradiol levels in obese women. One group
(45) reported increases in both hormones; Judd's group (10,
22, 23, 33) reported a correlation between estrone and estradiol
levels and the degree of obesity, but the values in the
obese subjects were not outside the range of values in the
nonobese subjects. With regard to premenopausal women, the
reports of Kopelman et al. (29) and Kaufman et al. (24) agree
that there is no significant elevation of plasma estrone or
estradiol in obese women.

The studies by my group (comprising Drs. Gladys Strain,
Jacob Kream, Joseph Levin, John O'Connor, David Fukushima,
and myself) were based on measurement of 24-hr mean plasma
levels of estrone and estradiol. This approach was adopted
because of the widely reported episodic variations in the
plasma concentrations of many hormones, including estrogens;
24-hr mean concentrations are much less variable and there-
fore afford an opportunity for greater reproducibility, precision,
and discriminating power. The subjects of our studies were 18
obese women 20 to 44 years old and ranging from 53 to 218%
above ideal weight and 16 nonobese women 22 to 51 years
old; all subjects were cycling regularly, were rigorously
screened to rule out any significant past or present illness, and
were taking no medications. They were admitted to the Clinical
Research Center at Montefiore Hospital, where an indwelling
venous catheter was placed, and blood samples were with-
drawn every 20 min for 24 hr. Aliquots from each sample were
pooled, and the estrone and estradiol concentrations of the
pool were measured by radioimmunoassay.

Neither estradiol nor estrone levels showed a significant
difference between obese and nonobese women (Chart 1). The average estrone level of obese women was 72 compared with 64 pg/ml in controls and the average estradiol level of obese women was 65 compared with 57 pg/ml in controls. This is in marked contrast to the readily demonstrable elevations of both estrone and estradiol that we have observed in obese men (Chart 2), confirming the findings of Schneider et al. (39) and those of Kley et al. (27). When the plasma concentrations of estrone and estradiol were plotted against the percentage of deviation from ideal weight in the combined obese plus nonobese female group, a statistically significant ($p < 0.05$) positive correlation of low slope ($y = 63 + 0.12$) was seen for estrone but not for estradiol. This finding suggests that the formation of estrone (presumably by aromatization of $\Delta^4$-androstenedione) may indeed be slightly increased in obese premenopausal women. However, the magnitude of the effect seems to be too small in comparison with the ovarian production of estrogens to produce a statistically significant elevation of plasma estrone levels. Thus, unless increased estrone formation is also occurring within the breast, in direct contact with the target epithelial tissues (a possibility for or against which we have no evidence), these tissues would have no way of "seeing" the slightly increased overall estrone formation that seems to be mathematically demonstrable.

Summarizing the available data, there appears to be a consensus that obese women have increased formation of estrone by aromatization of $\Delta^4$-androstenedione, the extent of the increase being proportional to the degree of obesity. However, the weight of evidence in both postmenopausal and premenopausal women is that the increase in estrone formation is too small in magnitude to produce a detectable increase in plasma estrone or estradiol levels. This being the case, increased estrone formation cannot be "seen" by breast epithelial tissues and may therefore be biologically irrelevant unless it is also occurring within the breast in direct proximity to the epithelial tissues, a possibility that cannot be supported or ruled out at present.

References

Discussion

Dr. Judd: Dr. Zumoff, you have quoted me somewhat incorrectly. The paper that you quoted indicated that we did not find any difference between estrogen levels of fat and thin people. Indeed we did in our first paper in 1976, in which we studied 16 patients with endometrial cancer and 10 postmenopausal women without it. We expanded that study to include 35 patients with and 35 patients without endometrial cancer. The data published that results in 1979 in the American Journal of Obstetrics and Gynecology. We again found a striking correlation with body size not only for estrone but also for estradiol levels. We expanded our study further to 155 postmenopausal women and again in a 1980 publication reported finding a striking correlation between body size and both estrone and estradiol. And we expanded that even further in our study to include 35 patients with and 35 patients without endometrial cancer and published the results in 1979 in the American Journal of Obstetrics and Gynecology. We again found a striking correlation with body size not only for estrone but also for estradiol levels.


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