Plasma Androgen Concentrations in Diabetic Women

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SUMMARY

Plasma androgen levels were determined in women assigned to the following groups: idiopathically hirsute, diabetic, both idiopathically hirsute and diabetic, and normal. The androgens examined were androstenedione (AD), dihydrotestosterone (DHT), testosterone (T), and dehydroepiandrosterone (DHEA). We find statistical differences between young (<38 years) and older (≥38 years) controls at confidence levels of $p \leq 0.01$ for AD, DHT, and T and of $p \leq 0.05$ for DHEA. The results indicate that peak circulating androgen levels occur prior to age 30-35 years for women. There are no significant differences between the young controls and young idiopathically hirsute subjects, but a statistical difference exists between older hirsute and older controls for all four androgens ($p \leq 0.05$).

When a comparison is made among the diabetic, hirsute diabetic, and older control groups (all groups ≥38 years), the diabetic group is significantly higher than the control in plasma AD ($p \leq 0.01$) and DHEA ($p \leq 0.05$). These same two steroids are also higher in the diabetic group than in the hirsute diabetic group ($p \leq 0.05$), while the latter differs from controls only in testosterone levels ($p \leq 0.05$). DHT levels are similar for all three groups. DIABETES *26*:1125-29, December, 1977.

The incidence of culturally unacceptable facial and body hair among female patients in our diabetes clinic (29 per cent) exceeds that encountered in our general-medicine clinic (13 per cent). These statistics were obtained through a patient questionnaire followed by a physician's examination. Circulating levels of such androgens as androstenedione (AD), dihydrotestosterone (DHT), testosterone (T), and dehydroepiandrosterone (DHEA) often are elevated in idiopathically hirsute women.[1] Consequently, we have undertaken a study of plasma androgen spectra in women with diabetes mellitus in order to ascertain whether a correlation also exists between elevated plasma androgens and hirsutism in this group.

MATERIALS AND METHODS

The following conventional names and abbreviations are used: androstenedione = AD = androst-4-ene-3, 17 dione; dihydrotestosterone = DHT = 5α-androstan-17β-ol-3-one; testosterone = T = androst-4-ene-17β-ol-3-one; dehydroepiandrosterone = DHEA = androst-5-ene-3β-ol-17-one; and androstandiol = 5α-androstan-3α,17β-diol.

Blood was obtained between 8:00 and 9:30 a.m. from nonpregnant females who were assigned to the following groups: idiopathically hirsute, diabetic, diabetic with idiopathic hirsutism, and normal. None of these women were on birth control pills or other steroidal medication that might influence their androgen levels.

Among the diabetic patients without hirsutism ($n=15$, age 56.5 ± 10.2* years), the known duration of the diabetes was from 2 to 20 years, while for the diabetics with hirsutism ($n=17$, age 60 ± 9.5) it was 2 to 27 years. Diagnosis of diabetes in both groups was made in or following the third decade of life. Treatment for both groups included diabetic diets: In addition, some patients were prescribed oral hypoglycemic agents while 50 per cent of each group received insulin. All diabetics were followed in the diabetes clinic with serial fasting blood sugar determinations. A few patients in each group were under excellent control, with fasting blood glucose levels near normal, while some had good to fair control and a third of them had poor control, with fasting blood glucose levels generally greater than 160 mg./dl. The majority of patients

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*Mean ± standard deviation.

were obese; only two patients in each group had a normal body weight.

Most hirsute diabetics had had rather minimal hirsutism for several years. Other causes of hirsutism, such as Cushing's syndrome, the adrenogenital syndromes, ovarian and adrenal tumors, and polycystic ovaries, were ruled out.

Fifteen patients with idiopathic hirsutism (n=10, mean age 27.0±5.9; n=5, mean age 53.0±9.0) were followed in the endocrine clinic. None of these patients had diabetes mellitus as assessed by either a two-hour postprandial blood sugar or a three-hour glucose tolerance test. The control subjects in this study (n=10, mean age 25.5±3.2; n=12, mean age 53.2±10.8) were nurses, clinic aides, and laboratory technicians without diabetes mellitus.

The androgens were assayed by radioimmunoassay utilizing antisera purchased from Endocrine Sciences (Tarzana, Calif.) after separation of AD and DHT from the T and DHEA. For this purpose, the ethyl acetate extract of 2 ml. of plasma is submitted to descending chromatography on a 60-cm. Sephadex LH-20 column.[2] Elution peaks are located and recovery is estimated with the use of radioactive tracers. Excellent separations are achieved for AD and DHT and for both of these from T and DHEA. These last two, T and DHEA, elute together in the heptane/chloroform/ethanol (50:50:1) system used; however, cross-reactivity of their respective antisera is virtually nil, so that the quantitation of one in the presence of the other is no problem. All radioimmunoassays were performed in duplicate at two dose levels. Significance of apparent group differences was estimated by submission of the data to variance analysis allowing for multiple comparisons between groups.

RESULTS

Age Dependence of Circulating Androgens

Striking differences are obtained between the young (<38 years of age) and older controls (≥38 years of age) with statistical significance at confidence levels of $p \leq 0.01$ for AD, DHT, and T and $p \leq 0.05$ for DHEA (figures 1-4). The parabolic regression curve for each androgen versus age (figure 5) indicates that peak circulating androgen levels occur before age 30; therefore, it is important that comparisons of plasma androgen concentrations in females be conducted among age-matched groups.

Our population of older idiopathically hirsute women is small (n=5) because these women rarely present in the medical clinics for hirsutism as such.

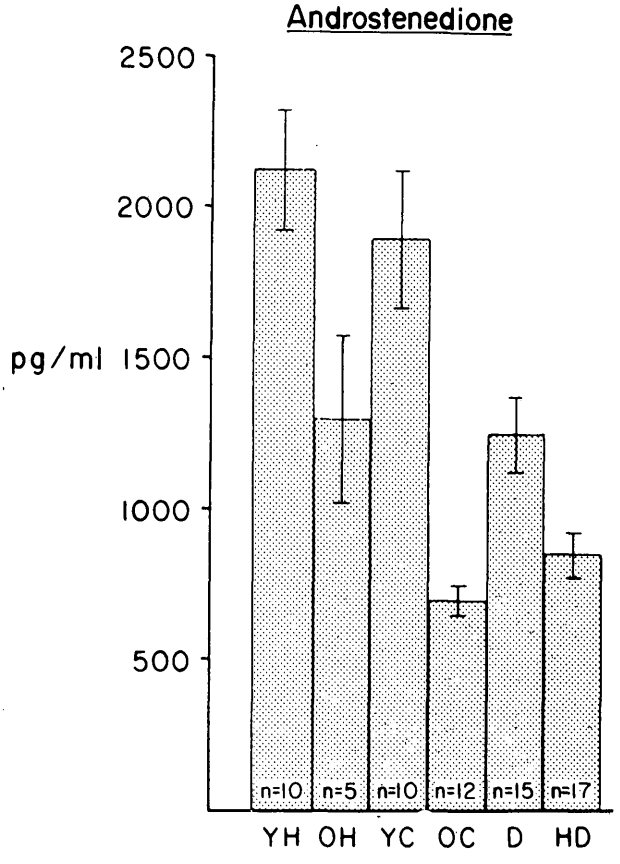

FIG. 1. Androstenedione levels (Mean ± S.E.M.) in picograms per milliliter for young hirsute (YH), old hirsute (OH), young control (YC), old control (OC), diabetic (D), and hirsute diabetic (HD) groups.

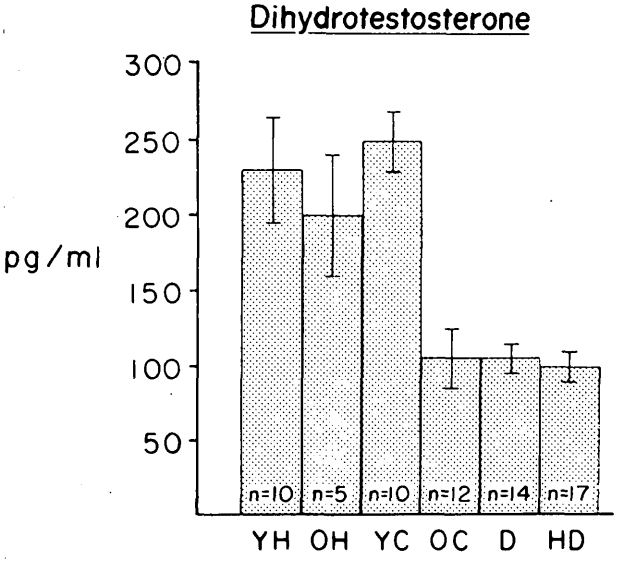

FIG. 2. Dihydrotestosterone levels (Mean ± S.E.M.) in picograms per milliliter for the same groups as shown in figure 1.

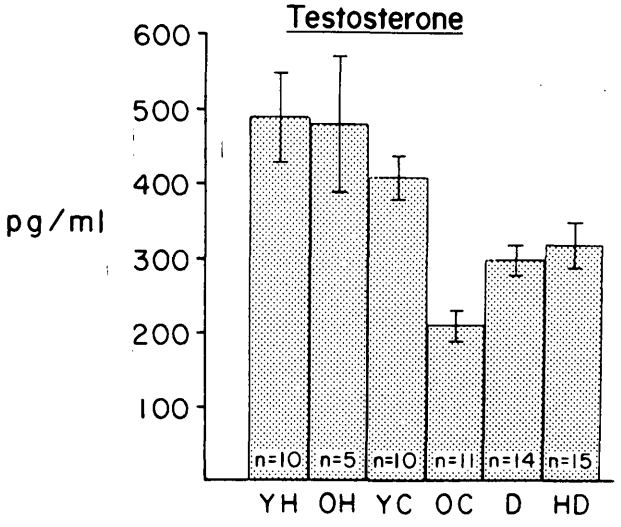

FIG. 3. Testosterone levels (Mean ± S.E.M.) in picograms per milliliter for the same groups as shown in figure 1.

The only significant difference between this group and the younger hirsute women is in AD ($p \leq 0.01$). No statistically significant differences in steroid patterns between the young controls and young idiopathically hirsute subjects are found, although the androgen levels of the latter group tend to be higher. In controls, the androgen levels decrease with increasing age (figure 5), which does not appear to be the case in subjects with idiopathic hirsutism (figures 1-4). As a consequence there is a significant difference between the older hirsute and older control populations for all four compounds ($p \leq 0.05$). Because the older idiopathically hirsute group was so limited, no further use was made of their data in the statistical analysis.

Diabetic, Hirsute-diabetic, and Age-Matched Controls

The incidence of adult-onset diabetes mellitus increases after age 40; consequently our study of the androgen levels in adult-onset diabetes was limited to women 38 years of age and older. When a comparison is made among the diabetic, hirsute-diabetic, and older control group (figures 1-4), the diabetic group is significantly higher than the control in plasma AD ($p \leq 0.01$) and DHEA ($p \leq 0.05$). These same two steroids are also higher in the diabetic group than in the hirsute-diabetic group ($p \leq 0.05$). Although T levels are very close in the hirsute-diabetic and diabetic groups, only the hirsute-diabetic group's level is statistically higher than that of the control ($p \leq 0.05$). DHT levels are similar for all three groups.

DISCUSSION

The difference in androgen levels encountered in the young and old controls indicates that great care must be exercised when comparisons are made among various age groups. All four of the androgens measured in this study decrease markedly between the ages of 30 and 50, after which they appear to plateau.

Neither duration of diabetes, control of the disease, nor obesity correlates with any of the parameters considered in this study, i.e., plasma A, DHEA, T, and DHT or the hirsutism per se. The various treatments employed—diet alone, diet plus oral hypoglycemics, and diet plus insulin—are represented equally in the

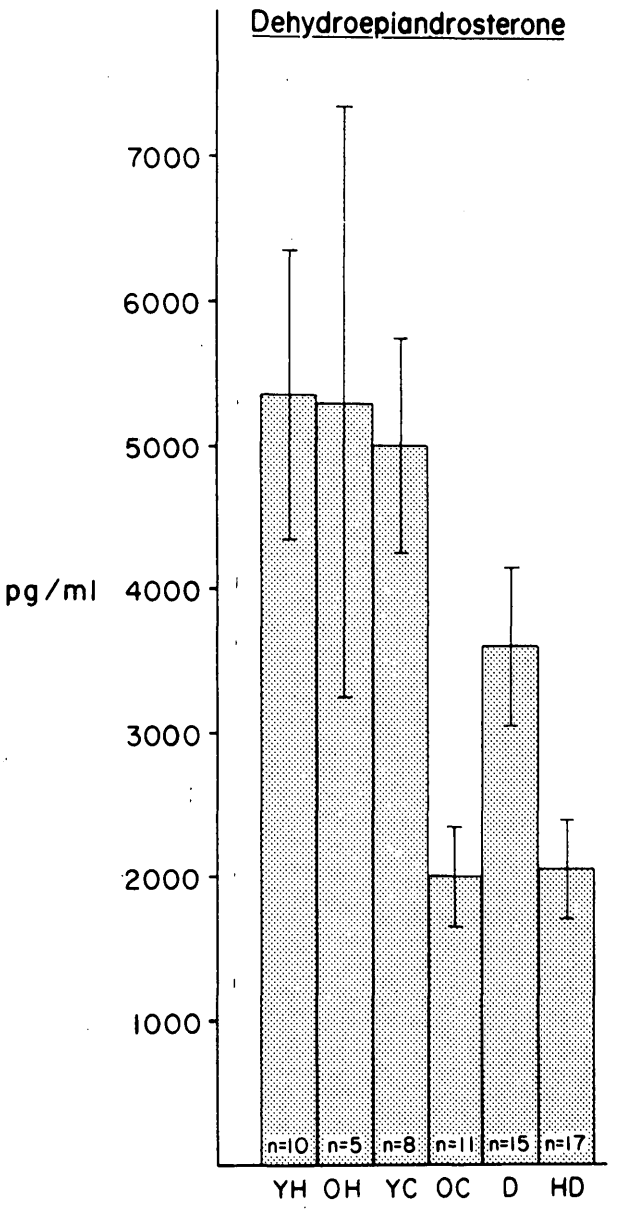

FIG. 4. Dehydroepiandrosterone levels (Mean ± S.E.M.) in picograms per milliliter for the same groups as shown in figure 1.

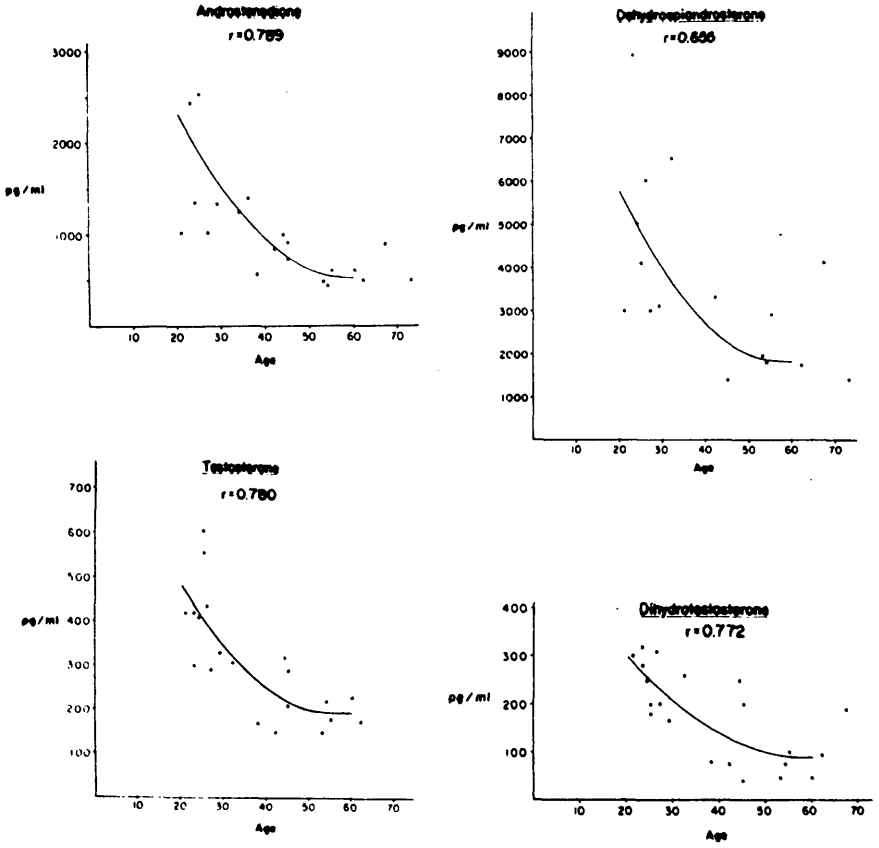

FIGURE 5

Parabolic regression curves for control androgen levels (pg./ml.) vs. age. (Equation for the parabolic regression on two variable data: $Y = a + bx + cx^2$. The coefficient for correlation is based on: $r = \sqrt{\Sigma y^2_c / \Sigma y^2}$).

two subgroups comprising the diabetic populations.

The AD and DHEA levels for the diabetics are significantly higher than either those of the control group or the hirsute-diabetic group. The two diabetic groups have similar T levels, but the value for the hirsute diabetics only is statistically higher than that of the control group ($p \leq 0.05$). DHT levels are similar for all three groups. Thus, we have a situation in which women with diabetes have an abnormally high level of two weakly androgenic steroids, AD and DHEA, and a somewhat higher than normal level of T. Perhaps more surprisingly, the diabetics have significantly higher levels of plasma AD and DHEA than the hirsute diabetics.

Circulating androgen levels have been reported elevated in idiopathically hirsute women elsewhere;[1,3,4] however, this is not a consistent finding, and overlaps of normal and hirsute values are common.[5] Furthermore, a suppression of high androgen levels to normal does not necessarily result in a decrease in the severity of hirsutism once established.[6] Since free or unbound androgen is considered to be the active androgenic moiety,[7,8] it has been suggested that a decrease in sex-hormone-binding globulins may be responsible for androgen activity in some cases.[9-12] Increased end-organ sensitivity also may play a part in hirsutism.[13]

It has been reported that DHT is the active androgen in certain skin areas and in hair.[14-16] Free AD enters the cell and is converted to T by a 17β-hydroxydehydrogenase and then to DHT by a 5α-reductase. Free T can enter the cell also and undergo the conversion to DHT. As a result, the effect of DHT can be local and independent of its circulating levels. DHT activity may increase in different target sites at different periods and then decrease to relatively low levels when activity or growth has been completed.[17] It also has been speculated that, in hair, AD is converted by the same 5α-reductase to androstanedione and that this steroid becomes the most important androgen in this site.[18]

Regardless of whether DHT or androstanedione is the major androgenic steroid, both originate from AD or T via 5α-reductase. A decrease in 5α-reductase activity has been demonstrated in vitro in the liver tissue of alloxan-diabetic rats.[19] The question arises whether such a decrease in enzyme activity occurs in adult-onset diabetes. Diabetic women have available an excess of total circulating AD that could enter the cells of the hair follicles and be converted to active

hormone. Simultaneously, the decreased 5α-reductase levels may prevent conversion to excess active androgen, whether DHT or androstanedione. This would be reflected in a lack of hirsutism, which is what we find in the majority of diabetic women.

The hirsute diabetic woman does not display the same excess AD in her circulation as the diabetic does. She does, however, display a significantly higher circulating T concentration than do controls. A similar argument can therefore be postulated for the hirsute diabetic—i.e., slightly depressed liver 5α-reductase activity permits some accumulation of circulating androgen precursors, while at the same time slightly depressed local 5α-reductase activity still permits a fairly efficient target tissue conversion of T to the active DHT.

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