Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities of hormonal treatment

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Objective: To evaluate the degree of E_2 deficiency in male congenital hypogonadotropic hypogonadism (CHH), and its response to different hormonal treatments.

Design: Retrospective and prospective studies.

Setting: Academic institution.

Patient(s): Untreated or treated CHH, healthy men, untreated men with Klinefelter syndrome (KS).

Intervention(s): Serum sex hormone-binding globulin (SHBG) and total E_2 (TE2) as well as bioavailable (BE2) and free (FE2) levels were measured and determined.

Main Outcome Measure(s): Total, bioavailable, and free testosterone, TE2, BE2, FE2 were compared in normal men, untreated and treated CHH and in untreated KS.

MATERIALS AND METHODS

Patients

This single-center study was approved by the institutional review boards of Bicêtre teaching hospital and Faculté de Médecine Paris Sud. All the patients and healthy volunteers gave their written informed consent. Men who used any anabolic medication were excluded from the study.

MATERIALS AND METHODS

Untreated patients with CHH We included 91 previously untreated patients with CHH referred to the Reproductive Health and Endocrine Department of Bicêtre Hospital in Paris, France, between January 2001 and August 2010. These patients' isolated gonadotropin deficiency was characterized by [1] absent or incomplete puberty at age 17 years; [2] low serum T levels and low or normal serum gonadotropin levels; [3] normal basal and stimulated levels of cortisol (F), growth hormone, PRL, and TSH in response to insulin-induced hypoglycemia and thyrotropin-releasing hormone (TRH), and normal basal serum DHEAS and thyroid hormone levels; [4] normal serum insulin-like growth factor I (IGF-I), iron, and ferritin concentrations; and [5] normal magnetic resonance imaging (MRI) of the hypothalamic-pituitary region (1, 2). Forty-one of these patients were considered to have Kallmann syndrome, as olfactometry showed anosmia or hyposmia and/or MRI showed olfactory bulb aplasia or hypoplasia (10, 11). None of the patients in this group had previously received androgen or gonadotropin replacement therapy.

MATERIALS AND METHODS

Healthy men Sixty-three men, 17 to 46 years of age, were evaluated in our department between March 2001 and May 2010 because they belonged to couples presenting with infertility of female origin. They were chosen for the evaluation of normal gonadotropin and gonadal steroid secretion on the basis of the following criteria (collected by J.Y.): no unusual history, sexual activity and physical examination, including testicular volume more than 15 mL (Prader orchidometer); normal serum concentrations of LH, FSH, and T; and normal semen analysis (>20 million sperm/mL, >50% motility, >2-mL volume).

Patients with Klinefelter syndrome For comparison with a classic testicular cause of hypogonadism, we also included 45 untreated patients with Klinefelter syndrome (34.5 ± 11.8 years; mean ± SD) who were referred to our department during the same period for pubertal delay, gynecomastia, or infertility. All of these patients had peripheral karyotyping, showing that all cells harbored a 47,XXY complement (homogenous Klinefelter syndrome).

Assays

Serum sex hormone-binding globulin and T Serum sex hormone-binding globulin (SHBG) was measured with a solid-phase chemiluminescent immunometric assay (Immulite; Siemens Healthcare Diagnostic Products, Llanberis, United Kingdom) with a detection limit of 0.02 nmol/L. The intra-assay and interassay coefficients of variation (CV) were 3.2% and 4.6% for a SHBG concentration of 56.4 nmol/L (12).

Serum total T (TT) was measured with a direct radioimmunoassay on an Orion Diagnostica device (Spectria, Espoo, Finland) with a detection limit of 0.02 ng/mL (0.06 nmol/L). The intra-assay and interassay CVs were, respectively, 3.8% and 4.8% at 3.3 and 2.6 ng/mL (11.4 and 9.1 nmol/L) and the intra-assay and interassay CVs were 7.5% and 7.0% at, respectively, 0.46 and 0.35 ng/mL (1.6 and 1.2 nmol/L) for TT (13).

Serum concentrations of bioavailable and free T (BT and FT) were calculated with validated algorithms based on equations described by Vermeulen et al. (14), using measured TT and SHBG concentrations, an assumed constant for albumin (43 g/L), and affinity constants of SHBG and albumin for T. The FT fraction was determined with the FT calculation from Vermeulen et al. (14), owing to the poor reliability of commercial FT assays relative to the equilibrium dialysis method (14), as confirmed in the present study (data not shown).

SUPPLEMENTAL TABLE 1

Main characteristics of healthy men, untreated patients with CHH and Klinefelter syndrome.

Variable	Controls	CHH	Klinefelter
n	63	91	45
Age (y)	34.0 ± 11.4 (17–46)	28.8 ± 10.1 (17–45)	34.5 ± 11.8 (17–51)
BMI (kg/m^2)	22.8 ± 1.9 (18.6–27.1)	25.4 ± 5.4[a] (17.5–40.1)	25.0 ± 5.0[c] (17.0–33.2)
SHBG (nmol/L)	28 ± 10 (13–56)	36 ± 22[a] (3–107)	27.5 ± 15.1 (10–78)
FSH (IU/L)	3.5 ± 1.8 (1.3–8.6)	0.78 ± 0.8[b] (0.05–3.8)	31.0 ± 15.3[d] (12–78)
LH (IU/L)	3.5 ± 1.7 (1.6–8.0)	0.59 ± 0.7[b] (0.05–3.1)	17.4 ± 7.9[d] (9.0–39.0)
Total T (ng/mL)	5.2 ± 1.2 (3.4–8.9)	0.46 ± 0.4[b] (0.02–1.8)	1.8 ± 1.2[d,e] (0.2–4.8)
Bioavailable T (ng/mL)	3.0 ± 0.8 (1.8–5.6)	0.23 ± 0.2[b] (0.01–0.9)	1.0 ± 0.5[d,e] (0.1–2.0)
Free T (ng/mL)	0.11 ± 0.03 (0.07–0.20)	0.009 ± 0.01[b] (ND–0.03)	0.03 ± 0.02[d,e] (ND–0.07)
Total E_2 (pg/mL)	17.6 ± 6.6 (6–38)	7.65 ± 4.2[b] (2–19)	16.0 ± 7.2[e] (5–34)
Bioavailable E_2 (pg/mL)	13.7 ± 5.7 (3.2–33.5)	5.3 ± 3.6[b] (1.1–17.4)	12.4 ± 5.7[e] (4.6–25.3)
Free E_2 (pg/mL)	0.60 ± 0.23 (0.2–1.3)	0.21 ± 0.13[b] (0.05–0.65)	0.53 ± 0.22[e] (0.2–1.0)

Note: Data are expressed as mean ± SD (range: min-max). To convert total, bioavailable, and free T from nanograms per milliliter to nanomoles per liter, multiply by 3.467; to convert total, bioavailable, and free E_2 concentration from picograms per milliliter to picomoles per liter, multiply by 3.671. BMI = body mass index; SHBG = sex hormone–binding globulin; ND = not detectable.

[a] $P<.01$ CHH versus controls.

[b] $P<.0001$ CHH versus controls.

[c] $P<.01$ Klinefelter versus controls.

[d] $P<.0001$ Klinefelter versus controls.

[e] $P<.001$ Klinefelter versus CHH.

Trabado. E_2 deficiency in male CHH. Fertil Steril 2011.

Figure 1

Total (**A**), bioavailable (**B**), and free (**C**) E_2 levels in healthy young men (controls) and untreated young patients with CHH and Klinefelter syndrome. $P < .001$ for all groups. Conversion to SI units: To convert total, bioavailable and free E_2 concentration from pg/mL to picomoles per liter, multiply by 3.671.

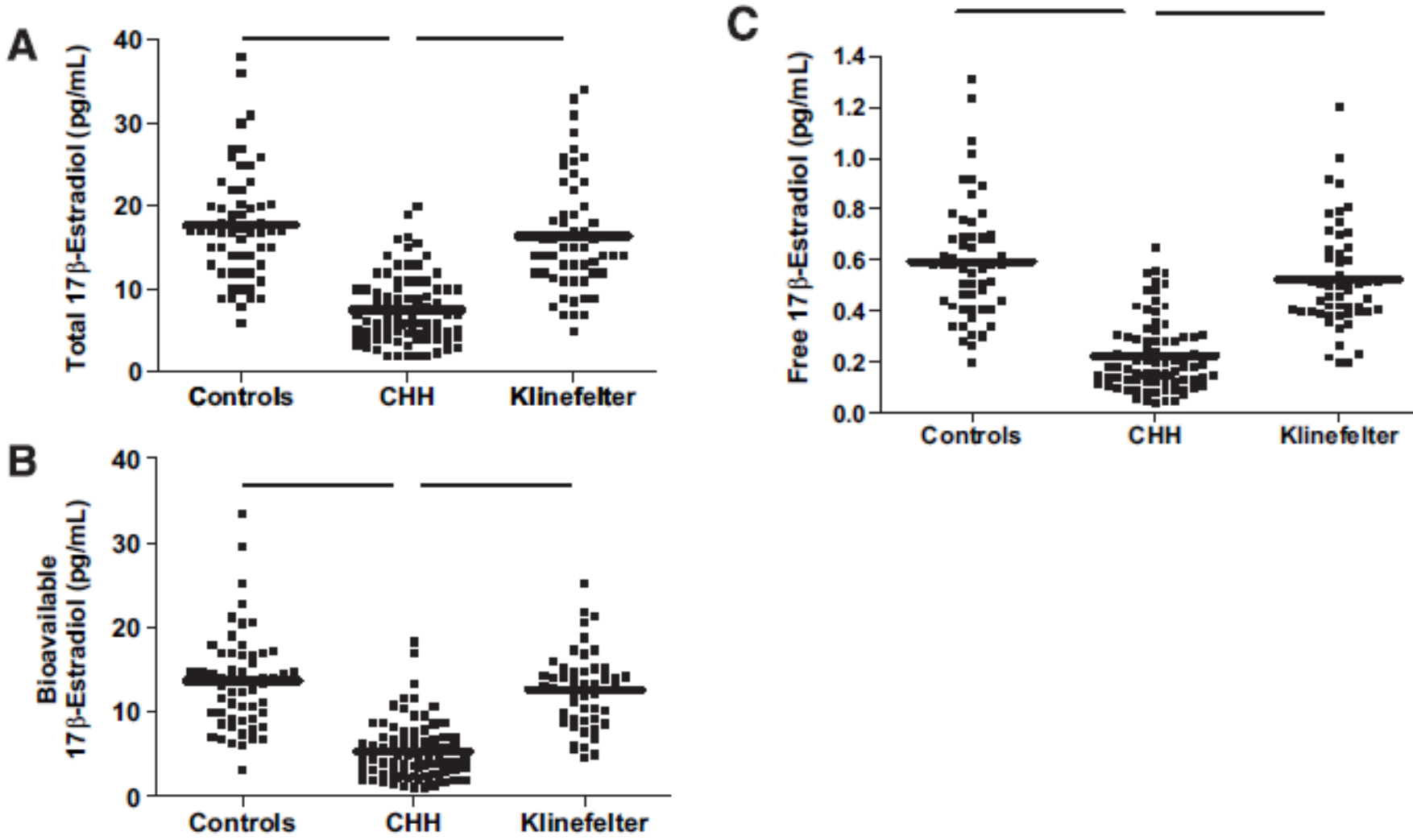
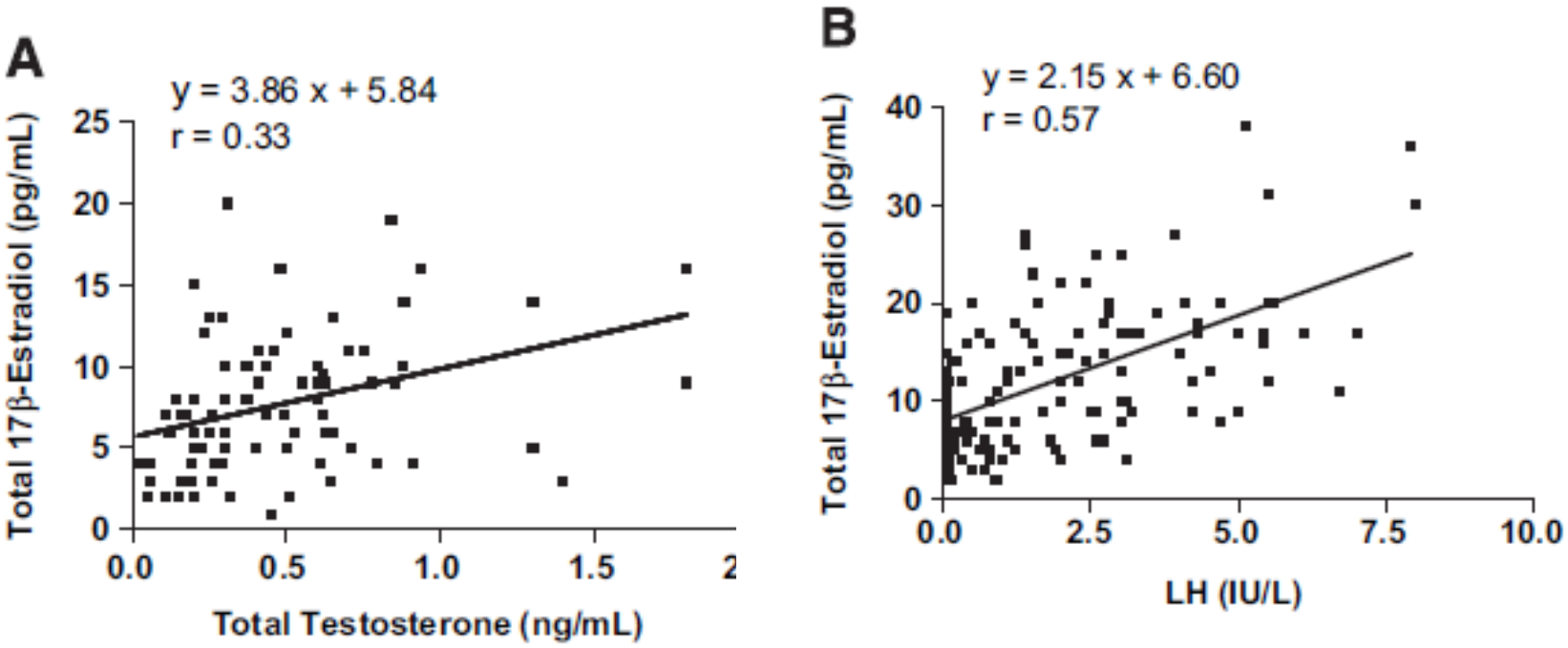


Figure 2

(**A**) Correlation between circulating total testosterone and circulating total E_2 levels in untreated patients with CHH; $P = .003$. (**B**) Correlation between serum LH and circulating total E_2 levels in the combined population of controls and untreated patients with CHH; $P < .001$.



Total E_2 (**A**), bioavailable E_2 (**B**), and free E_2 (**C**) in patients with CHH receiving either testosterone enanthate (TE) or FSH–hCG combination therapy, by comparison with untreated patients with CHH and healthy men (controls); $P < .001$ for all groups. To convert total, bioavailable, and free E_2 concentration from picograms per milliliter to picomoles per liter, multiply by 3.671.

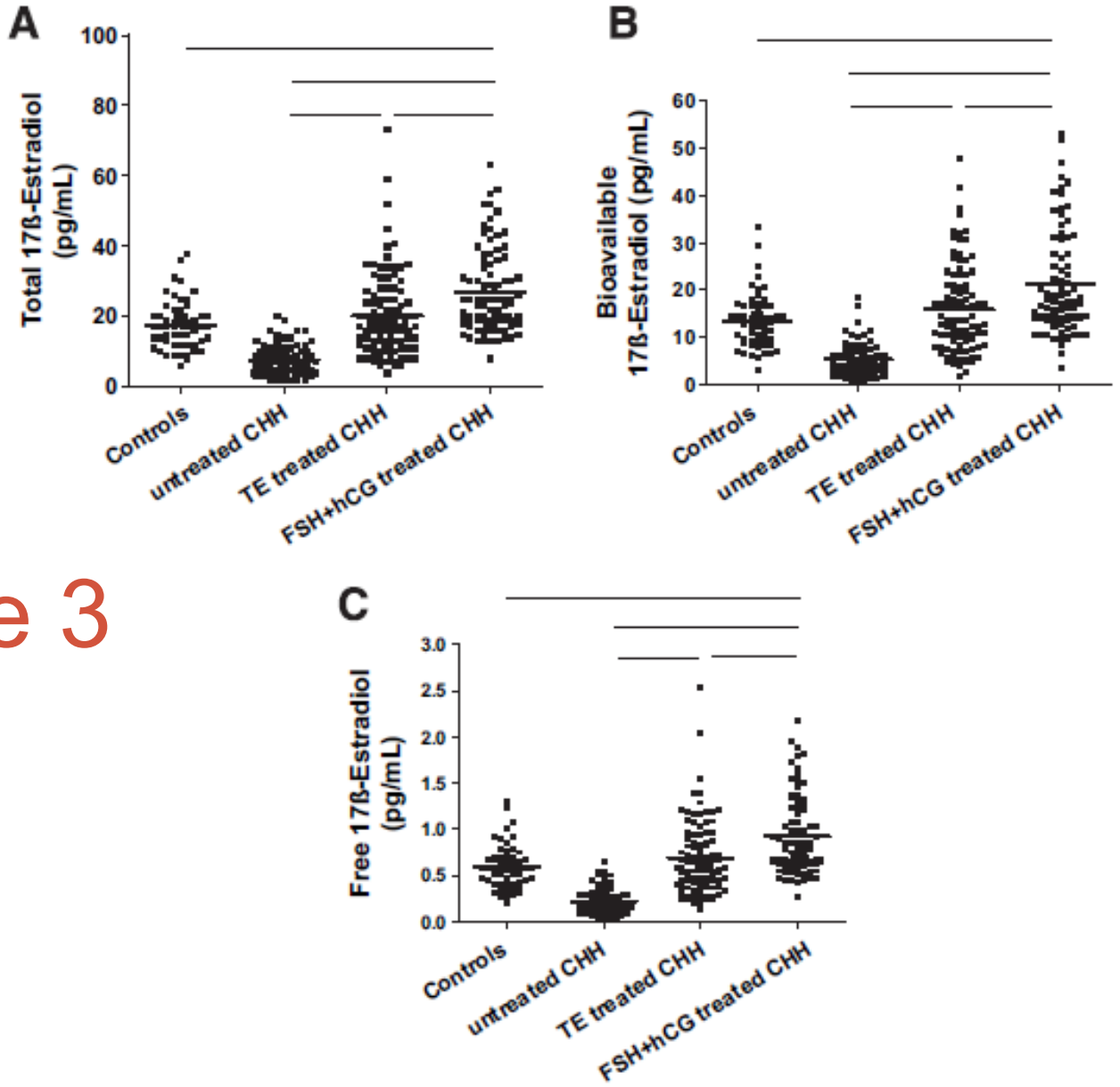
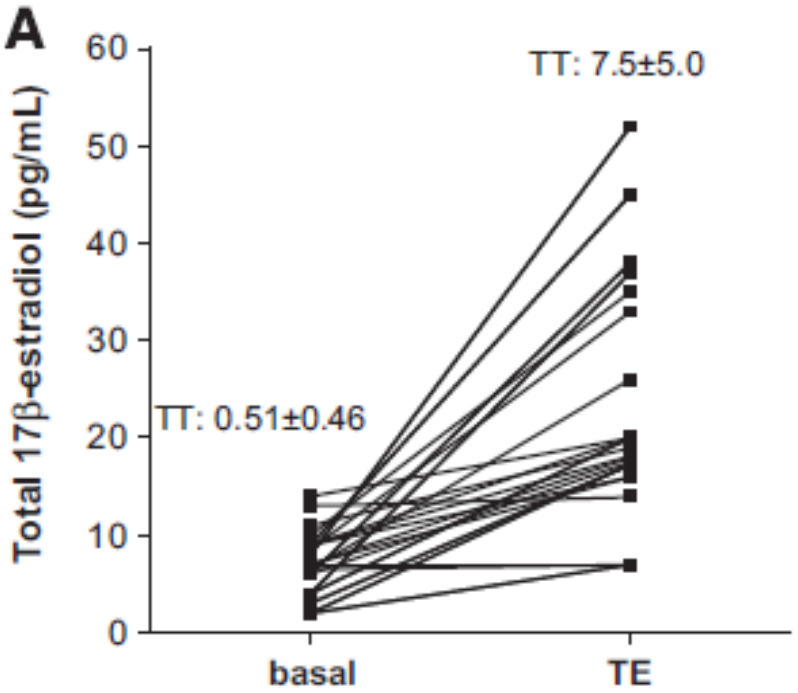
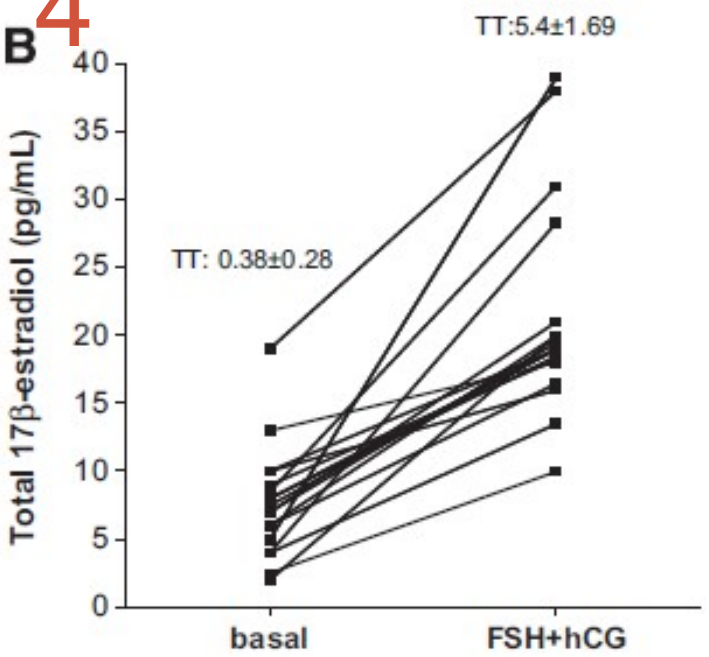


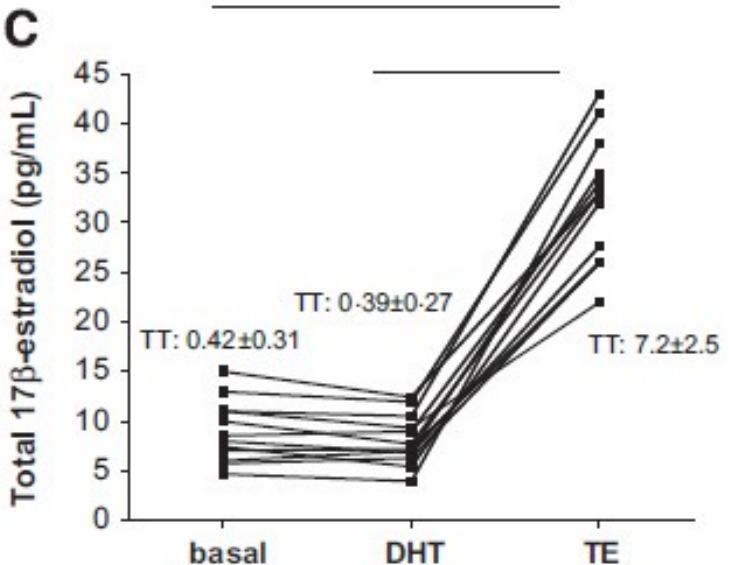
Figure 3

Figure 4

Effect of testosterone enanthate (TE) (**A**) and FSH-hCG combined therapy (**B**) on circulating total E_2 levels in patients with CHH; $P < .0001$. (**C**) Effect of percutaneous dihydrotestosterone (DHT) administration followed by TE therapy on circulating total E_2 levels in patients with CHH; $P < .001$. Mean (±SD, nanograms per milliliter) serum total T (TT) before and under therapy is indicated (TT normal range in healthy men: 2.8–8.9 ng/mL). To convert total E_2 concentration from picograms per milliliter to picomoles per liter, multiply by 3.671.







Discussion

As shown by the positive correlation between TE2 and TT, the E_2 deficiency in untreated patients with CHH was clearly linked to their T deficiency, in keeping with the substrate-product relationship between these two sex steroids. We also found that the decline in TE2 correlated with the decline in circulating LH, which is logical given the key role of this gonadotropin in the positive control of E_2 secretion by Leydig cells (20, 21), and suggests that the E_2 deficiency is linked to the circulating LH deficiency.

Interestingly, however, TE2 concentrations were not always very low in patients with very low LH concentrations (Fig. 2B). The persistence of noteworthy E_2 levels in patients with CHH with very low LH levels could be due to DHEAS conversion into E_2 (22, 23), as all the patients with CHH studied in the present study had normal concentrations of this adrenal precursor (data not shown).

Discussion

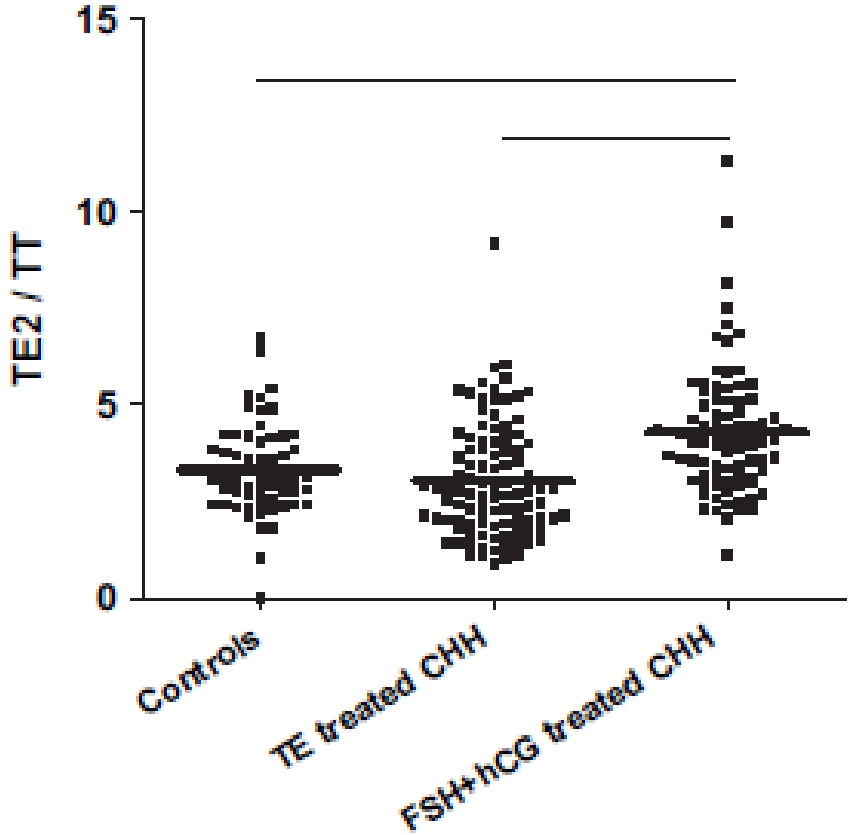
In patients with CHH treated with an aromatizable androgen, we found that the three fractions of circulating E_2 increased significantly, approaching those in healthy men. This result is in keeping with the T-induced correction of osteopenia observed in some studies of few patients with CHH (4, 5). Contrary to treatment with T, an aromatizable androgen, we found that percutaneous DHT enanthate therapy did not correct the E_2 deficiency in patients with CHH. Treatment with this nonaromatizable androgen would therefore be inappropriate for men with CHH, as it could potentially prolong the E_2 deficiency and thereby fail to improve, or even aggravate, the osteopenia or osteoporosis of these patients. The situation is different in patients with Klinefelter syndrome in whom E_2 deficiency is often less severe and gynecomastia prevalent (24–26). In such patients it may be better to attempt to correct the abnormal breast development with percutaneous DHT, as this nonaromatizable androgen would not compromise mineral bone density (27, 28).

Discussion

It is interesting to note that gonadotropin therapy increased E_2 levels significantly more than T enanthate therapy. This could be related to preferential stimulation of the aromatase of Leydig cells chronically stimulated by hCG (29) and might explain the gynecomastia observed during treatment with hCG, both alone and combined with FSH (30). Additional work is needed to determine whether combined gonadotropin therapy is superior to T ester administration with respect to acquisition of mineral bone density in adolescents and young men with CHH.

SUPPLEMENTAL FIGURE 2

Serum total E_2 to serum total T (TE2/TT) ratio in healthy men (controls) and in T enanthate-treated (TE) or FSH+hCG-treated patients with CHH; $P < .001$.



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