Different Testosterone and LH Relationships in Infertile Men

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In both man and animals, changes in Leydig cell structure and function accompany seminiferous tubule damage. In this study of 1745 men attending an infertility clinic, 14% of men with elevated levels of FSH also had elevated LH levels. Groups with severe seminiferous tubule failure (eg, Sertoli Cell Only syndrome or high FSH levels) showed an inverse correlation between LH and testosterone levels. In contrast, groups with milder forms of seminiferous tubule disorders (mild hypospermatogenesis, or FSH levels in the low-normal range) showed a positive correlation between LH and testosterone. It is concluded that different mechanisms must be operative to explain the opposite relationships between LH and testosterone, and that their elucidation may point to the etiology of some forms of seminiferous tubule damage in man.

Key words: Seminiferous tubule failure, FSH, LH, testosterone, Leydig cell dysfunction.

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Serum levels of FSH commonly are elevated in men with primary seminiferous tubule failure, and many authors have emphasized the separate control of FSH and LH secretion (de Kretser et al, 1972; Leonard et al, 1972; Van Thiel et al, 1972; Kjessler and Wide, 1973). However, both gonadotropins predominantly show common regulation by steroid hormones and possibly inhibin (Baker et al, 1982). LH levels may be elevated in men with seminiferous tubule failure, and there is an inverse relationship between the mean LH and testosterone (T) levels in these men (Baker et al, 1976; Rosenfield et al, 1976). This study examines the relationships between LH and T in large groups of infertile men with different degrees of seminiferous tubule failure.

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Methods

Data on 1745 men referred to the Reproductive Medicine Clinic at Prince Henry's Hospital or seen privately by doctors associated with the Clinic between August 1967 and June 1984 because of an abnormal semen analysis or clinical suspicion of a male fertility disorder were collected for computer analysis as part of a survey of male infertility (Baker et al, 1986). This included clinical information, hormonal values, mean levels of at least three pretreatment semen analyses, and in 342 cases, testicular biopsy. Testicular biopsies were classified as showing normal testicular histology, hypospermatogenesis, germ cell arrest, Sertoli Cell Only syndrome, or seminiferous tubule hyalinization (de Kretser et al, 1972; de Kretser and Holstein, 1976). A testicular biopsy was said to show hypospermatogenesis if all stages of spermatogenesis could be identified in the seminiferous epithelium but the number of germ cells occupying the epithelium was either mildly, moderately, or severely depleted. The degree of depletion was a subjective assessment by one observer. Men with hypogonadotropic hypogonadism were excluded. The frequencies of various abnormalities in the female partners, determined as reported elsewhere (Baker et al, 1986), were: 1) persistent anovulation: 2.0%. 2) irregular ovulation: 13.1%, 3) unilateral tubal obstruction: 9.6%, 4) bilateral tubal obstruction: 3.2%, and 5) uterine abnormalities: 9.7%.

Hormone Measurements

Prior to the introduction of the WHO Matched Reagent Programme in March, 1980, serum FSH and LH were measured by double-antibody RIAs (Alford et al, 1973).

TABLE 1. Semen Characteristics and Hormone Levels in 1745 Infertile Men*

Group†	Sperm Concentration ($\times 10^6$/ml)	Motility (Percent)	Normal Morphology (Percent)	FSH (IU/l)	LH (IU/l)	T (nmol/l)
0 (n = 267)	—	—	—	6.8‡ (0.8-58.7)	5.6‡ (1.5-20.1)	19.1 (4.4-33.8)
1 (n = 184)	0.2	24.8 (0-68.7)	33.2 (0-74.9)	7.3‡ (1.3-39.6)	5.8‡ (2.0-16.6)	20.3 (5.6-35.0)
2 (n = 163)	2.5	26.9 (0-61.5)	42.8 (5.2-80.4)	5.9‡ (1.6-21.9)	5.0‡ (1.7-15.2)	20.7 (3.5-37.9)
3 (n = 366)	10.7	35.2‡ (1.7-68.7)	51.7 (15.6-87.8)	4.6‡ (1.2-17.1)	4.4‡ (1.7-11.4)	22.2 (6.9-37.5)
4 (n = 637)	54.7	36.1‡ (8.5-63.8)	59.6‡ (27.4-91.7)	3.1‡ (0.8-11.7)	4.1 (1.5-11.2)	21.0 (6.3-35.7)
5 (n = 128)	67.0	66.9 (55.1-78.8)	68.1 (39.2-96.9)	2.7 (0.9-8.3)	3.8 (1.3-11.0)	20.9 (5.6-36.2)

*Values for motility, morphology, and T levels are the mean and 95% confidence limits. Values for FSH and LH are the geometric mean and 95% confidence limit, and for sperm concentration are the geometric mean.

†Semen group 0: azoospermic; semen group 1: sperm count $>0<1\times10^6$; semen group 2: sperm count $\geq 1\times10^6, \leq 5\times10^6$; semen group 3: sperm count $>5\times10^6, \leq 20\times10^6$; semen group 4: sperm count $>20\times10^6$, motility $<60\%$; semen group 5: sperm count $>20\times10^6$, motility $\geq 60\%$.

‡$P < 0.05$ compared with group 5.

Using WHO standards 75/549 and 68/40 for FSH and LH, the interassay variations were 7.3% and 7.8%, and the mean intra-assay variations were 3.2% and 4.7%, respectively. Conversion factors were determined and employed to convert values obtained prior to the introduction of WHO reagents to those currently in use.

Different methods of assaying plasma T were employed during the period of the study. Initially, a competitive protein-binding assay (Alford et al, 1973) was used. The earlier RIA was an extracted tritiated assay using overnight incubation at 4 C of a commercial rabbit antiserum (Calbiochem-Behring, Kingsgrove, NSW, Australia) and using dextran-coated charcoal to separate free from bound labeled ligand. Currently, a solid-phase assay incorporating [^{125}I] T as the labeled ligand is used. The interassay variations are 5.2% and 7.5% at concentrations of 8.8 nmol/l and 19.5 nmol/l, respectively. The normal range (mean ± 2 SD of log-transformed data) of FSH in our laboratory using WHO reagents is 0.9 to 7.0 IU/l, for LH is 0.9 to 13.0 IU/l, and for T is 10 to 40 nmol/l. Blood samples for the normal hormone ranges were collected from 121 male blood donors, 59 volunteers (medical students or members of staff), 29 men with normal sperm counts (volunteer semen donors), and 13 orthopedic inpatients studied for at least 2 weeks after administration of a general anesthetic.

Statistical Analysis

Statistical analysis of the FSH, LH, and sperm concentration values were performed after logarithmic transformation. Comparisons among groups were performed using Student's t-test of unpaired sample means.

In order to examine the relationships between LH and T in different subgroups of men with subfertility, the patients were categorized according to mean semen analysis results, testicular histology, the presence of an XXY karyotype, a history of undescended testes, or mean FSH levels. Mean LH and T values were obtained for each category. Because not every patient underwent all laboratory investigations, numbers in groups vary.

Semen characteristics and hormone levels are presented in Tables 1 to 4. Table 1 presents the data according to sperm concentration, ranging from a normal semen analysis to azoospermia. Table 2 presents the same data in men who underwent a testicular biopsy. Table 3 presents data in men with Klinefelter's syndrome or a history of undescended testes. Table 4 presents semen characteristics and hormone data from groups of men whose FSH levels were within certain defined ranges.

Results

LH Levels in Men with Seminiferous Tubule Failure: (Fig. 1)

There were 1387 patients with both FSH and LH values. Four hundred thirty-one had levels of FSH above the normal range, and 60 (13.9%) of these had levels of LH above the normal range. The higher the FSH level, the more likely the LH level was to be elevated.

Semen Characteristics and Hormone Levels in Men with Seminiferous Tubule Failure (Table 1)

Mean FSH and LH levels were higher in groups with lower sperm concentrations. The mean serum LH was significantly higher in all groups with a

TABLE 2. Semen Characteristics and Hormone Levels in 342 Men Who Underwent Testicular Biopsy*

Group	Sperm Concentration (× 10^6/ml)	Motility (Percent)	Normal Morphology (Percent)	FSH (IU/l)	LH (IU/l)	T (nmol/l)
Normal biopsy (n = 33)	—	—	—	3.1 (0.6–15.4)	4.6 (1.9–11.0)	21.7 (6.8–36.5)
Mild hypospermatogenesis (n = 58)	< 1 (0–140)	29.4 (0–66.1)	54.2 (17.9–90.5)	3.5 (0.9–13.9)	4.3 (1.8–10.4)	20.1 (6.0–34.2)
Moderate hypospermatogenesis (n = 114)	3.6 (0–207)	30.8 (0–64.5)	53.3 (13.9–92.7)	4.2 (0.9–20.1)	4.5 (2.0–10.3)	20.8 (6.8–34.6)
Severe hypospermatogenesis (n = 46)	< 1 (0–25)	33.2 (0–72.6)	56.4 (18.4–94.3)	4.5 (0.8–24.7)	4.9 (1.9–12.4)	21.3 (3.8–38.7)
Sertoli Cell Only (n = 42)	< 1 (0–12)	41.8 (4.5–79.0)	60.2 (18.4–100)	12.3† (2.9–51.6)	7.1† (2.7–18.7)	19.5 (2.0–37.2)
Germ cell arrest (n = 49)	< 1 (0–85)	22.9 (0–60.8)	36.4 (0–76.4)	4.8‡ (0.8–27.8)	4.4 (1.6–11.7)	19.5 (5.4–33.5)

*Values for motility, morphology, and T levels are the mean value and the 95% confidence limits. For FSH and LH, the values are the the geometric mean and 95% confidence limits and for sperm concentration, the values are the geometric mean and the range.

†$P < 0.001$ compared with normal biopsy.

‡$P < 0.05$ compared with normal biopsy.

sperm concentration less than 20 × 10^6/ml (groups 0–3) than in those men with normal sperm concentrations and motility (group 5). T values were similar in all groups.

Testicular Histology and Hormone Levels (Table 2)

Testicular biopsies were performed in 342 patients. Hormone levels were similar in all groups except for those with Sertoli Cell Only syndrome, in which both gonadotropins were elevated significantly, and germ cell arrest, in which FSH levels were elevated significantly.

Defined Causes of Seminiferous Tubule Failure and Hormone Levels (Table 3)

Twenty-six men had Klinefelter's syndrome and 126 had a history of nondescent of one or both testes. Gonadotropin levels were very high in the men with Klinefelter's syndrome, and T levels were significantly lower than in the other groups. The men with a history of nondescent of one or both testes also had

TABLE 3. Semen Characteristics and Hormone Levels in 26 Men with Klinefelter's Syndrome and 126 Men with a History of Nondescent of One or Both Testes*

Group†	Sperm Concentration (× 10^6/ml)	Motility (Percent)	Normal Morphology (Percent)	FSH (IU/l)	LH (IU/l)	T (nmol/l)
XXY (n = 26)	—	—	—	18.5‡ (1.9–83.6)	15.1‡ (0.9–25.9)	14.6‡ (1.9–27.2)
UDT (n = 126)	< 1 (0–181)	35.1 (2.9–67.4)	51.0 (14.8–87.2)	7.8‡ (1.3–49.4)	6.5‡ (2.3–18.4)	19.3 (5.5–33.1)

*Values for motility, morphology, and T levels are the mean value and 95% confidence limits. For FSH and LH, the values are the geometric mean and 95% confidence limits and for sperm concentration, the geometric mean, and the range.

†XXY = Klinefelter's syndrome; UDT = Undescended testis or testes.

‡$P < 0.001$ compared with normal biopsy; see Table 2.

TABLE 4. Semen Characteristics and Hormone Levels in 1479 Men with Different Levels of FSH*

Range of FSH (IU/l)	Sperm Concentration (× 10^6/ml)	Motility (Percent)	Normal Morphology (Percent)	FSH (IU/l)	LH (IU/l)	T (nmol/l)
FSH < 3 (n = 452)	5.3 (0-502)	38.2 (2.1-74.3)	58.7 (20.7-96.7)	1.8	3.4 (1.1-9.9)	20.6 (5.4-35.7)
3 ≦ FSH < 6 (n = 504)	4.7 (0-663.7)	36.5 (0-73.3)	56.2 (18.0-94.4)	4.1	4.4† (1.9-9.9)	21.5 (6.7-36.3)
6 ≦ FSH < 9 (n = 209)	2.2 (0-158)	34.6 (0-69.1)	52.6 (12.2-93.0)	7.2	5.3† (2.4-11.9)	20.8 (5.6-36.1)
9 ≦ FSH < 15 (n = 163)	< 1 (0-104)	32.3 (0-68.7)	50.1 (15.0-85.2)	11.3	6.2† (2.5-15.4)	20.6 (4.9-36.4)
FSH ≧ 15 (n = 151)	< 1 (0-73.1)	37.4 (0-74.4)	50.5 (13.5-87.5)	21.8	9.5† (3.8-24.4)	18.4† (4.3-32.5)

*Values for motility, morphology, and T levels are the mean value and the 95% confidence limits. For FSH and LH levels the values are the geometric mean (and 95% confidence limits for LH) and for sperm concentration, the values are geometric mean and the range.
†$P < 0.01$ compared with the preceding group.

high gonadotropin levels but T levels similar to other groups.

Hormone Levels in Men with Different FSH Levels (Table 4)

The 1479 men with serum FSH results were divided arbitrarily into five groups based on ascending FSH values. With increasing levels of FSH, sperm concentration decreased and LH levels increased.

T levels were similar in all groups except for the one in which FSH levels were highest. In this group, the mean T level was significantly lower than in all of the other groups.

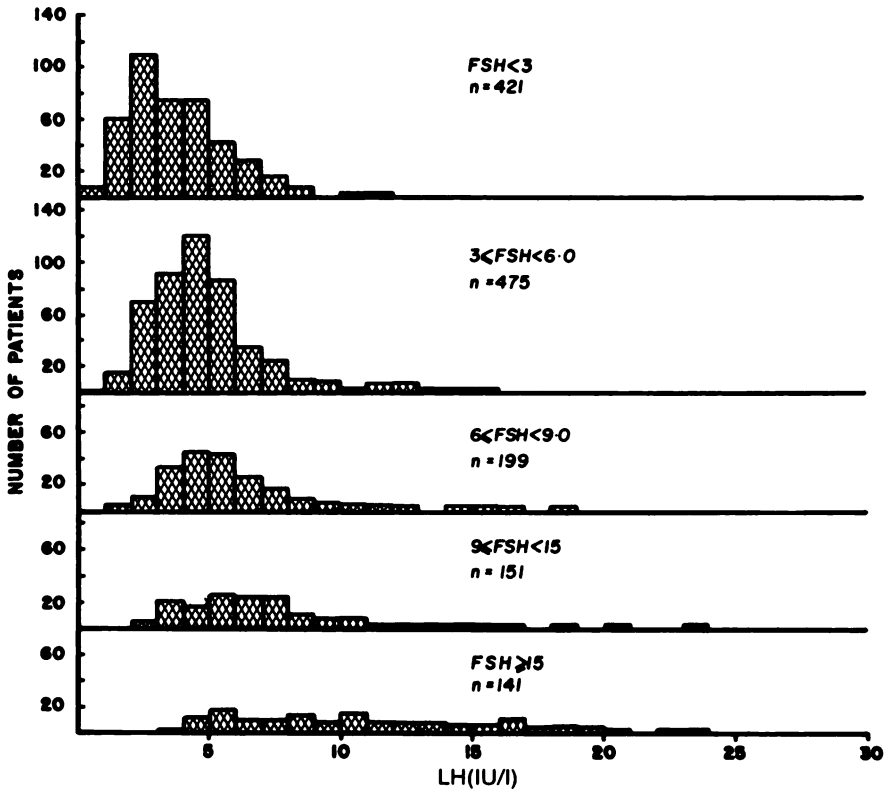

Fig. 1. The frequency distribution of LH levels in infertile men with different levels of serum FSH. Note the skewed distribution of LH and the tendency for the LH to be elevated with higher levels of FSH.

TABLE 5. Relationship Between $\log_{10}$ LH and T in Subgroups of Infertile Men

Subgroup	n*	b*	r*	P*
Sertoli Cell Only	42	−0.007	0.325	< 0.05
High FSH	134	− 0.010	0.335	< 0.001
Semen group 4	411	0.005	0.172	< 0.001
Germ cell arrest	49	0.010	0.329	< 0.05
Mild hypospermatogenesis	58	0.010	0.362	< 0.01
Low-normal FSH	386	0.006	0.225	< 0.001

*n = Number of subjects; b = regression coefficient; *r* = correlation coefficient; *P* = probability.

LH and T Relationships in Men with Seminiferous Tubule Failure (Table 5)

While there was no significant relationship between LH and T in the total group of men, it was found that this resulted from some groups having positive correlations while others had negative correlations.

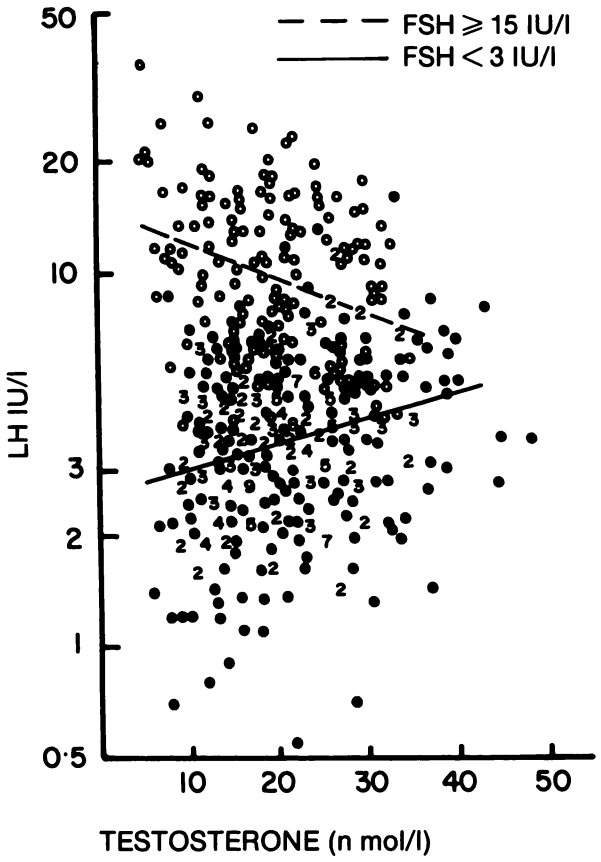

Fig. 2. The different relationships between LH and T in men with low (•) and high (o) levels of circulating FSH. Note the positive relationship in men with low levels of serum FSH and the negative relationship in those with high levels. For men with low FSH, where more than one data point exists for the same locus on the graph, a numeral has been used to indicate the number of men with those hormone values.

Groups with severe forms of seminiferous tubule failure (Sertoli Cell Only syndrome, serum FSH ≧ 15 IU/l) had significant negative correlations. Other groups (Semen group 4, serum FSH < 3 IU/l, mild hypospermatogenesis and germ cell arrest), however, had positive correlations. The positive and negative correlations between LH and T in groups with FSH < 3 greater than or equal to ≧ and ≥ 15 IU/1 are shown in Fig. 2.

Discussion

A remarkable difference was found in different groups of men presenting with infertility. In those with severe seminiferous tubule failure (Sertoli Cell Only syndrome or markedly elevated FSH levels), LH and T were inversely correlated. As LH levels increased, T levels decreased, whereas those with less severe forms of seminiferous tubule failure had direct correlations; the higher the LH level, the higher the T level. Finding an inverse correlation between LH and T with severe seminiferous tubule failure confirms the results of Rosenfield et al (1976), who compared single T values with mean LH levels in multiple samples collected over 3 hours and obtained a high negative correlation coefficient ($r = 0.68$). The lower values obtained in the present study probably result from the use of single sample LH values.

A positive correlation between LH and T in infertile men has not been reported before. Although Stanwell-Smith et al (1985) reported a positive correlation in normal men, it did not achieve statistical significance ($P = 0.06$). Finding a divergence of LH and T relationships in men with disorders of testicular function is important because it opens the way for subsequent investigations.

An inverse relationship between LH and T could result from a primary Leydig cell abnormality with a defect in steroidogenesis (Rodriguez-Rigau, 1983) or from an alteration in the hypothetical signal between the seminiferous tubule and Leydig cell compartments of the testis (Sharpe and Cooper, 1984; Parvinen et al, 1984). Speculation that LH is elevated because of reduced steroid feedback from primary or acquired defects of Leydig cell steroidogenesis is supported by the finding of reduced T responses to hCG in men with primary seminiferous tubule failure (de Kretser et al, 1975). An inverse relationship also could result from secretion of biologically inactive LH with reduced T levels (Dufau et al, 1983; Veldhuis et al, 1984). It is possible that some testicular disorders result from production of bioinactive LH (Isidori et al, 1984).

In contrast, positive correlations between LH and T in certain subgroups of infertile men must result from a different set of mechanisms. High LH and T levels may occur with androgen insensitivity (Aiman and Griffin, 1982; Warne et al, 1983). Low LH and T levels could result from defective LH secretion (low mean levels or decreased frequency of LH pulses) with consequent inadequate T production and abnormal spermatogenesis. Such a defect might explain some of the cases of men with abnormal sperm motility, germ cell arrest, mild hypospermatogenesis or low-normal levels of FSH. Finally, changes in plasma protein binding of T would alter free T and feedback inhibition of LH secretion, and LH and T levels would change with time, depending on the stage of compensation.

In conclusion, our findings of an inverse relationship between LH and T in men with severe forms of seminiferous tubule failure and a positive correlation in others indicate a heterogeneity of causes of testicular malfunction in infertile men. Studies to clarify the reasons for the difference in the LH-T relationships may uncover remediable causes of male infertility.

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