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hormones. However, there were differences depending on vaginal versus planned cesarean section deliveries. In women carrying a male fetus we found significantly higher levels of 17-OH-pregnenolone, progesterone, cortisol, corticosterone and significantly lower levels of estradiol in those undergoing spontaneous vaginal delivery. However, we found no significant differences in the cord blood of newborn males from either delivery type. We established reference ranges for our analysis methods, which should be useful for further studies as well as in standard clinical practice.

Acknowledgments

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Characterization of the expression and physiological roles of thyroid-stimulating hormone receptor in the male testis

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Thyroid-stimulating hormone receptor (TSHR) is typically known to be expressed in the thyroid gland of mammals for the control of body metabolism. However, because the TSHR ancestor is the only glycoprotein hormone receptor found in invertebrates, we hypothesized that TSHR evolves much earlier than FSHR and LHR and thus can be expressed in mammalian gonads for certain uncharacterized impacts. To prove this, real-time PCR quantification against *Tshr* in all male mouse reproductive organs was performed. The results indicated, that *Tshr* is mainly expressed in the testis where it is increased in an age-dependent manner. TSHR is located mainly in Sertoli cells and moderately in germ cells; such a profile was further confirmed using isolated primary mouse Sertoli cells. Gene regulatory test using the TM4 Sertoli cell line showed that *Tshr* expression can be increased via the cAMP cascade. In terms of the cognate ligands for TSHR, we demonstrated that the testicular TSHR is likely to be activated via an endocrine loop by the pituitary-secreted TSH since the negligible level of the genes encoding TSH or thyrostimulin can be detected in male reproductive organs. Furthermore, using cultured testis tubules or explants, TSH treatment can not only promote the proliferation of germ cells *ex vivo* but also increase the transcripts of *Tgn*, *Tpo* and *Slc5a5*. Taken together, activation of the TSHR signaling *in situ* can influence spermatogenesis and may potentially regulate the amounts of thyroid hormones locally. Therefore, our findings overthrow the traditional concept regarding the physiological roles of TSHR and may open a new era of TSHR functions in the reproductive system.

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Semen quality in uncontrolled acromegalic patients with hypogonadism

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Objective

Growth hormone (GH) activity might be implicated in male reproductive function. One previous study has suggested significantly reduced semen quality in untreated acromegalic patients due to both reduced sperm counts and motility.

Design and methods

A retrospective study comprising 10 uncontrolled hypogonadal acromegalic patients (median age 29y) who delivered semen for cryopreservation before initiation of testosterone therapy. Semen variables and hormone concentrations were compared to those of 10 non-acromegalic hypogonadal men with pituitary disease (age 31 years) and those of young healthy men ($n=340$).

Results

80% of acromegalic patients vs 50% of non-acromegalic patients had total sperm counts above 39 million and progressive motile spermatozoa above 32% ($P=0.18$) (WHO criteria for normal semen quality based on sperm counts and motility). The corresponding number in healthy controls was 82%. The prevalence of normal semen quality in acromegalic patients vs healthy controls was 80% vs 82% ($P=0.55$) and in non-acromegalic patients vs healthy controls 50% vs 82% ($P=0.022$). Serum IGF-1 was higher in acromegalic patients vs non-

acromegalic patients 1017 (421–1434) vs 211 (91–271) mg/l ($P<0.001$). For reproductive hormone levels there were no differences between acromegalic patients vs non-acromegalic patients (P -values between 0.10 and 0.61). Patients ($n=20$) vs healthy controls had lower serum testosterone 5.4 (2.2–7.6) vs 19.7 (15.5–24.5) nmol/l ($P=0.001$), calculated free testosterone 145 (56–183) vs 464 (359–574) pmol/l ($P<0.001$), LH ($P=0.002$), and inhibin b ($P<0.001$). Levels of FSH were similar ($P=0.63$).

Conclusions

Despite severe Leydig cell insufficiency acromegalic patients had semen quality similar to healthy controls based on determination of the number of progressively motile spermatozoa. By contrast non-acromegalic patients had reduced semen quality. Our data do not support reduced semen quality in acromegaly.

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P319

Characteristics, geographical distribution and age at diagnosis of patients with Klinefelter syndrome in Italy: a cohort study from the Klinefelter Italian Group (KING)

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Introduction

Klinefelter syndrome (KS) is the most frequent chromosomal disorders, occurring in 1:500 to 1:1000 live male births, associated to male infertility. Although significant research has been conducted, KS remains frustratingly underdiagnosed with a remarkable portion of cases being unidentified. Under diagnosis may be due to man's hesitancy about seeking medical counseling, low awareness of KS among health professionals, and failure by health professionals to perform routine genital examinations in adult men.

Aim

Our purpose was to describe the phenotypic characteristics and the hormonal patterns of a cohort of patients currently attending a national network of academic or general hospitals of the Klinefelter Italian Group (KING). Moreover, we focused our interest on the geographical distribution, and age at diagnosis of KS in Italy.

Methods

A multicenter, observational study of 594 KS was performed among the patients regularly attending the KING centers, after written informed consent has been obtained.

Results

The mean age was 37.4 ± 13.4 years (median IQR 28–46). The mean testicular volume was 3 ml in both testis, BMI was $26.6 \pm 5.5.8$ and 25.5% of KS meet the diagnostic criteria for metabolic syndrome (Mets). Mean total testosterone was 350 ± 9.1 ng/dl, LH and FSH mean levels were 16.6 (median IQR 8.8–22.5) and 28.5 (median IQR (17.5–39), respectively. A descriptive analysis performed in 594 KS, showed that 329 KS were referred to KING centers of Northern Italy, 65 and 200 KS patients to KING facilities in Central and Southern Italy, respectively. Analysis of variance showed significant statistical differences ($P<0.0000$) between the age at diagnosis of the KS of the three geographical groups. In particular, the age of KS patients was significantly lower in Southern Italy (33.3 ± 13 s.d.) compared to Central and Northern Italy (40.2 ± 12.5 s.d. and 39.2 ± 13.3 s.d.).

Conclusions

Our preliminary data showed that KS is highly underdiagnosed in Italy, raising the question of the true prevalence of KS. Our patients presented with a wide spectrum of the classical Klinefelter symptoms. KS were overweight and, surprisingly, only 25.5% of them were diagnosed with Mets. This figure is very close to the Mets prevalence in the Italian general population quoted around 26%. In adulthood, two features were consistently present in every subject: small testes and high FSH and LH/testosterone ratio, despite normal testosterone levels. The

differences of KS age between Italian geographical regions highlight the need for increased awareness leading to timely detection.

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Gonadal Function in Human Immunodeficiency Virus (HIV)-Infected Men: comparison between Isotopic Dilution-Liquid Chromatography-Tandem Mass Spectrometry (ID-LC-MS/MS) and Chemiluminescent Immunoassay (CI)

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Background

HIV-infection is associated to premature decline of serum T. However, prevalence and biochemical characterization of hypogonadism in HIV-infected men are still to be well defined.

Aim

To evaluate the gonadal status in HIV-infected men by assessing circulating total T (TT) with either ID-LC-MS/MS or CI.

Methods

Prospective, cross-sectional, observational study on HIV-infected men with ongoing Highly Active Antiretroviral Therapy (HAART). Serum TT, gonadotropins and sex hormone-binding globulin (SHBG) were measured by CI (Architect, Abbott, USA). TT was also assessed by a validated in house ID-LC-MS/MS. Free T (FT) was calculated by Vermeulen equation. Hypogonadism was defined as serum TT levels below 320 ng/dl and/or free T levels below 64 pg/ml. **Statistical analysis:** Parameters were not normally distributed and Mann-Whitney U test, was used to compare continuous variables. Categorical variables were compared using Chi-Square test, while correlations were performed using linear regression models.

Results

315 consecutive HIV-infected men were enrolled (mean age 45.56 ± 5.61 years; average duration of HIV-infection 16.57 ± 10.45 years). Serum TT levels assessed by LC-MS/MS (mean 652.1 ± 229.1 ng/dl) were significantly lower compared to CI (mean 740.2 ± 274.7 ng/dl) ($P < 0.0001$). As a consequence, prevalence of T deficiency was significantly higher comparing LC-MS/MS to CI (5.4% vs 3.2%, $P < 0.0001$). 56 patients (17.8%) showed SHBG above the normal range (> 71.4 nmol/l). Considering calculated FT, the prevalence of hypogonadism was 9.8% using LC-MS/MS and 7.0% using CI, with a significant difference between methodologies ($P < 0.0001$). TT assessed with LC-MS/MS was directly related to TT assessed with CI (Beta = 0.956, $R^2 = 0.913$, $P < 0.0001$), as well as FT (Beta = 0.934, $R^2 = 0.873$, $P < 0.0001$). TT combined with luteinizing hormone (LH) levels was used to classify hypogonadism. By including compensated form of hypogonadism, the prevalence raised to 15.6% for TT and to 17% for FT.

Conclusions

To the best of our knowledge, this is the first properly-designed prospective study aiming to investigate the gonadal status of HIV-infected men with both LC-MS/MS and CI, together with gonadotropins. Notwithstanding the strong correlation found between the two methodologies, the prevalence of hypogonadism results underestimated when CI is used compared to ID-LC-MS/MS in HIV-infected patients. In clinical practice, SHBG for calculated FT is essential for the detection of T deficiency, revealing the real prevalence of hypogonadism in this clinical setting.

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P321

Automated free testosterone assay: validation and usual values

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Introduction

Testosterone circulates under different forms in blood, mainly bound to proteins i.e. Sex Hormone Binding Globulin (SHBG) and albumin. Free testosterone (FT), the biologically active form, represents 2% of total testosterone (TT). FT measurement is mainly indicated when TT level is discordant with clinical picture but remains technically challenging. Indeed, as for all free hormones, gold standard method relies on equilibrium dialysis, unusable in routine. Direct immunoassays by competition have thus been designed, traditionally based on sensible radioactive detection signal (RIA). FT can also be calculated from TT, SHBG and albumin levels. Our work aimed to compare a new automated immunoassay to preexisting dosages and to propose adapted usual values.

Materials and methods

Analytical performances of this new FT assay were evaluated. FT was therefore determined in 164 patients (68 women, 96 men) using the new immunoassay (IS-5300, IDS-iSYS Free Testosterone), a RIA immunoassay (KIP119000, DIALsource), and a calculation based on TT (RIA TESTO-CT2, Cisbio), SHBG, and albumin (Cobas ROCHE) concentrations. Usual values for the new dosage were established.

Results

Analytical performances of the new assay claimed by the manufacturer were confirmed and comparable with those of the RIA assay except for a higher detection limit. Correlation between immunoassays was satisfactory in men ($R^2 = 0.77$) but weaker in women ($R^2 = 0.45$), results with the new automated dosage being globally 30% lower. Correlation between both immunoassays and calculated FT was also satisfactory in men (respectively $R^2 = 0.68$ for automated and 0.76 for RIA immunoassays) and poor in women (respectively $R^2 = 0.15$ and 0.13). Calculated FT was much higher than measured FT, as the corresponding reference values proposed by the manufacturers. This discrepancy was confirmed by the analysis of external quality controls results whatever the direct immunoassay. We proposed preliminary usual values (minimal and maximum values observed in the subgroup of patients with normal testosterone and SHBG levels): 18.9–51.7 pmol/l in men < 50 years old ($n = 23$); 7.4–39.5 pmol/l in men > 50 years old ($n = 33$); < 6.2 pmol/l in women < 50 years old ($n = 34$) and < 4.3 pmol/l in women > 50 years old ($n = 23$).

Conclusion

IDS-iSYS FT assay is one of the first automated assays allowing FT dosage. Its analytical performances are suitable and provide valuable results in comparison to both RIA immunoassay and calculated FT, at least in men. Clinicians should pay attention to FT usual values indicated by the laboratories, given the large differences observed, particularly between direct immunoassays and calculated FT.

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P322

Assessment of biochemical hyperandrogenism in PCOs by liquid chromatography tandem mass spectrometry using a multiteroid kit: focus on testosterone and androstenedione

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Objective

The identification of hyperandrogenism represents the cornerstone for the assessment of polycystic ovary syndrome (PCOs). However, its definition has always been troubling, mostly because of the poor accuracy shown by routine

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