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MALE REPRODUCTIVE HEALTH

Evaluation of Free Light Chains of Immunoglobulins in Seminal Plasma of Infertile Patients: Preliminary Data

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Seminal plasma is a complex fluid with various components (proteins, enzymes, macro-and microelements, lipids and nutrients) and its role is fundamental for spermatozoa motility, viability and fertilizing capacity maintenance. Many molecules have been measured in seminal plasma to explore some secretion functions of male accessory glands, but effects of biochemical components in human seminal plasma are still debated. Immunoglobulin-free light chains (FLCs) κ and λ are produced by plasma cells in slight excess for the need of immune response and are therefore assayable in blood and in other biological fluids, such as urine, saliva, liquor and synovial fluid. Recently, different biological functions have been attributed to these molecules, suggesting that they are not just a secondary product of immunoglobulin synthesis. No data are reported about presence of FLCs in seminal plasma and their role in physiology of male reproductive system and/or in pathophysiology of infertility. The aims of our study were to investigate the presence and detectability of FLCs in seminal plasma and to evaluate the usefulness of this assay in the diagnostic approach to infertility patients. We enrolled 32 patients aged 19-40 ys, affected by primary infertility; among them, 7 were normospermic (mean±SEM concentration 100.0±16.0 $*10^6$/ml; progressive motile forms 39.1±4.9%; normal forms 45.3±4.5%), 25 were oligo- and/or asthenoteratospermic (mean±SEM concentration 23.8±5.4$*10^6$/ml; progressive motile forms 19.3±4.1%; normal forms 36.05±2.7%); moreover, 17 patients presented II-IV degree varicocele (VAR) according to Dubin-Amelar classification by Doppler technique, the remaining 15 patients did not present varicocele (NO-VAR). After abstinence for 3-5 days, semen samples were collected. FLCs concentrations were assayed by turbidimetric method. Standard semen analysis was performed according to WHO laboratory manual for the examination and processing of human semen, fifth edition, 2010. As main results, independently from sperm count, a significantly difference was observed concerning FLCs concentrations, with higher levels of k and k/λ ratio in NO-VAR vs VAR patients (mean±SEM k 36.4±13.2 vs 17.7±9.0 g/l and 7.7±2.9 vs 2.65±0.7, respectively; $p<0.05$). λ FLCs did not significantly differ between the two groups. This work shows for the first time that FLCs are assayable in seminal plasma, even if their source is to be determined (plasma filtration or local synthesis from lymphoid tissue in accessory gland). Our preliminary data also showed a peculiar pattern with prevalence of k FLCs in infertile patients without VAR, suggesting that FLCs could be in interesting field of investigation in idiopathic infertility. Further studies in large and stratified patients may reveal a possible usefulness of FLCs as a biological marker and/or gain insight about their etiopathogenetic role in male infertility.

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Factors Impacting Quality of Life in Patients With Klinefelter Syndrome: A Systematic Review with Narrative Synthesis and Meta-Analysis.

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Objective: To identify how Klinefelter's Syndrome affects patients' quality of life (QoL) and to determine which subsections of QoL are affected guided by the WHOQOL100-tool as an overarching framework for QoL. To determine the effects and impact KS has on patients' QoL when compared to the QoL of healthy controls and general population. DESIGN - Systematic review of studies reporting QoL factors among patients with KS which included narrative synthesis and thematic analysis of 17 studies and a meta-analysis of intelligence quotient (IQ) completed in 7 studies. QoL factors were reviewed based on the parameters of the WHOQOL-100: physical health, psychological, level of independence, social relations, environment, and religion/spirituality/personal beliefs. DATA SOURCES - Medline, Cochrane, Embase, Psychinfo, CINAHL, BASE and grey search from the reference lists of key publications. **Eligibility Criteria**: RCT's, Cohort studies, cross sectional studies and Epidemiology studies involving patients with KS and reporting on QoL parameters. Only human studies published in English were considered with no limits for publication date. **Results:** Out of all studies included (n=1266), (87.5%) had suggested KS negatively affected the outcomes measures tested, where recorded (91.1%) of studies had small/medium/large effect sizes (Cohen's d). Narrative synthesis suggests all subgroups of QoL excluding 'environment' and 'spirituality/faith/personal beliefs' were negatively impacted for patients with KS, whilst meta-analysis showed statistical significance ($P<0.00001$) which identified patients with KS having lower full-scale IQ compared to healthy controls. Psychological parameters were the most affected in this patient group, showing that patients with KS experienced greater social anxiety, distress during social interactions, self-esteem, self-injuries behaviours and symptoms or traits related to Autism spectrum. **Conclusions:** This review identifies the significant evidence supporting that QoL is reduced in patients with KS. There is a large spectrum of symptoms and no standard phenotype for KS suggesting that multiple facets of QoL are negatively impacted in these patients due to the complex nature of KS and the severity of symptoms and phenotype associated with KS. PROSPERO REGISTRATION NUMBER - CRD4202017343

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Impact of Short-Acting vs Long-Acting Testosterone Therapy on Intratesticular Testosterone Using Data

From Two Open-Label Randomized Clinical Trials of Testosterone Pellets, Injections, and Intranasal Gel in Hypogonadal Men

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Introduction & Objective: Exogenous testosterone (T) replacement therapy (TRT) is typically long-acting and can potentially cause infertility in a majority of men due to suppression of HPG axis. Intratesticular testosterone is vital for spermatogenesis and can be reliably evaluated with serum 17-hydroxyprogesterone (17-OHP). Based on this observation, we hypothesized that we used serum 17-OHP as a serum biomarker for evaluating intratesticular T in men receiving TRT. We hypothesized that long-acting TRT will have a significant impact on suppressing HPG axis as compared to short-acting preparations. We evaluated data from two simultaneous open-label, randomized, two-arm clinical trials amongst different treatment preparations (Trial I) subcutaneous T pellets and (Trial II) Intranasal Testosterone (Natesto) or Intramuscular Testosterone cypionate (TC).
Subject & Methods: Hypogonadal men (2 AM serum T < 300 ng/dL assayed by LC-MS/MS) aged 18-65 years were randomized into open-label randomized clinical trials. Eligible subjects received: 800mg subcutaneous Testopel T pellets (n=47); or 11mg TID Intranasal testosterone (Natesto) (n=10) or 200mg x 2 weeks TC (n=10) for 2 months. Serum T and 17-OHP were collected at baseline and after 2 months of therapy. Data are presented as a post-hoc analysis of the two randomized clinical trials and reported as the median and interquartile range [25^{th}-75^{th}], paired sample analysis (baseline versus follow-up) was performed with the Wilcoxon test to determine change during time within the different TRT modalities, with $p<0.05$ considered significant.
Results: Median change for serum T between baseline and 2mo follow-up to subcutaneous T pellets was 542 [454-757] ng/dL, Intranasal Testosterone 706 [517-1010] ng/dL, and TC 525 [280-712]ng/dL.; 96% of subjects in each trial achieved mean T concentrations in the eugonadal range. We demonstrated that serum T levels were within normal range among men receiving the various therapies. As expected, we found a statistically significant decrease amongst the different T preparations in serum 17-OHP. Longer acting T preparations such as T pellets and TC demonstrated the greatest decrease in 17-OHP, from 41 [20.3-65.6] to 14 [10.3-20.8] ng/dL and 80 [48-121] ng/dL to 20 [17-36] ng/dL ($p<0.001$), respectively. Shorter acting T preparations such as Natesto demonstrated a statistically significant decrease in 17-OHP, from 52.5 [26-67] ng/dL to 26.5 [18-39.8]ng/dL ($p=0.007$), but to a lesser extent as compared to the longer-acting preparations.
Conclusions: Natesto, and other short acting forms of TRT may help hyogonadal men maintain Intratesticular T that is critical for maintaining spermatogenesis. The differential effects of TRT on intratesticular T based on their half-lives is novel and should be considered during the decision making for hypogondal men who wish to preserve fertility and / or testis size.

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Impact of Testosterone Therapy on Hematocrit and Polycythemia: Evaluation of Data From Two Ongoing Open-Label Randomized Single-Center Clinical Trials

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Introduction & Objective: Testosterone (T) replacement therapy (TRT) is the mainstay treatment for male hypogonadism. The most commonly reported adverse event among men using TRT is polycythemia. What is unknown is whether the short-acting vs. long-acting testosterone preparations have different effects on hematocrit. We hypothesized that short-acting testosterone therapy will be physiologic and have lesser effect on hematocrit compared to long-acting TRT. We evaluated data from two simultaneous ongoing open-label, randomized, two-arm clinical trials to evaluate the impact of TRT on Hematocrit and compared prevalence rates of polycythemia among subcutaneous T pellets (long-acting) and Intranasal Testosterone (Natesto) or Intramuscular Testosterone cypionate (TC) (short-acting).
Subject and Methods: Hypogonadal men (2 AM serum T < 300 ng/dL assayed by LC-MS/MS) aged 18-65 years were randomized into open-label randomized clinical trials. Eligible subjects received: Trial 1: 800mg subcutaneous Testopel T pellets; Trial 2: 11mg TID Intranasal testosterone (Natesto) or 200mg x 2 weeks TC for 2 months. Serum T, Hematocrit (HCT), and prevalence of polycythemia (as defined as HCT >50%) were collected at baseline and after 2 months of therapy. Data are presented as a post-hoc analysis of the two randomized clinical trials and reported as median and interquartile range [25^{th}-75^{th}], paired sample analysis (baseline versus follow-up) was performed with the Wilcoxon rank test to determine change during time within the different TRT modalities, with $p<0.05$ considered significant.
Results: Median change for serum T between baseline and 2mo follow-up to subcutaneous T pellets was 542 [454-757] ng/dL, Intranasal Testosterone 706 [517-1010] ng/dL, and TC 525 [280-712]ng/dL. T pellets showed a statistically significant increase in HCT from 44.6 [42.0-46.6] to 46.7 [42.6-48.9] ($p<0.001$), with a prevalence of 7/47 (14%) men developing polycythemia. A safety trigger for HCT greater than 54% occurred in 2/47 (4%). The treatment effect was independent of baseline serum testosterone. TRT with Natesto decreased HCT, from 43.4 [41.6-46.1] to 43.4 [40.6-46.5], however not statistically significant ($p=0.262$). TC statistically increased HCT from 41.6 [40.3-43.1] to 43.8 [43.5-47.4] ($p=0.018$), with 0% of men developing polycythemia in both groups.
Conclusions: Long acting TRT appears to increase hematocrit compared to short-acting testosterone therapies. Treatment of hypogonadal men with Intranasal T Natesto and testosterone cypionate successfully achieved target serum T level and maintained HCT levels. Longer-term durability and safety effects of the intervention remain to be further investigated.