PROJECT REVIEW

"Androgen/Growth Factor Study in Young (AGSY)"

C. Hagen (Odense University Hospital, Odense, Denmark), **E. Haug** (The Hormone Laboratory, Aker University Hospital, Trondheimsvien, Norway)

Androgen replacement therapy is usually life-long, and should only be started after androgen deficiency has been proven by hormone assays. The therapeutic goal is to maintain physiological testosterone levels (lc). However, the normal range for serum-testosterone for 20-30 yr. old men has not been established. The existing studies have been on limited number of subjects using recruited healthy subjects, who have not been evaluated for hypogonadism, or blood donors (la, 3,4, 4a). The study design of earlier studies may not have taken into account the circadian rhytm in testosterone levels. The acrophase (time of maximum value) of the rhytm occurs several hours prior to the time of awakening and the nadir is in the late afternoon or early evening (lb).

These problems with physiological levels of testosterone may be especially important when looking at use, misuse and abuse of androgens. Therefore when defining "hypogonadism" as serum total testosterone levels consistently below the lower limit of normal, it is impossible from the data available in the literature to extract an estimated prevalence for hypogonadism. The best estimation in otherwise healthy, non-obese male subjects aged 20-30 yrs. is between 2 and 4% (4a).

Testosterone circulates in the blood in a free form and in a protein bound form. Only approximately 2% of the circulating testosterone is free, 30% is tied to albumin and the remaining part is tied to the sexual hormone-binding-protein (SHBG), which is a glucoprotein with special affinity to androgens and oestrogens. The concentration of SHBG is increased by hypogonadism, cirrhosis of the liver and decreased by obesity and treatment with androgens in supraphysiological doses.

Muscle mass, strength and exercise

Androgens are known for the anabolic effects, especially in high doses. Patients with hypogonadism can increase muscle mass during androgen substitution therapy *(5,* 6, 7, 8, 11). In cell cultures, androgens will stimulate mitosis of mioblasts and initiate a cascade of biochemical changes. In studies using eugonadal young males, pharmacological doses of testosterone did only influence muscle mass if they were administrated during increased physical activity or weight lifting training *(5,* 7). Large population-based studies on the relationship between muscle mass, exercise, strength, and testosterone levels are not avaiable. Neither do we know of any publication, which in a controlled study show long-term effects of testosterone substitution therapy on these parameters in hypogonadal men.

Cardiovascular risk factors (fat mass, lipids, and glucose metabolism)

Patients with hypogonadism have increased total cholestrole, increased LDL and increased HDL *(5-7,* 12). These patients have increased fat mass and decreased lean body mass (LBM) (6,7, 11, 13, 14). The increased fat mass is accompanied

by increased s-leptin and decreased s-IGF- 1 and growth hormone concentration in blood (7). It has been shown that the increased fat mass is mainly located as abdominal fat. This leads to increased glucose concentration, insulin concentration and later probably to increased blood pressure. One of the hypotheses for these changes is that the decreased testosterone leads to increased frequency of syndrome X. The primary trigger mechanism should be increased stress and thus increased activity of the hypothalamus pituitary adrenal access (10, 14, 16-
18).

Bone metabolism

Long-term treatment of hypogonal men with testosterone decreases bone resorption and increases bone formation markers (8) and increase bone mineral density (9). Behre et al. (9) found that 36 months of T substitution therapy of hypogonadal men restored BMD to the age-dependent reference range. A larger increase was seen in patients with initial low BMD during the first year of treatment. There was no significant changes in BMD after 18 to 24 months of treatment.

There are no clinical control studies available in this area.

Androgen/Growth factor study in young (AGSY).

Results and conclusions

The Odense Androgen study is a population-based cohort study of hypogonadism and growth factor (IGF-1) deficiency in male subjects, 20-30 years of age.
783 males aged 20-30 years were included in the study. The 783 participants included responded to a detailed questionnaire and underwent: full physical examination, blood tests (including androgens/estrogens, bone metabolism, general metabolism, thyroid function, liver parameters, hemoglobin, endocrine parameters), urine tests, DNA analysis of the androgen and estrogen receptor, diverse physiological measurements, DEXA scan, MRI scan, muscle strength tests. The objectives of these studies are:

a) To establish a reference interval for the serum concentration of total-T, free-T, total-E_2, free-E_2 using probit evaluation.
b) To evaluate the impact of BMI, fat parameters, chronic disease (gynecomastia, microtestis etc.) and medication on testosterone, free-testosterone and estradiol levels.
c) To evaluate a positive role of high, medium, and low testosterone levels on:
    a) muscle mass, muscle strength, muscle power, and oxygen uptake
    b) bone mineralization (BMD) and bone metabolism
    c) cardiovascular risk factors/metabolic syndrome: fat mass, serum lipids, glucose, metabolism, blood pressure
    d) hematocrit, growth factors
    e) signs of hypogonadism by medical history as well as clinical signs.
    f) sexual function
    g) quality of life

Publications and poster presentations

1) Odense Androgen Study – A population-based Cohort Study of 20-29 year old Men: Implications of Body Composition, Disease, and Lifestyle Parameters on Cut-off Values for Total and Bioavailable Testosterone.
   ENDO2004 - The Endocrine Society's 86th Annual Meeting.
   New Orleans, Louisiana, USA, 15-19 June 2004.

2) No association between 11-beta-hydroxysteroid dehydrogenase activity and peak bone mass or bone turnover in young healthy men.
   31st European Symposium on Calcified Tissue Society.
   Nice, France, 5-10 June 2004

3) Smoking is associated with low peak bone mass in men – a population-based study.
   National Osteoporosis Society Tenth Conference.
   Harrogate, United Kingdom, 28 November-1 December 2004