



BESINS HEALTHCARE SCIENTIFIC LITERATURE REVIEW – July 2021

Must Read Articles in Men’s Health

Is a Fasting Testosterone Level Really Necessary for the Determination of Androgen Status in Men?

Livingston et al

Clinica Chimica Acta 2021:521:64-69

Pubmed Link: <https://doi.org/10.1016/j.cca.2021.06.026>

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European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update: Male Sexual Dysfunction

Salonia A et al

EURURO 9434:1–25

PubMed link: <https://doi.org/10.1007/s11255-021-02876-w>

Other Articles of Interest - Men’s Health

Efficacy of testosterone replacement therapy for treating metabolic disturbances in late-onset hypogonadism: a systematic review and meta-analysis	Kim S.H. <i>et al</i> International Urology and Nephrology Apr 2021. https://doi.org/10.1007/s11255-021-02876-w	This study looked at the efficacy of TRT for treating metabolic disturbances through a meta-analysis of RCT’s. This study demonstrated that TRT had a positive effect on metabolic profiles in patients with Late Onset Hypogonadism.
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Hypogonadism and its treatment among prostate cancer survivors	Choi E.J. <i>et al</i> Your Sexual Medicine Journal (2021) 33:480–487 https://doi.org/10.1038/s41443-020-00387-3	Historically Testosterone has been contraindicated in men with Prostate Cancer. This publication looks at the burden of adult-onset hypogonadism in Prostate Cancer survivors and discusses the latest evidence around the use of TRT in select PCA survivors.
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Title	Authors	Journal and Issue	Article Type
Is a Fasting Testosterone Level Really Necessary for the Determination of Androgen Status in Men?	Livingston <i>et al</i>	Clinica Chimica Acta 2021: 521:64-69	Retrospective analysis.

What this review brings:

This study provides evidence that fasting samples are not necessary for serum T measurements. Confirmation of this data is needed in other larger, multicenter studies. If confirmed, it would improve convenience for both patients and the healthcare system.

Background:

- Factors effecting testosterone measurements in men include: Circadian rhythm, day to day variability, physical exercise, time of day, stresses and fasting versus non fasting status.
- Laboratory reference ranges do not take the above factors into consideration and considerable variation exists between immunoassays and laboratories for serum T measurements.

Aim:

- To determine the effect of providing a fasting versus non-fasting serum sample on total testosterone levels in men in a real-world setting.

Methods:

- Differences between T level in the following samples were analysed retrospectively (213 men included)
 - **Group 1:** Men with a fasting and a non-fasting sample – n= 69
 - **Group 2:** Men with both non-fasting samples- n= 126
 - **Group 3:** Men with both fasting samples – n=18

Results:

- No significant differences were found in T levels for paired samples (in the same individual) between the fasted and non-fasted states taken \leq 2hours apart within 6 months of each other (Group 1).
- No differences were seen between paired non-fasting T levels (Group 2).
- No differences were seen between paired fasting T levels (Group 3).
- No significant differences were seen between fasting and non -fasting T levels in men stratified by T -levels of \leq 10.4nmol/L or those stratified by T levels of \leq 12.0nmol/L (levels indicative of adult-onset Hypogonadism).
- No significant differences were seen between fasting and non -fasting T levels in men stratified by a median age of 50.

Discussion:

- The result from this study has significant implications for patients, in terms of convenience as a fasting sample does not appear to be necessary for the measurement of serum T based on this data.
- The difference in T results between the paired samples was not significantly different between the 3 groups examined. Any difference seen can be accounted for by analytical and within subject biological variation.
- As this is a retrospective analysis involving a single center, a separate clinical study is necessary to confirm these results.
- The idea that reductions in T after a meal may only apply in younger men is put forward by the authors, citing a previous study by Van de Velde and it is noted that the population in this study were mostly $>$ 40.

Practice Points:

- **Guidelines all still recommend fasting samples, however generating more evidence to show that this is not necessary would greatly facilitate the diagnosis of hypogonadism as it would make it more convenient for both patients and the healthcare system if fasting bloods were not necessary.**
- **Therefore, producing more evidence to support the findings of this study, via audits or IIRs would be of interest to Besins to help support the patient journey.**
- **Note it is also stated in this study that in most instances there was no record of whether the blood sample was actually a fasting sample or not.**

Title	Authors	Journal and Issue	Article Type
European Association of Urology Guidelines on Sexual and 4 Reproductive Health—2021 Update: Male Sexual Dysfunction	Salonia A <i>et al</i>	EURURO 9434 1–25	EAU Clinical Guideline March 2021

What this guideline update review brings:

These guidelines provide us with the latest recommendations for the management of male sexual health including the management of late onset hypogonadism. The diagnostic threshold for detecting a Testosterone deficiency has changed from the 2019 guidelines of 12.1nmol/L to 12nmol/L for total serum T and from 243 pmol/L to <225 pmol/L for FT.

Background:

This article provides a summary update of the EAU Guidelines published in March 2021 and focuses on the aspects of male sexual health management including late on-set hypogonadism.

Each recommendation in the Guideline has been given a strength rating or GRADE.

Definitions of hypogonadism:

- Male hypogonadism: A disorder associated with decreased functional activity of the testes with decreased production and or action of androgens and or impaired sperm production caused by poor testicular function or as a result of inadequate stimulation of the testis by the hypothalamic pituitary gonadal axis.
- Late onset hypogonadism: A clinical condition in the aging male which by definition must comprise specific symptoms and biochemical evidence of testosterone deficiency; usually found in men over 40.

Incidence:

- The incidence of symptomatic hypogonadism varies between 2.1% and 5.7%
- The incidence of hypogonadism has been reported to be between 12.3 and 11.7 cases per 1000 people per year
- Higher prevalence of hypogonadism has been observed amongst men with type 2 diabetes, metabolic syndrome, obesity, cardiovascular disease, chronic obstructive pulmonary disease, renal disease and cancer.

Key messages:

- Testosterone therapy is effective when T levels are **below 12 nmol/l**.
 - Higher efficacy is seen in symptomatic patients with more severe forms of hypogonadism (testosterone <8nmol/l).

- **12 nmol/l should be considered a threshold to start testosterone therapy in the presence of hypogonadal symptoms.**
- Patients with symptomatic hypogonadism without specific contraindications are suitable candidates for receiving T therapy.
- Evidence indicates that T therapy in hypogonadal men may have a beneficial effect on several aspects of sexual function but not in eugonadal men.
- Data suggests that T therapy may reduce percentage body fat and increase lean mass in men with late onset hypogonadism (LOH) but important to note that this data has mostly come from registry and observational studies.
- RCT data suggests that T Therapy may improve insulin resistance and hyperglycaemia and lower cholesterol including lowering LDL cholesterol.
- Severe hypogonadism (Total Testosterone <3.5nmol/l) is frequently associated with bone loss and Osteoporosis and a number of studies have confirmed that T Therapy increased bone mass density in hypogonadal aging men, however this evidence is not sufficient to determine the effect of T therapy alone on risk of bone fractures.
- Selection of the appropriate Testosterone formulation should be based on clinical situation, availability, patient need and expectation.

Recommendations for testosterone therapy outcome:

Recommendations	Strength rating
The use of testosterone therapy in eugonadal men is not indicated.	Strong
Use testosterone as first-line treatment in patients with symptomatic hypogonadism and mild ED	Strong
Use combination of PDE5Is and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight, and benefit cardiometabolic profile.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong
ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.	

Recommendations for choice of treatment for late on-set hypogonadism:

Recommendations	Strength rating
Treat, when indicated, organic causes of hypogonadism (eg, pituitary masses, hyperprolactinemia, etc.).	Strong
Improve lifestyle and reduce weight (eg, obesity); withdraw, when possible, concomitant drugs that impair testosterone production; treat comorbidity before starting testosterone therapy.	Weak
Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in case of treatment-related adverse effects	Weak

Practice Points:

- Important to note that new EAU guidelines give total testosterone level of 12 nmol/L (3.5 ng/ml) as the threshold to diagnose LOH.
- Recommends using fT level of below 225 pmol/l but admits that there is no validated cut off for free testosterone level.
- Guidelines recommend against systematic screening with self-questionnaires and recommend an extremely thorough diagnostic screening, however, it would be Besins view that self-screening questionnaires help a man come to a conclusion that something may be wrong and he needs to present to his doctor.
- The new guidelines point to the fact that more data is needed to properly understand the beneficial effect of combined use of testosterone therapy and PDE5 inhibitors - this is a data gap and would be an interesting IIR proposition for Besins.
- The guidelines state that there are no grounds to discourage testosterone therapy in hypogonadal patients with benign prostatic hyperplasia (BPH)/LUTS. The only concern is related to patients with severe LUTS (International Prostate Symptom 345 Score >19), as these patients are usually excluded from RCTs, therefore limiting the long-term safety data of testosterone therapy in this specific setting – this is another data gap: Testosterone in moderate to severe LUTS that may of interest as a possible IIR.
- No association between Testosterone therapy and raised PSA levels, however caution is urged in the case of prostate cancer survivors as there is still a lack of evidence for men who had high grade prostate cancer who are now in remission, the guidelines recommend a careful conversation explaining the benefits and risks and going through the existing evidence – therefore this is another data gap for Besins (IIRs, observational data would be encouraged).