Reevaluation of testosterone cut-offs for the reflex testing for SHBG in the investigation of androgen status

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Background & Aim: Testosterone measurement is important for the diagnosis and monitoring of several clinical conditions[1], but can be skewed by binding protein levels, particularly, Sex Hormone Binding Globulin (SHBG). Measurements which adjust for SHBG are often considered more useful clinically; specifically, Free Testosterone (FT) in males, and the Free Androgen Index (FAI) in females. In our department we presently reflex SHBG on any male TT between 0.7-10.0nmol/L (Ref: 7.1–31.1) and any female TT >1.5nmol/L (Ref:0.5-1.8nmol/L), with subsequent calculation of FT/FAI. (Figure 1). Our aim was to re-evaluate the effectiveness of these reflex cut-offs.

Methods: Results were gathered from all patients who had TT and SHBG assayed on the same sample within our laboratory during 2019. Additional data previously obtained for our reference range studies were combined with these, and FT (Vermeulen) and Free Androgen Index calculated.

Results & Discussion: Of 834 male patients, 10% of TT values were clinically discordant with FT values (Figure 2A). Of these, 95% were detected by our current reflex cut-offs (Figure 2B). Two-thirds (66%) of all TT<7.1 (LRL) had normal FT. The lowest/highest discordant values were found for a TT of 4.2/11nmol/L respectively. Using such reflex limits detected all discordant results and reduced unnecessary reflexing at levels <4nmol/L. For the 680 female samples, 22% (n=149) of results were discordant, 80% of these discordant results (n=119/149) were detected by our current reflex limit (TT>1.5nmol/L) (Figure 2A and B). A total of 42% of TT >1.8 had normal FAI. For lower TT (0.2–1.5nmol/L) within the RR, there was 8% discordance with FT i.e. raised FAI. Setting a lower reflex limit for TT of 0.5nmol/L would detect all discordant results.

Conclusions: Our data support an overall increase in the testosterone threshold for reflexing SHBG (0.7 to 10.1) for male testosterone. Any decision to lower the current reflex threshold for females requires further logistical consideration however our data support a new upper testosterone limit above which SHBG would not be required. Additional further refinement of the reflex algorithm may be possible by incorporation of androstenedione, already available from our androgen panel (LCMS)

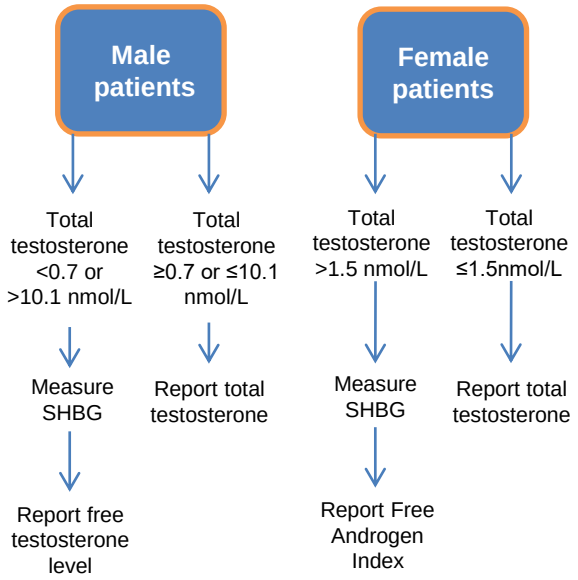

Figure 1: MMUH protocol reflexing total testosterone results for SHBG measurement

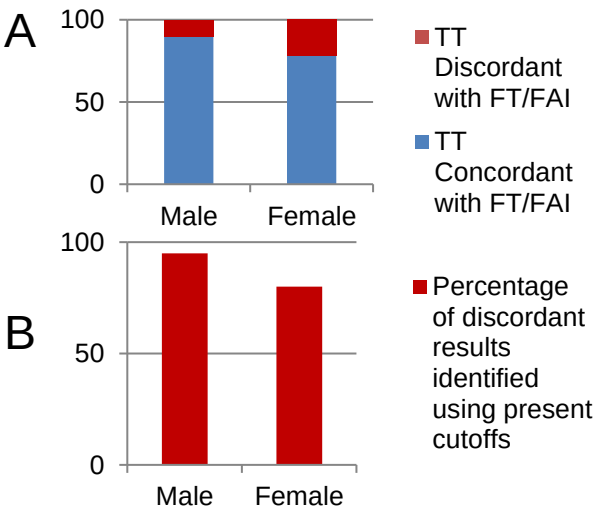

Figure 2: Clinically discordant values presently by reflexing for SHBG. Graph A shows the percentage of patients (Total 834 male, 680 female) whose total testosterone values were found to give discordant clinical interpretations to their calculated free testosterone/ Free androgen index. Graph B shows the percentage of these discordant results that would be picked up using our present cut offs.

References:
1. M Diver (2009) Laboratory Measurement of Testosterone. Front Horm Res. 37, 21-31.