**Asian Journal of Andrology (2015) 17,** 334


www.asiaandro.com; www.ajandrology.com

*Open Access*

# INVITED COMMENTARY

Male Aging

## Commentary on "Late-onset hypogonadism - beyond testosterone"

**Geoffrey Hackett**

*Asian Journal of Andrology* (2015) **17**, 334; doi: 10.4103/1008-682X.137679; published online: 16 September 2014

The paper from Floresta *et al.*[1] presents data from two cohorts of men (mean age 35) attending for infertility assessment. A distinction is made between the classical hypogonadism (total testosterone [TT] 12 nmol $l^{-1}$ or less) and "subclinical" hypogonadism with a normal TT but marginally raised luteinizing hormone (LH). They also stress that too much emphasis should not be placed on the need for the presence of sexual symptoms and stress the importance of obesity, insulin resistance, and type 2 diabetes. They rightly point out the relationship between low testosterone (T), low-vitamin D, and increased mortality along with increased risk of type 2 diabetes.[2-4] These are vitally important issues that should concern us all and yet we must ask ourselves why these accepted views in the fields of andrology and sexual medicine are not widely held by our colleagues in diabetes and endocrinology.

Many of us regularly attend endocrine conferences and frequently note that T will not even be considered in discussions on insulin resistance and type 2 diabetes. The numerous long-term studies showing loss of visceral fat, and increased lean muscle mass but will not even be considered as relevant to the treatment for obesity,[5,6] even though conventional management strategies continue to produce disappointing long-term outcomes. Even the concept of "classical" hypogonadism at TT of 12 nmol $l^{-1}$ is often replaced by the suggestion that a "cautious" approach is required and that T replacement therapy (TRT) should be reserved for those with "overt" hypogonadism, with levels as low as 6 nmol $l^{-1}$ being suggested for treatment.[7] Many laboratories quote levels as low as 4.9 nmol $l^{-1}$ for the normal range. Frequent reviews warn of potential "androgen Armageddon" quoting poorly designed studies reported as showing increased cardiovascular events and warning of scenarios similar to hormone replacement therapy in women recently.[8,9] Against this background of extreme caution, it will be very challenging to convince skeptics that there are a group of men with "normal" T levels, but LH levels in the upper normal range who merit treatment. Most current guidelines do not support the measurement of LH unless there is definite evidence of low T, meaning that most of these men currently go undiagnosed.

The current study from Floresta *et al.*[1] involves younger men in their thirties referred with infertility but with no information as to whether these men suffered from sexual dysfunction or merely reduced fertility. The beneficial effect of the 25-hydroxylated form of vitamin D, but not the precursor, is an important message as many health systems are probably treating vitamin D deficiency ineffectively by failing to identify co-existing hypogonadism. Unfortunately, the study was not powered and of insufficient duration to show an effect on T level but other studies have shown modest rises in serum T after 12 months (from 10 to 13 nmol $l^{-1}$) by presumed effect on androgen receptors and reduced peripheral aromatase actions.[10] Skeptics link the findings of low T and low-vitamin D levels with chronic disease and see these associations as being nonspecific markers of chronic illness, questioning both the value of both routine measurement and particularly interventional treatment.

Floresta *et al.*[1] question the over-reliance of sexual symptoms in the diagnosis of hypogonadism despite European Male Ageing Study (EMAS) strongly suggesting that loss of morning erections, loss of libido, and erectile dysfunction (ED) were the best predictors of "true" hypogonadism.[2] EMAS also shows that ED, low TT and free T and low vitamin D all independently predict cardiovascular and all-cause mortality. Two recent uncontrolled studies suggest reduced long-term mortality in follow-up over 5 years with TRT.[11,12] Current guidelines consistently stress the importance of clinical symptoms in hypogonadism and ED is now widely accepted as an important marker for cardiovascular risk.[13] Patients present to doctors with sexual symptoms and demand effective treatments. Recent controlled studies confirm that TRT is associated with significant improvement in sexual symptoms in diabetes, especially in men with TT below 8 nmol $l^{-1}$. The same authors showed that depression markedly reduced all the symptomatic benefits of TRT.[14] As men with type 2 diabetes and metabolic syndrome have ED levels of 75%–80% and all these patients are screened for ED, men will sexual symptoms are ideal candidates for routine T and vitamin D measurement and early intervention. Improvements in sexual symptoms were also associated with subjective quality of life improvement within 3 months.[14] Similarly we will only detect men if we can provide clear and consistent guidance as to which men should have levels of T and vitamin D routinely assessed.

## REFERENCES


1 Foresta C, Calogero AE, Lombardo F, Lenzi A, Ferlin A. Late-onset hypogonadism: beyond testosteronesss. *Asian J Androl* 2014; doi: 10.4103/1008-682X.135985. [Epub ahead of print].
2 Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, *et al.* Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010; 363: 123–35.
3 Pye SR, Huhtaniemi IT, Finn JD, Lee DM, O'Neill TW, *et al.* Late-onset hypogonadism and mortality in aging men. *J Clin Endocrinol Metab* 2014; 99: 1357–66.
4 Lee DM, Tajar A, Pye SR, Boonen S, Vanderschueren D, *et al.* Association of hypogonadism with vitamin D status: the European Male Ageing Study. *Eur J Endocrinol* 2012; 166: 77–85.
5 Traish AM, Haider A, Doros G, Saad F. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. *Int J Clin Pract* 2014; 68: 314–29.
6 Yassin DJ, El Douaihy Y, Yassin AA, Kashanian J, Shabsigh R, *et al.* Lower urinary tract symptoms improve with testosterone replacement therapy in men with late-onset hypogonadism: 5-year prospective, observational and longitudinal registry study. *World J Urol* 2014; 32: 1049–54.
7 Gan EH, Pattman S, Pearce SH, Quinton R. A UK epidemic of testosterone prescribing, 2001-2010. *Clin Endocrinol* (Oxf) 2013; 79: 564–70.
8 Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, *et al.* Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013; 310: 1829–36.
9 Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, *et al.* Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014; 9: e85805.
10 Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, *et al.* Effect of vitamin D supplementation on testosterone levels in men. *Horm Metab Res* 2011; 43: 223–5.
11 Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012; 97: 2050–8.
12 Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013; 169: 725–33.
13 Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, *et al.* The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012; 87: 766–78.
14 Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, *et al.* The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). *Int J Clin Pract* 2014; 68: 203–15.


Good Hope Hospital, Sutton Coldfield, University of Bedfordshire, UK.
Correspondence: Prof. G Hackett (Geoff.hackett@virgin.net)