Review Article

Hypogonadism and erectile dysfunction as harbingers of systemic disease

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Abstract: Prescription sales of Testosterone and erectile aids such as phosphodiesterase-5 inhibitors are at an all-time high, underscoring the importance of hypogonadism (HG) and erectile dysfunction (ED) to men's health. The effect of these debilitating conditions has a major impact on the quality of men's lives. Some risk factors for HG or ED including aging, obesity, smoking, and a sedentary lifestyle. Notably, these are the same risk factors for several other medical co-morbidities that contribute to significant morbidity and mortality in men. HG and ED often co-exist with cardiovascular disease, diabetes, and osteoporosis. This review will explore these three co-morbidities that overlap with HG and ED, and will provide a review of their relationship with each other.

Keywords: Testosterone; erectile dysfunction (ED); cardiovascular disease; diabetes; osteoporosis

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Introduction

Today's global population has never been older than it is now, nor is it as old as it will be tomorrow. As the age of the population is advancing, so must our knowledge of age-related physiologic changes and disease processes. Harman *et al.* looked at the change in free and total Testosterone (fT and tT, respectively) in eight hundred and ninety healthy men ranging in age from their twenties to their eighties (1). Using <325 ng/dL as their definition of hypogonadism (HG), they found increasing prevalence of HG with age. Twelve percent of men in their fifties qualified as HG, and the rates of low tT for men in their sixties, seventies, and eighties were 19%, 28%, and 49%, respectively. Naturally, these numbers are not meant to suggest that all of these men have symptoms of HG, as the study was only looking at lab values and subjective outcomes were not available. Instead, these data provide a framework for appreciating how prevalent low tT is in the aging male population.

It has been equally well-established that erectile dysfunction (ED) also increases with age. Johannes *et al.* sought to determine the incidence of ED from the Massachusetts Male Aging Study (MMAS) (2). These authors found that there will be 26 new cases of ED per 1,000 men, which translates to just over 617,000 cases of ED in the United States annually. Notably, these rates are likely underestimated because of the limitations of the population enrolled in the MMAS. The prevalence of ED is even more impressive because of the cumulative nature of chronic conditions. Feldman *et al.* determined, again from data accumulated by the MMAS, that the prevalence of ED in men aged forty to 69 years old is 52% (3). Importantly, this study also demonstrated the overlap that ED has with multiple other medical co-morbidities. For example, ED was more likely in diabetics and men with heart disease. The overlap that HG and ED have with other systemic diseases is not surprising when considering the overlap in common risk factors each entity shares. Advancing age, for example, clearly increases the prevalence of these chronic conditions, as does smoking and a sedentary lifestyle. This review will focus on three of the most common co-morbidities which overlap with HG and ED, and will provide a review of the relationships of these entities with each other.

Cardiovacular disease

Few controversies within the field of andrology have garnered more public attention in the past few years than the question of whether testosterone is poison or panacea regarding cardiovascular health in men. Much of this controversy stems from a retrospective study by Vigen *et al.* that sought to look at the outcomes of veterans who were hypogonadal (defined in this study as tT less than 300 ng/dL) (4). Hypogonadal men who elected to fill one prescription of any form of testosterone supplementation (TS) were compared to hypogonadal men who chose not to supplement. The authors looked at all-cause mortality, myocardial infarction (MI) and stroke, and concluded that TS increased the rates of adverse events in hypogonadal men; this conclusion was only possible because they failed to consider several significant methodological flaws within their study design (5). The much-maligned conclusion of these authors has been the subject of multiple editorials and professional society position statements (6). In 2014 an advisory committee of the Federal Drug Administration (FDA) convened in order to assess whether or not the safety of TS had been adequately established. The committee concluded, and the FDA ultimately agreed, that T formulations required a change in labeling to reflect what they considered a "signal" within the literature that there may be some degree of cardiovascular risk associated with TS (7).

The controversy regarding TS safety must not be confused with the role HG plays in men's cardiovascular health. The question that the FDA would like answer through carefully designed, well-controlled clinical trials is whether or not TS worsens clinically relevant outcomes such as all-cause mortality or thrombotic events. This is not to suggest that there is any confusion regarding whether hypogonadal men have worse outcomes compared to their (non-supplemented) eugonadal counterparts, because several decades worth of research firmly support this concept. Shores *et al*. retrospectively analyzed a population of Veterans, and categorized them as having low testosterone (defined as tT <250 ng/dL or fT <0.75 ng/dL; n=166) or not (n=692) (8). The mean ± standard deviation (SD) follow-up was 4.3±1.78 years. These authors found that low T was associated with increased mortality [hazard ratio, 1.88 (95% CI, 1.34–2.63)]. Corona *et al.* performed a meta-analysis to look at low T as a risk factor for cardiovascular mortality (9). These authors included seventy articles [1969–2011] in their analysis. They found that men in cross-sectional studies with cardiovascular disease had lower T levels, and in longitudinal studies men with lower T levels had increased all-cause and cardiovascular mortality compared to controls.

Erectile function is another facet of men's health that allows a window into overall CV health. Vasculogenic ED can reside on the same spectrum as other atherosclerotic disorders, such as coronary artery disease and MIs (10). It is well-established that ED often precedes CVD. Montorsi *et al.* investigated men who had angiographically proven coronary artery disease (11). Of 300 men included in this study, 147 (49%) were identified as having ED prior to their acute coronary event. Even more revealing was their finding that the mean time from onset of ED to development of symptomatic coronary artery disease was only 39 months (range, 1–168). Furthermore, Mulhall *et al.* studied 49 men with documented vasculogenic ED and no history of coronary artery disease, and found that 20% had abnormal stress echocardiograms, which was over 6 times the incidence found in age-matched, healthy historical controls (12). Vlachopoulos *et al.* looked at the prevalence of asymptomatic coronary artery disease in men with organic ED (13). Of 47 men who underwent cardiac testing, 9 (19%) of men had silent coronary artery disease documented by angiography.

The "artery size hypothesis" possibly explains the temporal relationship between ED and vascular disease (14). This hypothesis suggests that because atherosclerosis functions to narrow lumens, the narrowest lumens (e.g., the penile or cavernosal arteries) will preferentially be affected before larger vessels such as the coronary arteries. The relationship of ED to CVD is so strong that the Princeton III guidelines state that any man with organic ED should be considered to be at risk for a major adverse CV event (MACE) within 5 years of the onset of ED (15). Furthermore, these guidelines recommend that men with ED should undergo a CV risk assessment as preventative measures. Importantly, the relationship of ED and MACE appears strongest in younger men, and these men are increasingly being identified as the subset that may hold the greatest risk of MACE (16,17).

Diabetes

Diabetes is an expanding health threat with an increasing prevalence world-wide (18). The strong relationship

between diabetes and ED is not surprising given the number of risk factors which they share, such as obesity and aging. Anywhere from 35–90% of diabetics eventually suffer from ED (19,20). Men with diabetes not only have more severe ED, but they also have the greatest concomitant decrease in quality of life, and the poorest response to medical management (21). Bacon *et al.* used the Health Professionals Follow-up study cohort to try to determine the relative risk (RR) of ED in diabetics compared to non-diabetics (22). Over 30,000 men were queried regarding erectile function and their self-reported health information. The RR of ED in diabetics was 1.32 (95% CI, 1.3–1.4). They also demonstrated that the RR for type I diabetics was 3.0 (95% CI, 1.5–5.9), and 1.3 (95% CI, 1.1–1.5) for type II diabetics. The risk of ED increased with increasing time since diagnosis of diabetes. Mazzilli *et al.* sought to determine how many men with ED suffered from diabetes (23). They found that of 934 men with ED, 182 (19.5%) had diabetes. Increasing age was associated with increased prevalence of diabetes in their population.

An interesting and equally important question to answer is whether or not ED can be used to identify men with impaired insulin sensitivity that would therefore be at risk for developing diabetes. The association between ED and impaired fasting glucose or pre-diabetes is not well defined. Deutsch *et al.* looked at the results of an oral glucose challenge in 58 men with ED compared to 131 controls (24). These authors identified that seven (12%) of their subjects with ED were diabetic, no one in the control group had diabetes, and there was no difference between the groups in incidence of impaired glucose tolerance. Ettala *et al.* similarly questioned if they could identify pre-diabetics from screening men with ED (25). They enrolled 926 men, and challenged them with an oral glucose tolerance test. Using the results of the International Index of Erectile Function questionnaire, they determined that 516 (56%) had ED. There was no association between presence or severity of ED and the result of the glucose challenge.

Low T is also associated with diabetes. Ding *et al.* performed a meta-analysis to discern the relationship between endogenous hormone levels and diabetes (26). After identifying 43 articles used for this analysis, data from 6,427 men was pooled. They found that tT was significantly lower in diabetic men (mean –76.6 ng/dL, 95% CI, –99.4 to –53.6). Furthermore, men with higher tT (range, 449.6-605.2 ng/dL) had a lower RR of diabetes (RR 0.58, 95% CI 0.39–0.87). El Saghier *et al.* also looked at the relationship between T level and ED in diabetic men (27). They found that almost 90% of men with low T had ED, while only 30% of men with normal T had ED. Also, tT was lower in diabetic men with ED compared to men without ED. Muraleedharan *et al.* looked at the clinical implications of low T in diabetics (28). These authors looked at 581 men that they followed for a mean ± SD of 5.8±1.3 years. They show that mortality is increased in the men with tT <300 ng/dL (17.2%) compared to men with normal T levels (9%; P=0.003). Interestingly, unlike ED, low T does appear to have a correlation with impaired fasting glucose. Yeap *et al.* looked at 2,470 non-diabetic men, and demonstrated that lower T levels are related to insulin resistance (29).

Bone and muscle health

The effects of T level on lean muscle mass and bone health are increasingly being appreciated. Finkelstein *et al.* sought to demonstrate the role that endogenous T plays in maintaining bone health and muscle mass in an elegantly designed clinical trial (30). They treated 198 healthy men with a gonadotropin releasing hormone agonist in order to suppress endogenous T and estradiol production. Men were then randomized to receive either placebo or increasing concentrations of exogenous T. After 4 months, men with lower serum tT saw a decrease in lean muscle mass and strength as well as increased adiposity. The implications of the decreased bone density are significant because of the associated risk of osteopenia and osteoporosis. Although decreased bone density is traditionally thought to affect women, the risk to men is real and likely underappreciated. Up to one third of fractures occur in men, and the fracture-related morbidity and mortality is higher in men than in women (31). The Third National Health and Nutrition Examination Survey (NHANES III) was used to look at the association between decreased bone mineral density and fT and tT levels (32). Paller *et al.* demonstrated an increased risk of osteopenia in men in the lowest quartile of fT (odds ratio 3.82, 95% CI, 1.87–7.78). Interestingly, they were not able to identify this same increased risk of decreased bone mineral density when looking at tT, suggesting nuanced roles of the various T iterations and the importance of sex hormone binding globulin. The NHANES III was also used in a separate study to determine the relationship between fT and tT and frailty (33). Interestingly, this study also revealed that fT had a positive association with frailty although again tT did not reach statistical significance. Tuck *et al.* looked at the relationship between fT, tT, and symptomatic vertebral

fractures (34). They too found that fT was lower in the men with fractures compared to controls, and did not find any difference in tT levels between the two groups. Declining sex hormone levels also contribute to frailty in the aging male by effects on muscle mass (35). Schaap *et al.* looked at 623 men enrolled in the Longitudinal Aging Study of Amsterdam, and found that fT and tT were positively associated with increased muscle strength and mobility (36).

Recently, the relationship between osteoporosis and ED has also been questioned. Dursun *et al.* looked at 95 men with ED and 82 men with normal erectile function (37). They found lower bone mineral density in the men with ED compared to control. Naturally, work remains to be done to elucidate the mechanism of such an association, and evaluating the role that T level plays in this relationship is paramount. Lee *et al.* looked at the relationship between sexual dysfunction and frailty in 1,504 men involved in the European Male Aging Study (38). Frailty was not only associated with increased risk of ED, but with greater distress associated with sexual dysfunction.

Conclusions

HG and ED overlap with multiple significant co-morbidities that affect men's health, including CVD, DM, and bone/muscle mass decline. This association, however, must not be confused with causation as very little high quality research has been performed which can help elucidate the temporal relationship of these associated entities. Appreciating that our knowledge is still quite limited in our understanding of the mechanisms of these disease processes allows healthcare workers to appreciate the need for additional research.

Several important take-home messages, however, are quite clear. ED, particularly in a young man, could be a warning sign for occult CVD. The lag time between ED and symptomatic cardiac disease provides healthcare providers with a window of opportunity for intervention and possibly prevention. The overlap between HG and ED with DM should also be appreciated because of the common risk factors which contribute to the individual development of each of these disease processes. In addition, hormonal changes and ED can translate to increased frailty and declining quality of life in men.

Thoughtful consideration of HG and ED as harbingers of other systemic diseases will help improve the care we can provide men. Healthcare providers invested in men's health need to be aware of these associations in order to appropriately screen patients or make appropriate referrals as needed.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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