Molecular and Cellular Endocrinology 418 (2015) 120–133

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

# Obesity and late-onset hypogonadism

G. Corona [a], L. Vignozzi [b], A. Sforza [a], E. Mannucci [c], M. Maggi [b, *]

[a] *Endocrinology Unit, Maggiore-Bellaria Hospital, Medical Department, Azienda-Usl Bologna, Bologna, Italy*
[b] *Sexual Medicine and Andrology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy*
[c] *Diabetes Agency, Careggi Hospital, Florence, Italy*

ARTICLE INFO

*Article history:*
Received 29 December 2014
Received in revised form
1 June 2015
Accepted 5 June 2015
Available online 2 July 2015

*Keywords:*
Testosterone
Late onset hypogonadism
Erectile dysfunction
Obesity

ABSTRACT

Obesity and male hypogonadism (HG) are often associated, as demonstrated in all cross-sectional studies. Prospective studies have indicated that i) having HG at baseline increases the risk of visceral obesity (and metabolic syndrome) and that ii) obesity induces incident HG. Hence, there is a bidirectional relationship between the two conditions. This is the main topic of this review, along with some pathogenic considerations. Meta-analysis of intervention studies indicates that treating obesity is a very efficient treatment for obesity-induced HG. The mechanism by which obesity induces HG has not yet been completely understood, but dietary-induced hypothalamic inflammation, along with a decreased GnRH release, is plausible. Among patients seeking medical care for obesity, the proportion of HG is relatively high. The prevalence of obesity among patients referring for sexual dysfunction is also elevated. Hence, in symptomatic, obese, hypogonadal subjects, testosterone supplementation (TS) can be considered. Whereas long-term uncontrolled register studies suggest that TS could decrease weight, analysis of controlled studies only support a parallel increase in lean mass and decrease in fat mass, with a resulting null effect on weight. Considering that T induces an increase in muscle mass, it is conceivable that the amount of activity obese people can undertake after TS will increase, allowing a closer adherence to physical exercise programs. Some studies, here meta-analyzed, support this concept.



## 1. Introduction

Male hypogonadism (HG) is classically categorized in primary (testicular) and secondary (central) HG, according to the site of origin of the disease (Morelli et al., 2007), although, quite recently, a new category, i.e. compensated HG, has been proposed (Tajar et al., 2010, Corona et al., 2014a). In primary HG, the testis is unable to release a sufficient amount of testosterone (T), even if supra-maximally stimulated by gonadotropins (hypergonadotropic hypogonadism). In secondary HG, the testis is potentially functional, but not adequately stimulated by gonadotropins (hypogonadotropic hypogonadism). Finally, in compensated HG, T production is reduced, although maintained in the normal range, and gonadotropins are higher than normal, to "compensate" the subclinical gonadal failure.

All the guidelines suggest that a biochemically-detected reduction of T – even if confirmed by a second determination – is not sufficient enough to define a clinically relevant hypogonadal state, especially in the "gray area", with circulating T between 8 and 12 nmol/L (Wang et al., 2009; Buvat et al., 2013). Interestingly, it is in this "gray area" that the large majority of hypogonadal subjects, as diagnosed in adulthood, is clustered in a condition termed late-onset hypogonadism (LOH. Wang et al., 2009). It is universally recognized that, to define LOH, specific hypogonadism-related symptoms and signs should also be present (Wang et al., 2009; Buvat et al., 2013; Corona et al., 2012a, 2013a). Data from the European Male Aging Study (EMAS), a survey of more than 3400 community-dwelling, middle-aged and older men, indicated that the most common and specific LOH-related symptoms are the sexual ones, including erectile dysfunction (ED) and reduced sexual desire and morning erections (Wu et al., 2010). According to the EMAS survey, the presence of at least three sexual symptoms, along with a total T level of less than 11 nmol/L and a free T (FT) level of less than 0.225 nmol/L, is considered as the minimum criterion for the diagnosis of LOH (Wu et al., 2010).

Considering that impaired erections and low libido are the best clinical hallmark of LOH (Wu et al., 2010), the investigation of

* Corresponding author. Sexual Medicine and Andrology Unit Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy.
*E-mail address:* m.maggi@dfc.unifi.it (M. Maggi).

http://dx.doi.org/10.1016/j.mce.2015.06.031
0303-7207/

clinical correlates of low T in subjects consulting a dedicated medical care unit for sexual dysfunction may provide interesting insights into the characteristics of the disease (Corona et al., 2014b). In a large (more than 4000) symptomatic cohort of individuals with sexual dysfunction, we observed that obesity, defined as body mass index (BMI) $\geq$ 30 kg/m$^2$, triples the risk of having LOH, i.e. T level of less than 11 nmol/L + sexual symptoms (Corona et al., 2013a). A similar picture is obtained when visceral obesity, defined as waist circumference (WC) > 102 cm, was considered (Corona et al., 2013a). Fig. 1 shows the prevalence of the different types of HG (primary, secondary and compensated), according to BMI classes or WC quartiles in the same cohort. In normal weight subjects, only one out of six individuals resulted as being affected by LOH (Fig. 1, panel A). A similar figure was obtained in the lowest quartile of WC (Fig. 1, panel B). The prevalence of secondary HG was increased in a stepwise fashion by (visceral) obesity: in severely obese patients (BMI > 35 kg/m$^2$), almost 2/3 of the individuals consulting for sexual concerns showed low T, with inadequate gonadotropins (Fig. 1).

Visceral (abdominal) obesity is the key factor of metabolic syndrome (MetS), a cluster of abnormalities leading to an increase of cardiovascular (CV) and metabolic risk, which is closely associated with LOH (Corona et al., 2009a, 2011a, 2011b). By meta-analyzing available cross-sectional data, we demonstrated that MetS is significantly associated with an overall lower total T (about 3 nmol/L), this difference being more evident in studies conducted in subjects with ED (Corona et al., 2011a). Meta-analysis of longitudinal studies demonstrated that a low baseline T was associated with an increased risk of incidence of MetS in comparison to controls (2.17 [−2.41;−1.94] nmol/L) (Corona et al., 2011a). MetS factors contributing to male HG are increased WC, glucose and triglyceride levels (Corona et al., 2011a). A more recent meta-analysis (Brand et al., 2014) confirmed that men with low T were more likely to have both prevalent or incident MetS (odd and hazard ratio per quartile T decrease = 1.69 and 1.25, respectively). Even in this meta-analysis, the strongest association of low T was observed with abdominal obesity, along with hypertriglyceridemia and hyperglycemia (Brand et al., 2014). Although in epidemiological surveys the causal directionality of the obesity-low T association is difficult to assess, the finding that, in prospective studies (Corona et al., 2011a; Brand et al., 2014), a baseline low T is associated with incident MetS indicates LOH as a predisposing factor for forthcoming metabolic abnormalities. However, other longitudinal studies indicate that having obesity at study entry is a risk factor for developing low T at follow-up and that weight gain is associated with a decline in T and SHBG, without a compensatory elevation in LH (Derby et al., 2006; Camacho et al., 2013). All this evidence indicates that male HG – in particular the secondary (hypogonadotropic) form - is closely associated with (visceral) obesity, and that the two conditions are mutually interacting.

In this review, we will analyze in depth the bidirectional relationship between obesity and male HG, considering both causal directions: obesity inducing HG and vice versa, i.e. HG inducing obesity. For each direction, pre-clinical and clinical intervention studies will be scrutinized.

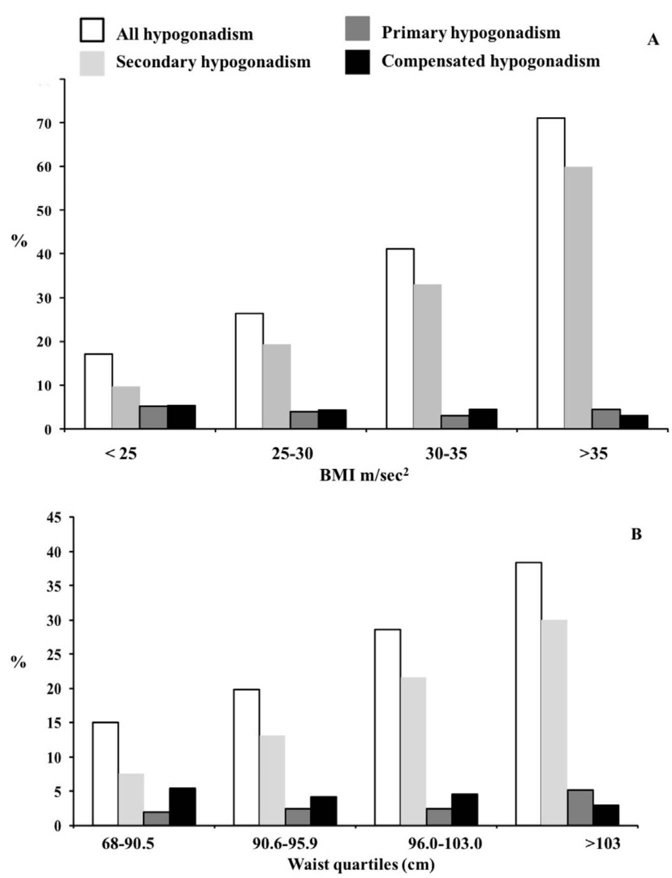


**Fig. 1.** Prevalence of different types of hypogonadism according to the European Male Aging Study criteria (see Tajar et al., 2010): compensated hypogonadism (total testosterone, T $\geq$ 10.5 mM, and luteinizing hormone, LH > 9.4 U/L), primary hypogonadism (T < 10.5 mM, and LH > 9.4 U/L) and secondary hypogonadism (T < 10.5 mM, and LH $\leq$ 9.4 U/L). Data (unpublished) are derived from a non-selected series of 4173 men (mean age = 51.3 ± 13.3 years) attending our Andrology Clinic for sexual dysfunction between 2000 and 2013.

### 1.1. *Obesity inducing hypogonadism*

#### 1.1.1. *Pre-clinical studies*

The mechanisms though which visceral obesity and other metabolic abnormalities might affect T secretion is a matter of debate (Rao et al., 2013; Corona et al., 2011b). Although some data indicate that obesity-related hormones, such as leptin, might directly decrease testicular production of T (Isidori et al., 1999), an impairment in the hypothalamus–pituitary–gonadal axis is often considered the major alteration leading to HG (Rao et al., 2013; Morelli et al., 2013a, 2014; Corona et al., 2011b). A recent study indicates that in subjects with type 2 diabetes mellitus (T2DM) there is a decreased gonadotropin-releasing hormone (GnRH) pulsatility, without significant change in pituitary sensitivity to GnRH or in testis sensitivity to human chorionic gonadotropin (Costanzo et al., 2014). Giagulli et al. (1994) reported similar results 20 years ago in obese subjects. Several adipokines (e.g. leptin), cytokines (e.g. TNF$\alpha$), and gastrointestinal hormones (e.g. ghrelin, peptide YY), along with an increased estrogen production by the expanded fat deposits, have been advocated as causing the gonadotropin failure (Fernandez-Fernandez et al., 2006; Morelli et al., 2013a, 2014a). However, leptin has a permissive role on GnRH neuron activity (Morelli et al., 2009) and its levels are increased, and not decreased, in obesity. It is possible that a specific leptin resistance could explain this paradox; however, this resistance has never been clearly demonstrated in humans. Circulating levels of TNF$\alpha$ are increased in experimental models of MetS with hypogonadotropic HG (Vignozzi et al., 2014a). However, treating MetS rabbits with a monoclonal antibody against TNF$\alpha$ did not ameliorate gonadotropin and T deficiency (Morelli et al., 2014). In the same animal model, we demonstrated that increased visceral fat and the overall MetS condition were associated with hypothalamic inflammation and derangement in the neuron network controlling GnRH release, including the expression of kisspeptin