Research Article

Clinical significance and association of subclinical hypogonadism in aging men and endothelial dysfunction

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Abstract
Background: Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age, as recognized by the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), the European Association of Urology (EAU), European Academy of Andrology (EAA), and American Society of Andrology (ASA). It is characterized by symptoms and a deficiency in serum T levels below the young healthy adult male reference range. LOH may adversely affect quality of life and the function of multiple organ systems (wang et al., 2019). **Methods:** Our study included 38 patient with sbclinical hypogonadism ,30 clinical hypogonadism and 20 apparently healthy as controle group. **Results:** IHD incidence and endothelial dysfunction increase significantly in subclinical and clinical hypogonadism groups. **Conclusion:** this study suggests that higher LH levels IN cases with aubclinical hypogonadism are associated with increased IHD events and impaired endothelial function
Keywords: hypogonadism, IHD, endothelial dysfunction

Introduction
Population-based cohort studies using data from the Boston Area Community Health (BACH) Survey (men 30-79 years old) and the Massachusetts Male Aging Study (MMAS) (men 40-69 years old) have estimated the prevalence of symptomatic androgen deficiency to be 5.6% and 6%, respectively (Araujo, Esche, et al., 2007; Araujo et al., 2004).

Among the various difficulties encountered when investigating SH is how to establish the normal range for the various hormones. Testosterone levels decline with age, leading some authors to suggest the adoption of an age-dependent reference range. However, the American Endocrine Society proposes a single cut-off value (300 ng/dL or 12 nmol/L), while the consensus of several European andrological societies is that any subject with T levels within a “grey” area (250–350 ng/dL or 10-14nmol/ L) might have biochemical hypogonadism.

Similarly, the reference range for gonadotropins – especially with respect to FSH and fertility, but also LH – has recently been questioned. Although most reference ranges give an upper normal limit of up to 9 or 11 IU/ml for FSH, recent analyses indicate that the upper limit of the confidence interval in fertile men is below 7 IU/ml. This introduces the concept of peripheral-to-central hormone ratio. The finding of normal serum T levels with serum LH and FSH concentrations in the upper part of the normal range, or marginally elevated, could be defined as mild SH, while the same T level in association with markedly elevated gonadotropins would be severe SH. This distinction could be useful in managing the condition. It can also be used to monitor progression towards overt hypogonadism (reduced T levels), disclose markers predictive of SH evolution and indicate whether any treatment is needed (Werns, et al., 1989).

Atherosclerosis is a chronic process with a characteristic sex difference resulting in an earlier and more extensive cardiovascular disease in men compared to women (Tunstall-Pedoe et al., 1994). This difference has been suggested to be partly sex hormone-induced.

Disturbances in vascular function occur in atherosclerosis. Vascular function is mediated through endothelium and the underlying smooth muscle cells and is commonly characterized as the vessel ability to vasodilatate to a standard stimulus. Vascular endothelial and smooth

muscle functions can be assessed non-invasively with ultrasound by measuring flow- and nitrate-mediated dilatations (FMD, NMD), respectively, in the brachial artery.
Osteocalcin is a 49 amino acid polypeptide protein with a 5.7 KDa molecular weight. It is also known as gamma-carboxyglutamic acid-containing protein or bone gla protein[1]. Osteocalcin is the most abundant non-collagenous protein within the bone matrix, primarily produced by osteoblasts during the late stage of their differentiation(Ferron et al., 2012).

Osteocalcin favors testosterone production by the Leydig cells of the testis. The well-known regulation of bone remodeling by gonads suggested also that bone may in turn, through its endocrine capacity, affect reproductive functions in one or both genders, Verifying this hypothesis would further enhance the emerging concept that bone, energy metabolism and reproduction are co-ordinately regulated (Ferron et al., 2012).

The function of osteocalcin as a regulator of testosterone production has been recently extended to humans. It was shown that osteocalcin and the bone turnover is associated with T circulating levels in general population and in patients with bone disorders 40. Moreover, Dr. Khosla's group has also shown that there is a significant association between serum osteocalcin and T levels during mid-puberty in males (Ducy et al., 2012).

Several epidemiological studies have examined associations of osteocalcin with outcomes related to cardiovascular events and mortality (Ferron et al., 2010).

The relationship between ucOC levels and atherosclerosis in hypogonadism patient or late onset hypogonadism is not fully under stood. Therefore, we performed a cross-sectional study to investigate the relationship between uOC levels and in aging males with late onset hypogonadism.

Aim of the Work
To explore cardio-metabolic risk factors and endothelial dysfunction among males with sub clinical hypogonadism in comparison with clinical hypogonadism and apparent healthy males Explore association of gonadotrophin with cardiovascular metabolic and endothelial dysfunction .

Patients and methods
The current hospital based case cotrole study will be carried out on 90 old males at age group above 50 years:

- 30 males with sub clinical hypogonadism
- 38 males with clinical hypogonadism
- 20 apparent healthy males

All will be subjected to:

- **Full history**

1- Personal history
2- Sexual function
3- Androgen defiecincy in aging male quationer ADAMS
4- Aging males symptoms AMS scale
5- New England research institute hypogona-dism quationier
6- Psychological QHT Test

- **Examination**

1- Size of testis
2- Secondary sexual chrachters

- **Lab investigation**

1- Serum LH
2- Serum FSH
3- Serum Teststeron (Free-Total and SHBG)
4- Free androgen index
5- Testosteron \Estradiol ratio
6- LH\Testosteron ratio
7- Estradiol
8- FBS
9- 2 hours post prandial
10- Lipid profile
11- CRP

- **Radiology**

1- Testicular ultrasound
2- ECG
3- Echocardiography
4- Brachial FMD%
5- Carotid duplex

❖ **EXCLUSION CRITERIA**

1- Not diabetic
2- BMI less than 30
3- Not having chronic renal illness
4- No testicular malignancy

Summary and cnclusion,
The present cross sectional case controle sstudy was conducted in minia university hospital from the period 2018-2019 .this study included

88 hetero sexual men aged 50 – 69 years old.30 men with clinical hypogonadism 38 men with subclinical hypogonadism and 20 men was

apparently healthy as control group. the subclinical and clinical hypogonadism were selected from community dewelling other men from general population.these men exceed threshold for andropausal symptoms and furtherly undergoes laboratory assay.the study protocol was approved by the institutional ethics committee and carried out according to ethical guide lines of the deceleration of Helsinki and international conference of harmonization guide lines for good clinical practice.

This study suggests that higher LH levels IN cases with aubclinical hypogonadism are associated with increased IHD events and impaired endothelial function in men. The possibility of an independent role for LH in the pathogenesis of IHD requires further investigation. Although not statistically significant, there appeared to be a graded relationship between decreasing testosterone levels and increasing risk, suggesting that androgen deficiency could be involved in the aetiology of IHD and endothelial dysfunction.

A graded rather than threshold effect suggests that risk may not be confined to men with the very lowest levels. However, given conflicting data from other observational studies and safety concerns raised by a recent trial, it would be premature to suggest testosterone therapy for the prevention of IHD or endothelial dysfunction in men with subclinical hypogonadism. Further studies are warranted, with particular emphasis on men with elevated LH in addition to those with low testosterone levels.

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