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## ORIGINAL ARTICLE

## MALE HYPOGONADISM AT A TERTIARY CARE HOSPITAL IN KARACHI, PAKISTAN

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**Background:** Male hypogonadism is defined as 'inadequate gonadal function, manifested by deficiency in gametogenesis and/or secretion of gonadal hormones'. Signs and symptoms of hypogonadism depend primarily on the age of onset. It can be classified according to the site primarily involved: the gonads, the hypothalamus, or the pituitary gland. The objective this study was to determine the presentation and aetiology of male hypogonadism seen in a tertiary care hospital. **Methods:** This cross-sectional study was conducted at Endocrine Clinics, Aga Khan University Hospital Karachi. Data of male patients with hypogonadism who attended clinics during January 2009 to August 2011 were reviewed. All male patients with clinical and biochemical evidence of hypogonadism were included in the study. Patients with Diabetes Mellitus, Metabolic Syndrome, Andropause, AIDS, Chronic Renal Failure, and Cirrhosis were excluded. Mean±SD were computed for quantitative variables. Frequency and percentages were computed for qualitative variables. Aetiology of male hypogonadism was categorised as primary and secondary hypogonadism. **Results:** A total of 85 patients with male hypogonadism attended the endocrine clinic. Mean age of patients was 25±10 years. Clinical presentations were small genitalia (65%), absent secondary sexual characteristics (53%), not attained puberty (47%), infertility (53%), erectile dysfunction (41%) and loss of libido (29%). Seventy-three (86%) patients had hypogonadotrophic hypogonadism (secondary hypogonadism) and 12 (14%) patients had hypergonadotrophic hypogonadism (primary hypogonadism). Among the patients with hypogonadotrophic hypogonadism 38 had idiopathic hypogonadotrophic hypogonadism, 7 had pituitary adenoma, 6 had empty sella syndrome, 3 had Kallman's syndrome, and 1 patient had haemosiderosis due to thalassaemia major; 18 patients did not undergo brain imaging. **Conclusion:** Small genitalia, absent secondary sexual characteristics and infertility were the main presenting features of hypogonad men. Majority of patients had hypogonadotrophic hypogonadism.

**Keywords:** Male Hypogonadism, Erectile dysfunction, Libido, Infertility

## INTRODUCTION

Male hypogonadism is defined as 'inadequate gonadal function, manifested by deficiency in gametogenesis and/or secretion of gonadal hormones'.<sup>1</sup> It can be classified according to the site primarily involved in the hypothalamus-pituitary-gonadal axis. If the serum testosterone level is low and FSH and LH levels are elevated, the defect lies in the testis and hypergonadotrophic hypogonadism is present. In these cases karyo type should be performed to rule out a chromosomal abnormality, such as Klinefelter's syndrome (47, XXY; 46, XX; or 45, X/46, XY) which may occur in 10–15% of such patients. If testosterone is low and gonadotropins levels are low or normal, the patient has hypogonadotrophic hypogonadism due to hypothalamic or pituitary disease.<sup>2</sup>

A detailed history, physical examination and hormonal evaluation are required to diagnose male hypogonadism. In certain cases, further tests are needed to define the aetiology and the extent of Hypothalamic Pituitary Gland axis dysfunction. These include pituitary imaging studies, genetic studies, bone densitometry, testicular ultrasonography, testicular biopsy, hormonal

dynamic testing and semen fluid analysis in those patients desiring fertility.

Symptoms and signs of hypogonadism depend primarily on the age of onset. Before puberty patient may present with small testis, small phallus, scant pubic and axillary hairs, disproportionately long arms and legs and gynaecomastia. After puberty, signs and symptoms may include decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, hypercholesterolemia and increase in visceral fat mass. Hypogonadism is often unrecognised before puberty unless it is associated with growth retardation or other anatomic or endocrine abnormalities. In most cases the first sign is delayed puberty, defined as 'absence of secondary sexual characteristics at an age more than 2SD above the population mean for the onset of puberty'.<sup>2-6</sup>

Currently there are no studies from Pakistan on male hypogonadism. In the West most common cause of male hypogonadism is primary hypogonadism, i.e., Klinefelter's syndrome with the prevalence of 1:500, but we are seeing more cases of secondary hypogonadism (pituitary and hypothalamic) mostly idiopathic

hypogonadotrophic hypogonadism (IHH) in our practices which is unusual compared to West.

The objective of this study was to determine the aetiology and presentation of male hypogonadism at a tertiary care hospital.

## MATERIAL AND METHODS

This cross-sectional study was done at Endocrine Clinics of Aga Khan University Hospital Karachi. Data of male patients with hypogonadism who attended clinics during January 2009 to August 2011 were reviewed. Study was approved by Ethical Review Committee of the Hospital.

All male patients with clinical and biochemical (serum AM testosterone level <200 ng/dl) evidence of hypogonadism were included in the study. Patients with diabetes mellitus, metabolic syndrome, andropause, Acquired Immunodeficiency Syndrome (AIDS), chronic renal failure, and cirrhosis were excluded.

Mean±SD were computed for quantitative variables like age etc. Frequency and percentages were computed for qualitative variables. Aetiology of male hypogonadism was categorised as primary and secondary hypogonadism.

## RESULTS

A total 85 patients with male hypogonadism attended the endocrine clinic. Mean age of patients was 25±10 years. Clinical presentations were small genitalia (65%), absent secondary sexual characteristics (53%), not attained puberty (47%), infertility (53%), erectile dysfunction (41%) and loss of libido (29%). There was no history of substance/alcohol abuse among all patients. Among primary hypogonad patients, 3 had history of mumps. Among secondary hypogonad patients, 3 had anosmia/hyposmia (Table-1).

**Table-1: Clinical presentation of male hypogonadism in 85 patients**

Symptoms, Sign & History	Frequency	%
Small Genitalia	55	65
Absent Secondary Sexual Characteristics	45	53
Infertility	45	53
Not Attained Puberty	40	47
Erectile dysfunction	35	41
Loss of libido	25	29
Family History	6	7
History of Mumps	3	3.5
Gynaecomastia	17	20
Undescended Testis	14	16.5
Anosmia/Hyposmia	3	3.5

Seventy-three (86%) patients had hypogonadotrophic hypogonadism (secondary hypogonadism) and 12 (14%) patients had hypergonadotrophic hypogonadism (primary hypogonadism). Among the patients with hypogonadotrophic hypogonadism 38 (52%) had idiopathic hypogonadotrophic hypogonadism (IHH), 7

(9.6%) had pituitary adenoma, 6 (8.2%) had empty sella syndrome, 3 (4.1%) had Kallman's syndrome based on presence of anosmia/hyposmia with normal MRI brain and one patient had hemosiderosis due to thalassaemia major, while 18 (24.65) patients did not undergo brain imaging (Table-2). Mean testosterone level in patients with IHH was 27.5±40 ng/dL (Table-3)

**Table-2: Aetiology of male hypogonadism (n=85)**

Aetiology	n (%)
Hypogonadotrophic hypogonadism (Secondary hypogonadism)	73 (86)
Idiopathic hypogonadotrophic hypogonadism (IHH)	38 (52)
Pituitary adenoma	7 (9.6)
Empty sella syndrome	6 (8.2)
Kallman's syndrome	3 (4.1)
Haemosiderosis (Thalassaemia Major)	1 (1.3)
Hypergonadotrophic hypogonadism (Primary hypogonadism)	12 (14)

\*18 (24.65%) patients did not undergo MRI/Brain scan

**Table-3: Clinical and laboratory parameters in 38 men with idiopathic hypogonadotrophic hypogonadism**

Parameters	Mean±SD
Age (years)	25±8.5
Serum testosterone (ng/dL)	27.5±40
Follicle stimulating hormone (IU/L)	2.9±4.5
Luteinizing hormone (IU/L)	1.9±2.1

## DISCUSSION

In normal male, puberty is characterised by increased size of testis, increased penile length, spermatogenesis and appearance of secondary sexual characteristics under the influence of testosterone. We found small genitalia, absent secondary sexual characteristics and infertility the major presenting features which indicate pubertal deficiency of testosterone. Patients with total testosterone level less than 300 ng/dL usually have signs and symptoms of classic hypogonadism.<sup>1</sup> In our study hypogonadotrophic hypogonadism was present in 86% of patients and majority among them had IHH defined as pubertal delay at 18 years of age or older, low testosterone level with low/normal FSH and LH levels and no pituitary or hypothalamic lesion. IHH is a disorder caused by genetic defect in biosynthesis and secretion of GnRH by hypothalamus or its action on pituitary. It is five times more prevalent in men.<sup>7</sup> Two thirds of patients with isolated GnRH deficiency have anosmia/hyposmia (called Kallman syndrome) and one third have normal sense of smell.<sup>8</sup> Most cases of Kallman syndrome are sporadic,<sup>9</sup> but familial occurrences is also observed. In our study, among hypogonadotrophic hypogonadism patients 3 had Kallman syndrome. Specific genetic mutations, i.e., DAX-1, KAL-1, FGFR1, GPR54, Prop-1, and Hex1, have been identified causing hypogonadotrophic hypogonadism.

Our results concur with the study done by Citron *et al*, who found primary hypogonadism in 51 patients, 164 patients had secondary hypogonadism among 238 patients with erectile dysfunction.<sup>10</sup> In secondary hypogonadism group pituitary imaging was normal in 137 (83.5%) patients, empty sella and pituitary adenoma was found in 11 (6.7%) and 14 (8.5%) patients respectively.<sup>10</sup>

Secondary hypogonadism was not frequent in some case series of patients evaluated for erectile dysfunction, unless associated with hyperprolactinemia.<sup>11,12</sup> Slag *et al* found 9% prevalence of secondary hypogonadism in 188 patients with impotency.<sup>13</sup> In a study by Rhoden *et al* on pituitary imaging in male hypogonadism, MRI pituitary was normal in 74.5% of patients, partial empty sella in 17.6% and pituitary microadenomas were found in 7.8% of patients, and like our study, 89% of patients younger than 40 years had normal MRI.<sup>14</sup>

Klinefelter's syndrome is the most common cause of primary hypogonadism. The fundamental chromosomal abnormality in Klinefelter's syndrome is the presence of one or more extra X chromosomes. The principal karyotype in 90% of men with Klinefelter's syndrome is 47, XXY. In adults, the most prominent clinical feature is very small testes size, <4 mL (<2.5 cm) in length on clinical examination.<sup>15,16</sup> In our study 14% of patients had hypergonadotrophic hypogonadism (primary hypogonadism); among them 3 had history of mumps. Chromosomal analysis was not done in these patients of Klinefelter's syndrome. Opioids and alcohol also cause male hypogonadism, in our study there was no history of substance abuse.

The limitations of this study include retrospective study, limited number of patients, and no control group. Certain number of patients with hypogonadotrophic hypogonadism did not undergo brain imaging due to cost issue and were not followed up, so aetiology in these patients remained unknown.

## CONCLUSION

Majority of hypogonad males have idiopathic hypogonadotrophic hypogonadism, further studies are needed to look at specific genetic mutations in IHH patients.

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