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High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment

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ABSTRACT

Background: Obesity can be associated with biochemical evidence of isolated hypogonadotropic hypogonadism (IHH) in men. Prevalence and severity of IHH in obese men are not exactly known.

Objective: To assess the prevalence of IHH in obese men.

Design and Subjects: Cross-sectional study of 160 obese men, BMI >30 kg/m², who applied for medical or surgical treatment of obesity in a general teaching hospital.

Main outcome measures: Total and calculated free testosterone (TT and FT) in relation to body mass index (BMI).

Results: Mean age of the study population was 43.3 ± 0.8 years (mean ± SEM), BMI ranged from 30.0 to 65.7 kg/m². TT and FT levels were inversely related to BMI (-0.48, p<0.001). Total testosterone was subnormal in 57.7% and free testosterone in 35.6% of the subjects. The group of men with IHH was more obese, had higher HbA_{1c} levels and had a 2.6 higher risk for cardiovascular disease. Decreased libido and erectile dysfunction were 7.1 and 6.7 times as common in IHH than in eugonadal obese men.

Conclusions: Reduced T levels, well into the hypogonadal range, are common in male obesity. Assessment of its clinical implications, and a search for the best mode of treatment are warranted.

KEYWORDS

Cardiovascular disease, erectile dysfunction, libido, male hypogonadism, obesity

INTRODUCTION

Ageing, obesity, and chronic illness are major factors affecting serum testosterone (T) levels in men.[1-3] The magnitude of the impact of ageing on serum T levels is well established, for obesity this is less clear.[3,4] Severe obesity may lead to isolated hypogonadotropic hypogonadism (IHH).[5,6] Several explanations have been offered to clarify the presence of reduced T levels in obese men.[5-7] One relates to the technique that is generally employed to measure serum androgen levels, i.e. measurement of total testosterone (TT) instead of free testosterone (FT). TT represents the sum of FT and T bound to albumin and sex hormone binding globulin (SHBG) and is therefore subject to variations in the concentration of the binding proteins. A profound reduction in SHBG level is commonly found in obese men, and this is a major factor causing a decrease in TT.[2,8] FT, measured or calculated by a reliable technique, is not affected by changes in SHBG. The second explanation is based on the impact of increased oestrogen production in obesity, caused by enhanced conversion of T to oestradiol (E_2) by the enzyme aromatase cytochrome P450 that is abundantly present in the adipocyte.[9,10] This increases serum E_2 which exerts a negative feedback on pituitary luteinising hormone (LH) secretion.[11-16] Excess of circulating leptin has also been identified as an LH inhibitory factor in obese men.[17] Obstructive sleep apnoea, a common complication in severe obesity, disrupts hypothalamic-pituitary function which may reduce overnight LH secretion and testosterone production.[18]

Despite the high and still increasing prevalence of obesity in men, recent guidelines on male hypogonadism do not discuss the issue of obesity-related IHH and do not provide advice whether, when and how to treat if serum T levels in obese men are well into the hypogonadal range.[19,20] The present study is the first to estimate the prevalence of obesity-related hypogonadism in men. It is based on an aselective sample of men referred for obesity treatment in a general teaching hospital.

METHODS

Subjects

One hundred and sixty obese males, referred to the departments of internal medicine and surgery for analysis and treatment of obesity, were screened for the presence of biochemical hypogonadism if their body mass index (BMI) was greater than 30 kg/m^2. The evaluation was part of a standard biochemical screening procedure to detect the main causes and metabolic complications of obesity. It was performed without prior selection and irrespective of the presence or absence of symptoms or signs of hypogonadism. In case of intercurrent or unstable disease all measurements were postponed for at least three months until the subject was feeling well again. Medical history, medication and current symptoms were recorded, with special attention for loss of libido and erectile dysfunction (ED) which were both assessed by anamnesis. General physical examination included genital inspection and estimation of testicular size. Venous blood was obtained in the fasting state between 08.00 and 10.00 hours for the measurement of serum creatinine, liver enzymes, glucose, HbA_{1c}, C-peptide, lipids, albumin, thyroid-stimulating hormone (TSH), free thyroid hormone (fT_4), luteinising hormone (LH), follicle-stimulating hormone (FSH), TT, total E_2 (TE_2), prolactin, and SHBG. If hypogonadotropic hypogonadism was diagnosed, additional measurement of early morning serum cortisol, adrenocorticotrophic hormone (ACTH) and insulin-like growth factor-1 (IGF-I) was performed to complete the evaluation of pituitary function. Pituitary hormone stimulation tests were not performed.

Exclusion criteria were liver disease (liver enzymes four times above the upper normal limit), moderate to severe renal insufficiency (serum creatinine ≥200 μmol/l), serum transferrin saturation levels >60%, medication known to affect the gonadal axis, pituitary disease, and hypergonadotropic hypogonadism.

Hormone assays and calculations

Gonadotropins and gonadal hormones were measured by electrochemiluminescene immunoassays (Roche Diagnostics, Mannheim, Germany). Interassay coefficients of variation (CV) are: LH and FSH <3%, TT <6%, TE_2 <5%. SHBG was measured by chemiluminescent enzyme immunoassay (DPC, Los Angeles, USA, reference range 13 to 71 nmol/l, interassay CV <5%). FT and bioavailable T (BT) were calculated by the method of Vermeulen *et al.* which is based on the measurement of serum albumin, total testosterone and SHBG and the use of T binding affinities to albumin and SHBG.[21] Free E_2 (FE_2) was calculated by using affinity constants for binding of E_2 with SHBG and albumin. The affinity constant of E_2 to SHBG was 3.14E+08, the affinity constant of E_2 to albumin 4.21E+04, and the affinity constant of testosterone to SHBG was 5.97E+08.[22] Reference ranges validated by in-house measurements and calculations of samples obtained from 207 healthy men, ranging in age from 20 to 60 years, are as follows: LH 2.0 to 9.0 U/l, FSH 1.5 to 12.4 U/l, TT 11 to 28 nmol/l, BT 5.2 to 13.6 nmol/l, FT 225 to 625 pmol/l, TE_2 40 to 160 pmol/l, and FE_2 1.1 to 4.7 pmol/l.

Definitions

In this study the diagnosis of isolated hypogonadotropic hypogonadism (IHH) was based on a set of biochemical criteria including an FT level below 225 pmol/l, combined with an inappropriately low LH level of less than 9.0 U/l, and no biochemical evidence of additional pituitary hormone abnormalities as assessed in early morning serum samples.

Subjects were considered to have diabetes mellitus (DM) if they received oral antidiabetics or subcutaneous insulin, or had fasting plasma glucose levels >7.0 mmol/l or HbA1c levels >6.0%.

Cardiovascular disease (CVD) was considered to be present if documented in medical history or indicated by the use of specific cardiovascular drugs (not including statins or fibrates). The spectrum of CVD present in this population comprised hypertension, coronary artery disease, heart failure, and cardiac arrhythmias.

Statistical analysis

All continuous data followed a normal distribution and are presented as means ± standard error (SE). Differences between groups were evaluated by analysis of variance and subsequently by Student's t-test, if appropriate. Relationships between variables were explored by (multiple) regression analysis. Categorical data are shown as percentages. Proportions were analysed by Fisher's exact test. Differences between IHH and non-IHH subjects were adjusted for age by logistic regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

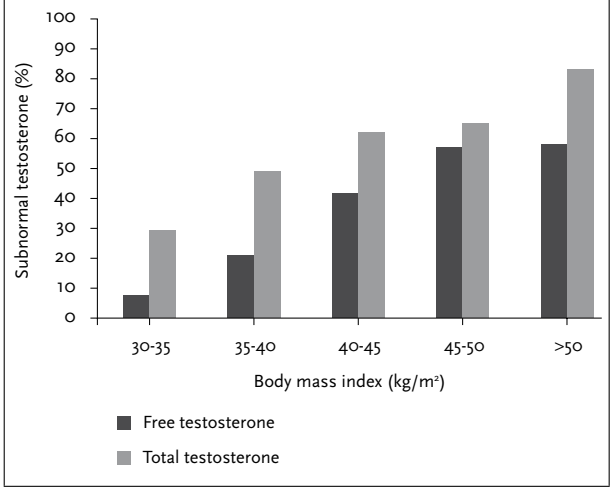
Eleven subjects were excluded for the following reasons: one because of Klinefelter syndrome, two subjects with post-orchitis hypergonadotropic hypogonadism, three had hypergonadotropic hypogonadism of unknown cause, two because of renal insufficiency, one because of chronic alcoholic hepatitis, one had a partial empty sella, and one patient because of macroprolactinoma. The final analysis comprised 149 men, mean age 43.3 ± 0.8 years (range 18 to 66 years), BMI 42.7 ± 0.7 kg/m^2 (range 30 to 65.7 kg/m^2). DM2 was present in 37% and CVD in 35%. The main manifestations of CVD were hypertension (78%), coronary artery disease (19%), cardiac arrhythmias (19%), and heart failure (7%). Twenty-seven percent used oral antidiabetics or

insulin, 33% were treated with antihypertensives, 17% took statins, 9% received thyroxin for primary hypothyroidism, 3% were treated with continuous postitive airway pressure (CPAP) for obstructive sleep apnoea and 3% were treated for depression. Mean HbA1c was 6.4 ± 0.1% (normal range 4.0 to 6.0%), fasting C-peptide 1.66 ± 0.7 nmol/l (normal value 0.36 to 1.66 nmol/l), total cholesterol 5.0 ± 0.1 mmol/l, HDL cholesterol 1.1 ± 0.1 mmol/l, and triglycerides 2.2 ± 0.2 mmol/l. Decreased libido was reported by 22.5%, erectile dysfunction (ED) by 31.7% of the subjects.

Table 1 summarises the results of hormone measurements according to BMI category. Mean age was comparable for all five categories, whereas mean BMI was significantly greater than each preceding category. Mean TT, BT and FT gradually decreased with increasing BMI, with mean declines of -1.1 nmol/category, -0.7 nmol/category and -29 pmol/category, respectively (p<0.001). TE_2 and FE_2 showed the opposite trend and gradually increased with every higher BMI category: TE_2 +11.4 pmol/category (p< 0.001), free E_2 +0.4 pmol/category (p<0.001). SHBG was already in the lowest quartile of the reference range in BMI category 30 to 35 kg/m², and remained stable at this level in the higher BMIs. Albumin tended to decrease gradually with increasing BMI (trend: -0.9 g/category, p<0.001). The ratio of FE_2 to FT increased linearly with increasing BMI (trend: +4.8 x 10^{-3}/category, p<0.0001).

TT levels <11 nmol/l were observed in 86 subjects (57.7%). BT was subnormal in 40.3% and FT levels <225 pmol/l were observed in 35.6% of the subjects. In every BMI category, the prevalence of subnormal TT levels was consistently higher than that of FT (*figure 1*). Subnormal FT levels were observed in 7.4% of cases with BMIs of 30 to 35 kg/m², in 21.0% for BMIs ranging from 35 to 40 kg/m², in 42.4% for BMIs ranging from 40 to 45 kg/m², in 58.3% for BMIs ranging from 45 to 50 kg/m², and in 59.2% of BMIs > 50 kg/m². Comparable figures were obtained if BT was used to assess androgen activity (data not shown).

Figure 1. *Prevalence of subnormal total testosterone (<11 nmol/l) and free testosterone (<225 pmol/l) levels in obese men, according to BMI category*



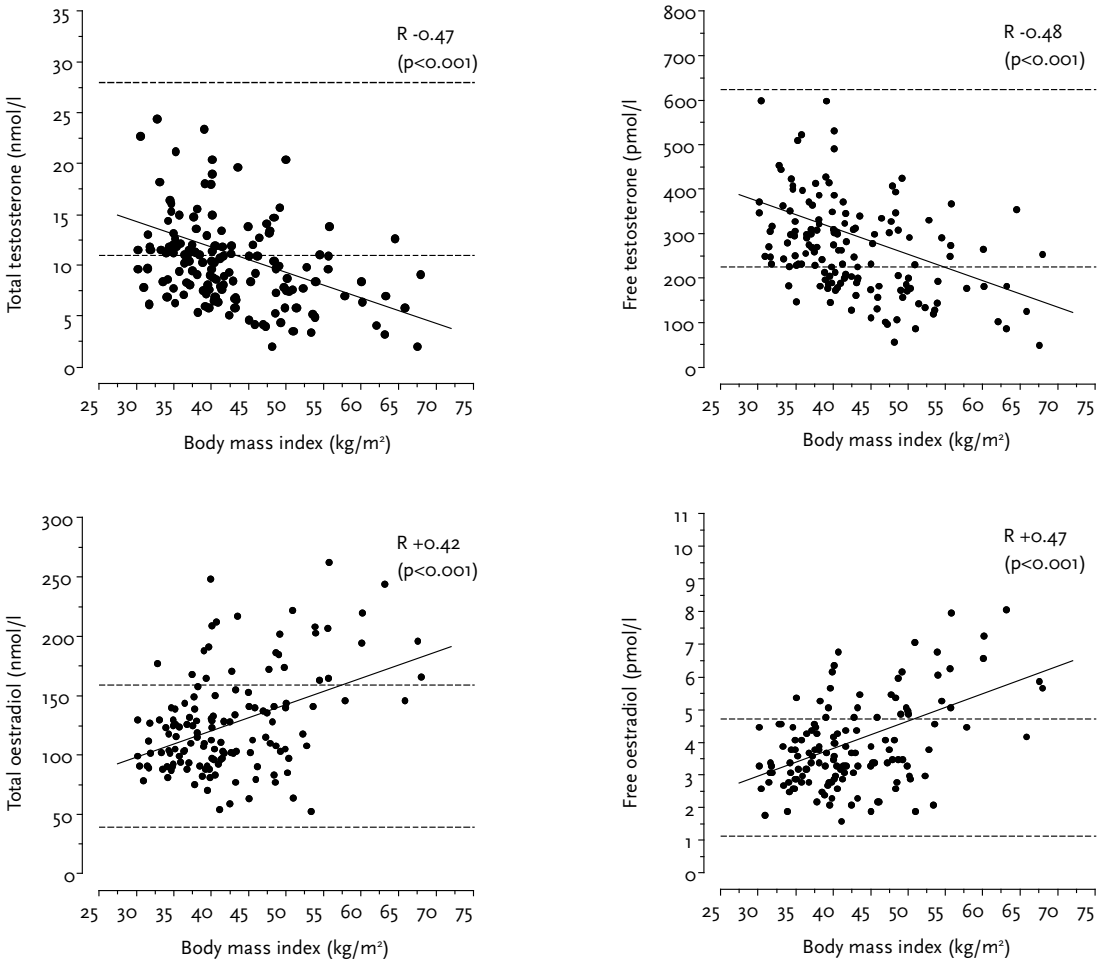
TT levels were inversely related to BMI (R -0.47, p<0.05), and positively correlated with albumin (R +0.22, p<0.005), SHBG (R +0.49, p<0.0001), and FT (R +0.85, p<0.0001). FT was only related to age (R -0.24, p<0.005) and BMI (R -0.48, p<0.0001), not to albumin or SHBG. Serum TE_2 and FE_2 levels were in the high normal range. Both were positively correlated to BMI (*figure 2*). SHBG levels were reduced to the same extent in all BMI categories (*table 1*).

Table 1. *Summary of gonadal hormone measurements in relation to BMI category*

	Reference range	Body mass index category				
		30-34	35-39	40-44	45-49	≥50
Subjects (n)		27	38	33	24	27
Age (years)		46.1 ± 1.5	42.4 ± 1.5	45.0 ± 1.9	43.8 ± 2.0	39.2 ± 1.7
BMI (kg/m²)		32.9 ± 0.4	37.8 ± 0.2	41.8 ± 0.3	47.8 ± 0.3	56.9 ± 1.1
Luteinising hormone (U/l)	2 - 9	3.5 ± 0.3	4.6 ± 0.3	4.8 ± 0.4	4.3 ± 0.4	4.0 ± 0.3
FSH (U/l)	1.5 - 12.4	4.3 ± 0.3	5.8 ± 0.6	4.7 ± 0.5	6.0 ± 0.7	5.1 ± 0.6
Total testosterone (nmol/l)	11 - 25	12.3 ± 0.9	11.3 ± 0.7	10.2 ± 0.7	9.6 ± 0.9	7.5 ± 0.6
Bio testosterone (nmol/l)	5.2 - 13.6	7.2 ± 0.4	6.9 ± 0.4	5.9 ± 0.4	5.5 ± 0.6	4.3 ± 0.4
Free testosterone (pmol/l)	225 - 625	320 ± 19	304 ± 17	262 ± 17	249 ± 26	200 ± 17
Oestradiol (pmol/l)	40 - 160	110 ± 4	122 ± 6	121 ± 7.3	130 ± 7.5	163 ± 12
Free oestradiol (pmol/l)	1.1 - 4.7	3.3 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	4.1 ± 0.2	5.1 ± 0.4
Albumin (g/l)	35 - 50	41.4 ± 0.7	42.3 ± 0.4	40.9 ± 0.6	39.5 ± 0.9	38.2 ± 0.6
SHBG (nmol/l)	13 - 71	21.3 ± 1.9	19.9 ± 1.6	21.4 ± 2.1	21.7 ± 2.6	20.4 ± 1.7

Data are shown as mean values ± SE. FSH = follicle-stimulating hormone; Bio = bioavailable; SHBG = sex hormone binding globulin.

Figure 2. *Relationship between body mass index and total testosterone, free testosterone, total oestradiol and free oestradiol*



To further examine the relationships between hypogonadism and several clinical variables, the study population was divided into IHH and non-IHH men, based on an FT level of 225 pmol/l as cut-off. *Table 2* summarises the results. Mean age, BMI, HbA1c and fasting C-peptide were higher in the IHH group. The differences in TT, BT and FT remained highly significant after correction for age (p<0.001). HDL cholesterol, LDL cholesterol and triglycerides were comparable for both groups, and this remained so after exclusion of those subjects taking statins or fibrates. The prevalence of type 2 diabetes was not significantly different, but CVD was more frequent in the IHH group. The odds ratio for CVD, corrected for age, was 2.6 (95% CI 1.1 to 6.1, p<0.05) in IHH men, compared with non-IHH men. The prevalence of decreased libido and ED was considerably higher in the IHH group. Decreased libido was reported by 46.5% of the IHH men, and by 9.1% of eugonadal obese men (p<0.001). ED was reported by 61.4% of the IHH men, and by 15.9% of the eugonadal men (p<0.001). Compared with eugonadal obese men, and corrected for age, the risk of ED or decreased libido was increased by a factor 6.7 (95% CI 2.8 to 16.1, p<0.001) and 7.1 (95% CI 2.6 to 19.5, p<0.001) in IHH obese men. The use of α- and/or β-blockers was comparable for both groups, 13.0 and 14.5%, respectively.

DISCUSSION

The results of this study indicate that male obesity is frequently associated with T levels within the hypogonadal range, biochemically classified as isolated hypogonadotropic hypogonadism (IHH). The prevalence of IHH increases linearly with BMI, and exceeds 40% in subjects with BMIs of 40 kg/m² or greater, for an FT <225 pmol/l as cut-off. The data were not obtained from a completely random population of obese subjects, but were based on subjects who were referred for obesity treatment. As the latter are more likely to be symptomatic, the prevalence figures assessed in this study may be somewhat higher

Table 2. *Comparison of hypogonadal (IHH) and eugonadal (non-IHH) obese men*

	IHH	Non-IHH	P
Subjects (n)	53	96	
Age (years)	46.1 ± 1.4	40.7 ± 0.8	<0.002
Body mass index (kg/m²)	47.2 ± 1.1	39.9 ± 0.7	<0.0001
Luteinising hormone (U/l)	4.2 ± 0.3	4.4 ± 0.2	NS
FSH (U/l)	5.9 ± 0.6	4.6 ± 0.2	NS
Total testosterone (nmol/l)	6.6 ± 0.3	14.4 ± 0.4	<0.0001
Bioavailable testosterone (nmol/l)	3.6 ± 0.1	8.6 ± 0.2	<0.0001
Free testosterone (pmol/l)	162 ± 5.6	384 ± 7.9	<0.0001
Oestradiol (pmol/l)	126 ± 6.5	131 ± 4.3	NS
Free oestradiol (pmol/l)	3.8 ± 0.2	4.0 ± 0.1	NS
Free oestradiol/Free testosterone	26.9 ± 2.8	12.7 ± 0.5	<0.0001
SHBG (nmol/l)	22.3 ± 1.7	20.2 ± 1.1	NS
Albumin (g/l)	39.9 ± 0.5	41.1 ± 0.4	NS
HbA_{1c} (%)	6.7 ± 0.2	6.1 ±0.1	<0.01
Fasting glucose (mmol/l)	7.2 ± 0.7	6.7 ± 0.3	NS
Fasting C-peptide (nmol/l)	2.0 ± 0.1	1.4 ± 0.1	<0.0001
LDL cholesterol (mmol/l)	3.0 ± 0.2	3.0 ± 0.1	NS
HDL cholesterol (mmol/l)	1.1 ± 0.1	1.1 ± 0.1	NS
Triglycerides (mmol/l)	2.3 ± 0.3	2.0 ± 0.1	NS
Diabetes mellitus	46.0%	31.8%	NS
Cardiovascular disease	52.1%	23.6%	<0.002
Hypothyroidism	12.2%	5.5%	NS
Decreased libido	46.5%	9.1%	<0.0001
Erectile dysfunction	61.4%	15.9%	<0.0001

All data are expressed as mean values ± SE, or as percentages. IHH = isolated hypogonadotropic hypogonadism; NS = statistically not significant; FSH = follicle-stimulating hormone; SHBG = sex hormone binding globulin.

than in a completely random population of obese men. Nevertheless, in view of the global epidemic of obesity, obesity-related IHH is likely to be one of the most common causes for reduced serum T levels in men, next to ageing.

The calculated prevalence of hypogonadism heavily depends on the type of biochemical variable chosen to define the condition. Gross overestimation will occur if measurement of TT is used to classify serum androgenicity in obese men. In the present study reduced serum TT levels were observed in 57.7%, whereas reduced FT levels were found in 35.6%. This large discrepancy is mainly due to the decrease in SHBG that typically occurs in obesity as a result of insulin-mediated inhibition of hepatic SHBG release.[2,8,23] Therefore, it is strongly recommended not to rely on TT levels but to use FT levels, either calculated by a validated method,[21,22,24] or assessed by equilibrium dialysis.[25] The use of currently available radioimmunoassays (RIA) for FT is strongly discouraged because they are subject to the same errors as measurements of TT.[26,27]

In this study we chose to calculate the prevalence of biochemical hypogonadism based on general reference ranges obtained from men between 20 and 60 years of age. We did not use cut-off values based on data obtained from age-matched non-obese adults nor on data from normal-weight young adults. To date, there is still an ongoing debate what should be the gold standard for comparison. Several authors advocate to use the normal range of FT levels in young adults as guideline, arguing that below this limit symptoms and signs of androgen deficiency become apparent irrespective of age.[28,29] Recent guidelines appear to agree with this point of view. If normal-weight young adult data had been used as reference in the present study, this would have increased the prevalence of IHH.

One of the main questions that is raised by the results of this study is whether the high prevalence of reduced T levels in severely obese men is clinically relevant and requires therapeutic intervention. To put the findings into perspective, it is useful to compare the FT levels of obese men with those of population studies using T and SHBG assays with reference values comparable to those employed in the present study.[2,30] FT levels are at their peak between 25 and 35 years with mean values of about 400 to 450 pmol/l. After the age of 35 a gradual decline occurs. At 45 years FT will be around 300 to 350 pmol/l, and at 65 years between 200 to 250 pmol/l. Note that about a third of the obese men in the present population (mean age 46 years) had FT levels corresponding with the mean levels found in healthy men 65 years of age (*figure 2*).

The issue about the clinical impact of reduced T levels in obese men definitely requires further exploration in studies focusing on the prevalence of all clinical signs and symptoms known to be associated with hypogonadism. The present study only provides some indications. The validity of the comparison of IHH and non-IHH subjects was limited because it was hampered by an incomplete match for all relevant variables. Nevertheless, decreased libido and ED was reported about six times as frequently by IHH than eugonadal obese men. It is not likely that the differences in libido and ED can be explained by diabetes or the use of cardiovascular drugs, since the prevalence of diabetes, and the number of patients using α- or β-blokkers was similar in the eugonadal and hypogonadal men.

It was observed that cardiovascular disease was two to three times as common in IHH as compared with non-IHH obese men, and this difference remained after adjustment for age. Due to the incomplete match it remains uncertain whether the increased prevalence of CVD in IHH men is related to a higher degree of obesity, the reduced T levels or a poorer glycaemic control. Due to the cross-sectional

nature of the study it can not be established whether the increased prevalence of CVD is a cause or a consequence of hypogonadism in this specific population.

Obesity is not only characterised by a decrease in T but also by an increase in serum E_2 levels. This is visible on inspection. Obese men commonly have pseudo-gynaecomastia and reduced beard growth. Serum TE_2 and FE_2 were comparable in IHH and non-IHH men; however, the ratio of FE_2/FT in IHH men was more then twice as high as in non-IHH men. At present the clinical impact of the relatively elevated E_2 levels in hypogonadal obese men is not known. We could speculate that it may be beneficial for bone but have adverse effects on fertility.[31-34] The disturbance in E_2/T balance may also affect brain function in general, and sexual as well as nonsexual behaviour in particular.[35-38] The impact that hypogonadism and gonadal hormone therapy may have on the behaviour of obese men could be an interesting new area to explore. Hypogonadal men usually show little initiative, have lack of drive, loss of motivation, and tend to reconcile even in unpleasant situations.[39-41] Adequate treatment of hypogonadism might restore normal male behaviour and drive, which might help dealing successfully with the problem of achieving a relevant degree of weight reduction. Profound improvements of psychopathology have been observed after surgically induced weight loss, but it is not known whether this is related to weight loss per se, or secondary to hormonal changes associated with weight loss.[42]

The observation that many severely obese men have a reduced serum T raises the question whether and when treatment is required, and what should be the most appropriate mode of therapy. Recently published expert panel recommendations state that symptoms of T deficiency become manifest with FT levels between 250 and 180 pmol/l, and there is consensus that FT levels less than 180 pmol/l definitely require treatment.[19] In the present study 21% of the men had FT levels less than 180 pmol/l. The conventional mode of treatment would be androgen-replacement therapy.[43] However, because of the high conversion of T to E_2, T replacement is likely to cause a substantial rise in serum E_2, and this could have adverse somatic and psychological effects. Alternatively, treatment of obesity-related IHH might be achieved by aromatase inhibition. It is a logical choice, considering that increased aromatase activity is a key abnormality in obese men.[44,45] Another approach to treat obesity-related IHH is induction of substantial weight loss, either by low calorie diet or by bariatric surgery. The number of studies evaluating this approach is limited, results are not in full agreement and so far none of the studies were placebo-controlled.[46-50] Although successful weight loss was generally associated with a rise in SHBG and TT, complete normalisation of these parameters did not occur. FT levels often remained unchanged or increased only slightly. Several factors may explain the discrepancies between these studies, including the use of inaccurate hormone assays, differences in degree of caloric restriction, treatment periods, timing of measurements, and the failure to achieve normal body weight in many subjects.

CONCLUSION

This study has shown that many obese men have severely reduced serum T levels of a degree that is likely to have clinical implications. At present we do not know how harmful these reduced T levels are in this specific population, nor whether treatment should be started, and what might be the most appropriate mode of treatment.

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