Journal of Internal Medicine 2003; **254**: 447–454

Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea

N. MESTON[1], R. J. O. DAVIES[2], R. MULLINS[2], C. JENKINSON[3], J. A. H. WASS[4] & J. R. STRADLING[2]

[1]*From the Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital;* [2]*Oxford Centre for Respiratory Medicine and University of Oxford, Churchill Hospital;* [3]*Health Services Research Unit;* [4]*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Infirmary; Oxford, UK*

Abstract. Meston N, Davies RJO, Mullins R, Jenkinson C, Wass JAH, Stradling JR (University of Oxford, John Radcliffe Hospital; Oxford Centre for Respiratory Medicine and University of Oxford, Churchill Hospital; Health Services Research Unit; Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Infirmary; Oxford, UK). Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. *J Intern Med* 2003; **254:** 447–454.

Objective. Obstructive sleep apnoea (OSA) is a relatively common condition producing disabling somnolence and profound physiological responses to hypoxaemic episodes during sleep, including significant oscillations in blood pressure. This study aimed to provide controlled data on the interaction between OSA and endocrine axes to establish whether overrepresentation of pathology such as hypertension and hypogonadism in OSA subjects might have an endocrine basis.

Design, setting and subjects. Parallel randomized sham placebo controlled 1-month trial of nasal continuous positive airway pressure (nCPAP) in 101 male subjects with OSA presenting to a respiratory sleep clinic.

Methods. Analysis of gonadotrophins, testosterone, sex hormone binding protein (SHBG), prolactin, cortisol, thyroid stimulating hormone (TSH), free thyroxine (free T4), insulin-like growth factor-1 (IGF-1), renin and aldosterone were performed at baseline and after 1 month's active or placebo nCPAP intervention. Quality of life questionnaire scoring was also recorded over the same time period.

Results. Testosterone and SHBG showed significant negative correlations with baseline OSA severity. Active treatment of OSA produced SHBG elevation and TSH reduction ($P \leq 0.03$). Both groups showed an increase in aldosterone ($P < 0.001$) and IGF-1 ($P \leq 0.03$), associated with a large improvement in subjective quality of life scoring.

Conclusions. These findings demonstrate significant changes in endocrine axes not previously reported in a placebo-controlled trial. OSA is a recognized reversible cause of testosterone reduction; SHBG suppression correlating to baseline OSA severity supports a diagnosis of secondary hypogonadism. Significant rises in aldosterone and IGF-1 on treatment coincide with increased physical activity and an improved quality of life score.

Keywords: hormones, hypogonadism, sleep apnoea.

Introduction

Obstructive sleep apnoea (OSA) is an upper airway respiratory disorder of varying severity affecting approximately 5–7% of the adult male population. It is characterized by recurrent airway collapse and obstructive apnoeic episodes during sleep resulting in hypoxaemia and arousal from sleep, up to 300–400 times a night. On the basis of uncontrolled trials OSA is thought to produce reversible alterations in the endocrine-gonadal axis which reverts back to physiological levels following effective treatment with nasal continuous positive airway pressure (nCPAP) [1].

Restoration of breathing following each recurrent apnoea is associated with intermittent blood

pressure elevation effected by increases in sympathetic drive mainly in response to arousal [2, 3]. Sustained hypertension often seen in longstanding OSA subjects may result from prolonged repetitive stimulation of the renin–aldosterone axis [4]. Prolactin (PRL) and cortisol are known to be reversibly elevated in an hypoxic stress response and analysis of these parameters in the context of effective treatment of OSA would therefore be expected to show significant improvement. As with other forms of systemic illness, suppression of gonadal and thyroid responsiveness occur during the development of OSA with reversal of these changes in treatment [1, 5].

Previous work on the endocrine changes seen in OSA has suggested an independent effect of the disease process [5]. However, some of the risk factors promoting the development of OSA (obesity, alcohol, etc.) may also have direct effects on hormone production, for example, sustained pseudo-cushingoid hypercortisolaemia in obesity or gonadal failure common in excessive alcohol consumption. This introduces difficulties in interpreting whether OSA is an independent risk factor for any associations found. One of the objectives of this study was to measure the endocrine axis alterations in response to effective treatment to circumvent this problem of confounding variables. There are substantial placebo responses in both self-reported health status and sleepiness following treatment [6] that might produce changes in hormone levels for reasons not related to the resolution of the OSA itself. For example, a reduction in PRL or cortisol stress-related response might be expected with an improvement in perceived health generated via a placebo effect.

This parallel sham placebo-controlled double-blind trial of nCPAP in the treatment of moderate to severe OSA in 101 patients allowed us the opportunity to initially examine baseline correlations between OSA severity and gonadal, adrenal, thyroid and growth hormone indices. These endocrine axes were then reassessed to explore the effects of 1-month nCPAP therapy compared with sub-therapeutically treated control patients. The data on subjective and objective sleepiness, including quality of life scores, has been published elsewhere [6].

This is the first published study of intra-individual endocrine variation in response to treatment for OSA compared with placebo control group.

Methods

Patients

Male patients with peripheral OSA were drawn from the Oxford Sleep Clinic – full details of this study are described in the initial publication [6]. They were considered eligible for entry if they had not received nCPAP treatment before, showed excessive daytime sleepiness (Epworth Sleepiness Score, ESS: ≥10) and had greater than 10 episodes per hour of a greater than 4% fall in arterial oxygen saturation (SaO_2) during a sleep study with confirmatory evidence of pharyngeal collapse (Visi Lab; Stowood Scientific Instruments, Oxford, UK). All eligible patients were invited to enter the study unless they chose an alternative therapy (e.g. weight loss, tonsillectomy), required urgent nCPAP therapy because of associated respiratory failure or imminent unemployment due to sleepiness, declined to participate or had a mental disability preventing the attainment of informed consent.

Analytical techniques

Follicle stimulating hormone (FSH), luteinizing hormone (LH), PRL, cortisol, thyroid stimulating hormone (TSH) and free thyroxine (free T4) were measured using specific heterogeneous sandwich magnetic separation immunoassays on an Immuno 1 analyser (Bayer, Newbury, UK). The imprecision of these measurements ranged from 2.6 to 15.4% for the above assays. No recognized causes of assay interference were identified.

Sex hormone binding protein (SHBG) and insulin-like growth factor-1 (IGF-1) were measured using manual monoclonal antibody immunoenzymometric assays. These systems show intra-assay coefficients of variation (CV) of less than 10% at all levels of testing. There was no evidence of cross-reactivity with other binding globulins in the SHBG assay, or insulin, IGF-2 or pro-insulin in the IGF-1 assay.

Total testosterone, renin and aldosterone were all measured using manual radioimmunoassay (RIA) techniques. The testosterone assay (Medgenix Diagnostics, Milton Keynes, UK) had greater imprecision at low values with CV values of 20% at 0.8 nmol L^{-1}, reducing to less than 9% for values up to 30 nmol L^{-1}. The renin and aldosterone assays have maximum recorded CV values of

8.1%. There were no identified interferences in any of these RIAs.

Protocol

Following the diagnostic sleep study, patients were seen in the outpatient department to confirm eligibility. After obtaining informed consent they were booked into the sleep laboratory for an overnight trial of nCPAP. Sleepiness (objective and subjective measures) and quality of life (SF-36 [7]) were assessed prior to the start of the trial by questionnaire [6]. The SF-36 quality of life scale explores eight areas of self-reported health status including 'energy and vitality'.

All blood samples were obtained mid-morning to allow direct comparisons of diurnally variant hormonal production. Plasma and serum samples were separated, spun and frozen at −70 °C until analysis.

All patients were shown a video about nCPAP and a specialist nurse taught each patient how to use the equipment. Patients were then assigned randomly to either therapeutic or sub-therapeutic (placebo) nCPAP using a numbered series of opaque sealed envelopes prepared in advance of the trial. Patients randomized to therapeutic nCPAP had their treatment pressure determined using the DeVilbiss Horizon autotitration device (Sunrise Medical, Somerset, PA, USA) [8]. Patients' randomized to placebo had an identical system, but the pressure was set to minimum with extra holes cut in the collar at the mask end of the connection tubing. This maintained pressure at a sub-therapeutic level (about 1 cmH_2O) and ensured no re-inhalation of CO_2.

The following morning, patients were sent home with either a therapeutic or placebo nCPAP machine, according to the randomization schedule. All patients had telephone access to specialist nurses (blind to the randomization). At 4 weeks, the patients were readmitted for an identical series of tests and blood sampling. The cumulative time from the clock in the nCPAP machine was used to calculate mean nightly use over the month.

The overall severity of the OSA in the patients on placebo nCPAP was not altered by the use of a sub-therapeutic pressure [6]. All subjects were changed to therapeutic nCPAP at the end of the trial month, which fell within the normal NHS waiting time for treatment. The study received approval from the local ethics committee (COREC number 96.127) and all subjects gave their informed consent. It was funded partly by the NHS Executive (Anglia and Oxford), grant number HSR/UOX/0296/72, and partly from internal charitable funds.

Statistical analysis

All data were entered into SPSS (version 7.5.1) and analysed using Pearson's correlation coefficients, paired and unpaired *t*-tests as appropriate. Results were normally distributed. Paired *t*-tests were used to look at the individual effects of placebo or active nCPAP. Unpaired *t*-tests were used to compare endocrine changes in hormone levels between groups. Stepwise multiple linear regression analysis was used to examine the independent effects of OSA, after adjusting for obesity.

Results

During the recruitment period 172 eligible patients were identified, of whom 65 patients were excluded because of the following reasons: 34 refused, seven were judged to be mentally impaired, 14 chose alternative therapies, eight needed urgent treatment and two entered a different study. Six patients did not attend the 1-month follow-up (four placebo, two active) and were excluded from the analysis. Therefore, a total of 101 patients (49 placebo, 52 active) completed the trial. A small number of blood samples were of inadequate volume to allow complete analysis; however the lowest number of paired (pre- and post-intervention) samples available for any particular analysis was 84. General baseline characteristics of the two groups were comparable and are reported in greater detail elsewhere [6].

Use of nCPAP by both groups was similar [4.6 h per night (SD 2.4) versus 5.4 h per night (SD 1.6) placebo and treatment groups, respectively]. There were large increases in SF-36 scores in both groups – reflecting improvement in perceived quality of life. Most significantly, the 'energy and vitality' dimension rose from 33.9 (SD 17.5) to 50.9 (20.5) in the placebo group ($P < 0.0001$) and from 35.4 (22.4) to 73.0 (17.0) in the active group ($P < 0.0001$). The full SF-36 data have been reported in a previous publication [6]. The similar use of nCPAP by the two groups and the marked placebo response strongly suggests that patients remained blinded to their treatment allocation.

Table 1 Hormone levels: correlation with OSA severity and obesity

Hormone	Correlation with OSA severity (>4% SaO_2 dips per hour)	*P*-value	Correlation with obesity (kg m^{-2})	*P*-value
LH	−0.24	0.024	−0.21	0.037
FSH	−0.30	0.004	−0.17	NS (0.07)
Prolactin	−0.02	NS	−0.04	NS
Testosterone	−0.44	<0.001	−0.49	<0.001
SHBG	−0.30	0.006	−0.18	NS (0.08)
TSH	0.04	NS	0.06	NS
Free T4	−0.23	0.037	−0.16	NS
Cortisol	0.02	NS	−0.13	NS
Aldosterone	0.18	NS	0.16	NS
Renin	0.06	NS	0.21	0.039
IGF-1	−0.10	NS	0.00	NS

NS, not significant.

Table 1 shows the correlations between baseline hormone levels and initial OSA severity (quantified from the number of greater than 4% SaO_2 dips per hour, desaturation index) as well as endocrine correlation to obesity (kg m^{-2}). LH, FSH, testosterone, SHBG and the free T4 correlated significantly with baseline OSA severity. In linear regression analysis the only positive correlations with obesity were testosterone and renin. Prior allowance for obesity lowered the correlation between testosterone and OSA severity from 0.44 ($P < 0.001$) to 0.34, but which still remained significant ($P = 0.002$).

Table 2 shows the hormone levels before and after placebo and active nCPAP intervention. In addition, *P*-values of unpaired *t*-test comparing the change in treatment between the two treatment groups have been calculated. Many of the analysed hormones undergo diurnal variation in secretion, and hence strictly timed blood sampling allowed direct comparison of the values obtained on both occasions. The reference intervals of these hormones from each analysing laboratory have been included.

The most striking changes in Table 2 were in aldosterone levels, which rose similarly in both the placebo and actively treated groups by about 30%. This was not associated with any change in renin levels. IGF-1 also rose significantly in both groups. TSH levels fell in the active nCPAP group ($P < 0.001$), with no alteration in the placebo group and statistical significance between the groups ($P = 0.02$), and no significant free T4 alteration in the therapeutic group. Total testosterone levels did not rise with active nCPAP as had been previously reported [1], although SHBG did increase significantly.

Discussion

The requirement to carry out a randomized placebo-controlled trial to prove the efficacy of nCPAP as a treatment for OSA [6, 9] allowed us to examine hormonal levels related to baseline severity and obesity as well as in response to treatment using nCPAP. The most striking findings were the elevations in aldosterone and IGF that occurred in both active and placebo groups, suggesting a nonspecific

Table 2 Hormone levels before and after treatment

Results are mean and SD	Reference range	Sham NCPAP			Active NCPAP			Sham/ active differences
		Pre	Post	*P*-value	Pre	Post	*P*-value	*P*-value
LH	3–8 U L^{-1}	6.07 (2.70)	5.34 (3.00)	**0.04**	5.99 (2.55)	5.81 (2.42)	**0.73**	**0.30**
FSH	0.5–5 U L^{-1}	6.50 (3.01)	6.00 (3.03)	**0.02**	6.53 (4.20)	6.61 (3.64)	**0.90**	**0.13**
Prolactin	<450 m U L^{-1}	161 (64)	162 (83)	**0.38**	160 (81)	167 (113)	**0.46**	**0.28**
Testosterone	9–42 nmol L^{-1}	14.4 (5.0)	12.9 (4.4)	**0.004**	13.5 (5.8)	13.2 (4.7)	**0.94**	**0.04**
SHBG	15–120 nmol L^{-1}	34.7 (20.1)	30.6 (13.4)	**0.20**	26.8 (10.8)	29.9 (15.1)	**0.04**	**0.03**
TSH	0.5–6.0 mU L^{-1}	1.63 (0.72)	1.67 (0.86)	**0.63**	1.72 (0.76)	1.40 (0.59)	**<0.001**	**0.02**
Free T_4	9–25 pmol L^{-1}	13.5 (2.1)	14.6 (1.5)	**<0.001**	14.3 (2.2)	14.9 (2.5)	**0.07**	**0.09**
Cortisol[a]	280–700 nmol L^{-1}	226 (88)	273 (100)	**0.024**	236 (92)	255 (114)	**0.400**	**0.35**
Aldosterone[b]	100–900 pmol L^{-1}	307 (102)	402 (132)	**<0.001**	321 (121)	411 (125)	**<0.001**	**0.78**
Renin[c]	1.1–4.3 pmol mL^{-1} h^{-1}	2.43 (0.81)	2.52 (0.98)	**0.52**	2.69 (2.45)	2.67 (2.23)	**0.88**	**0.56**
IGF-1[d]	7.5–30 nmol L^{-1}	9.73 (3.74)	11.15 (4.38)	**0.016**	10.50 (3.23)	11.59 (3.48)	**0.03**	**0.71**

Results are mean (SD).
[a]Reference range quoted at 09.00 hours. [b]Reference range quoted to include recumbent and up to 12.00 hours. [c]Reference range quoted to include recumbent and after 30 min erect. [d]Reference range quoted for 40–60-year-old subjects.

effect of intervention, which may be related to the improved quality of life scores reflecting improved physical activity.

Baseline correlation with obstructive sleep apnoea severity

The correlation between reduced testosterone and baseline OSA is thought to be due to increased sleep fragmentation [10] and reduced oxygenation, both of which are known to inhibit testosterone production [11]. The present study supports these data, with a corrected β coefficient for hypoxaemia of −0.32 equating to a reduction of 3.2 nmol L^{-1} in testosterone for every increase by 10 h^{-1} in the desaturation index. This baseline suppressive effect of OSA on total testosterone levels independent of obesity is consistent with secondary hypogonadism induced by systemic illness.

Baseline correlations with obesity

Luteinizing hormone, testosterone and renin showed significant independent correlations with obesity. Obesity has been shown to decrease both total testosterone and SHBG, thus maintaining free testosterone levels [except in the massively obese (weight >220 kg) in whom some reduction in the free hormone was seen] [12, 13]. This testosterone reduction may result from elevated adipose tissue aromatase activity increasing conversion of testosterone to more rapidly cleared metabolites, some of which feed back on the hypothalamo-pituitary axis to prevent gonadotrophin elevation [12], supported by LH suppression in the present data. Resultant reductions in gonadal hormones concentrations underlie clinical symptoms of reduced libido and possibly impotence [14, 15]. The β coefficient for body mass index (BMI) was −0.35, thus testosterone fell by a mean of 1.75 nmol L^{-1} for every rise in BMI of 5 kg m^{-2}.

Hypertension develops in almost 60% of obese individuals [16]. Metabolic changes seen in obesity-induced hypertension include volume expansion, sodium retention, elevated sympathetic nervous system and renin–aldosterone activity, reduced atrial natriuretic peptide (ANP) levels and disturbed insulin and glucose metabolism [17]. Elevated leptin-driven sympathetic renal outflow combined with reduced ANP levels – as a result of clearance receptor overexpression on adipocyte membranes – are possible underlying mechanisms of sodium retention and volume expansion [16]. There is also data suggesting elevated production of vasoactive substances, such as angiotensin II and nonesterified fatty acids from adipocytes. Although no significant changes in systolic or diastolic blood pressure were noted in the study group, an extension of this protocol using 24-h measurements has demonstrated diurnal falls in both systolic and diastolic blood pressure [18, 19].

Treatment effects

Gonadal axis

Testosterone. Previous uncontrolled studies have suggested an elevation of suppressed testosterone in response to treatment of OSA. In Santamaria *et al.*'s 1988 study of 15 men with OSA the reduction in testosterone levels correlated with the initial severity of sleep hypoxaemia [20]. Following pharyngeal surgery in 12 of the patients, there was a small average increase in testosterone but this study lacked untreated control subjects. A recent study of testosterone and LH production overnight in OSA and control subjects, employing frequent blood sampling, showed a significant reduction in overall testosterone release [21]. Of the small OSA group 40% were defined as hypogonadal with testosterone measurements below the reference interval on early-morning sampling.

In a much larger cross-sectional study of 225 men undergoing sleep studies [1] the reductions in total testosterone, SHBG and free testosterone were significantly correlated to baseline severity of sleep apnoea. A longitudinal study involving 43 OSA subjects with no control subjects [22] showed that total testosterone and SHBG levels rose following 3 months of nCPAP treatment. The present study supports SHBG elevation but showed no change in total testosterone, leading us to assume there was no clinically effective increase in free testosterone.

In Grunstein *et al.*'s study [1] the degree of OSA was more severe than in this study and the treatment interval was extended at 3 months. A subset analysis of the more severe patients (desaturation index >30 dips per hour, $n = 41$) did not show a significant change in testosterone compared with placebo. This could be explained if the observed hypogonadism in OSA was only indirectly related to

the OSA itself. Alternatively, it may require effective treatment beyond 1 month for measurable recovery of the pituitary-gonadal axis to occur.

SHBG. Grunstein *et al.* showed SHBG to be correlated to the degree of sleep fragmentation [1] and the increase in SHBG seen in this study may result from increased unbroken sleep, although the mechanism remains undefined. LH and FSH were significantly reduced at baseline, correlating to OSA severity and consistent with a central hypogonadotrophic hypogonadism rather than primary gonadal failure. This secondary hypogonadism may be influenced by the wider systemic repercussions of OSA pathophysiology, akin to the induction of hypogonadotrophic hypogonadism in any form of chronic illness.

This data supports OSA as a cause of acquired hypogonadism from baseline correlations although time restrictions of this study prevented conclusive demonstration of recovery in the gonadal axis with effective nCPAP treatment, in this first placebo controlled trial. In a future study it would be important to monitor gonadotrophin, SHBG and free testosterone changes over a longer treatment period, such as 6–12 months. The clinical relevance of this form of hypogonadotrophic hypogonadism on long-term well-being of subjects affected by OSA, particularly on bone mineral density and cardiovascular risk in males, has yet to be established, as has the extent of extrapolation of these data to females affected by OSA.

Thyroid hormones. There have been many reports of the association between hypothyroidism and OSA [23, 24] based on the assumption that hypothyroidism could exacerbate OSA. The prevalence of hypothyroidism in OSA is actually no greater than in the general population [25, 26]. In this study, there was a small significant inverse correlation between OSA severity and free T4 levels but not TSH. There was no apparent association between obesity and either hormone.

The thyroid axis responds to systemic illness by an elevation in free T4, stimulated by reduced T4 to T3 conversion in peripheral tissues, but the expected feedback-initiated elevation in TSH production is often prevented by direct hypothalamic suppression. Treatment of OSA compared with placebo in this study resulted in a significant reduction in TSH without a reciprocal elevation in free T4 levels, consistent with the pattern of recovery from non-thyroidal illness [27].

Adrenal hormones. **1** *Glucocorticoid:* Early reports suggested a stimulatory stress-effect of OSA on the pituitary-glucocorticoid axis [28] but subsequent data have not supported this. Grunstein et al. [1] found no significant alteration in cortisol in patients with OSA and no effect of treatment on this axis. The results of the present study agree with Grunstein et al., showing no relationship of cortisol to OSA severity and no measurable response to treatment compared to placebo.

2 *Mineralocorticoids:* No relationship was found between initial OSA severity and aldosterone or renin levels. Unexpectedly aldosterone levels rose about 30% in both the placebo and active treatment groups. Venepuncture was carried out strictly according to the protocol with standardizing time of sampling – as a result of diurnal hormonal variation – and immediate presampling patient activity. No published data was found specifically on the effects of OSA on the mineralocorticoid axis at the time of this study, although hypertension is common in OSA patients and alterations in mineralocorticoid production may provide an aetiological explanation.

In an original randomized controlled trial (RCT) published in 1999 by the authors [6] a substantial placebo effect has been reported on perceived sleepiness and quality of life, particularly energy and vitality components. This implies a more active existence in both groups at the end of the study. It is well recognized that renin is elevated in response to systemic illness [29, 30], implying a reduction in renin output might be expected in a study of extended duration. The lack of documented change in the renin axis in this data implies that aldosterone may normalize first on recovery, alternatively aldosterone may be more strongly influenced by other secretagogue factors.

IGF-1. Growth hormone (GH) secretion is pulsatile with peak production occurring at night in adults [31, 32]. The half-life of GH is short but its metabolic effects are exerted by local tissue and hepatic production of IGF-1, which usually correlates well with 24-h GH profiles in health [33]. Obesity is known to be a GH hyposecretory state, although IGF-1 levels tend to be preserved [34]; the results in the present study showed no correlation of IGF-1 with obesity.

In critical illness IGF-1 levels reduce secondary to loss of diurnal variation and pulsatility of GH secretion [27]. Grunstein found that IGF-1 levels

were reduced in men with OSA, correlating strongly with the lowest oxygen saturation reached during sleep [1]. No relationship was found between IGF-1 and OSA severity, even when reanalysed using mean nocturnal SaO_2 rather than >4% SaO_2 dips as OSA severity indices or severely affected individuals only.

In addition Grunstein *et al.* found a small rise in IGF-1 following nCPAP for 3 months [1]. In the present data the rise in IGF-1 in both active and placebo groups is more likely explained by increased physical activity, as evidenced by the increased energy and vitality dimension of the SF-36 scores. Akerstedt *et al.* [10] originally concluded that sleep deprivation resulted in lower levels of psychological and physical activity. Recovery from any systemic illness is also usually accompanied by reversal of suppression of GH secretion and IGF-1 activity. Exercise has been shown to directly stimulate GH secretion and elevation of activity levels may therefore be responsible for the return of physiological GH release [32].

Obstructive sleep apnoea results in a greater impairment of GH secretion and peripheral IGF-1 insensitivity than simple obesity [34]. Both of these changes may result from the occurrence of recurrent nighttime hypoxia. Obesity centrally reduces GH diurnal pulsatility – restored by nCPAP prior to measurable changes in BMI [35, 36] – similar to the hypogonadotrophic hypogonadism induced by OSA. Testosterone has a positive influence on IGF-1 synthesis and release, so elevations in IGF-1 seen in both groups may actually reflect recovery of OSA-induced GH or gonadotrophic axis suppression.

Prolactin. Prolactin levels were not correlated to OSA severity and were unaffected by nCPAP. This agrees with previous findings in uncontrolled studies [1, 37] although PRL can be a useful marker of acute, severe, illness-induced stress.

Conclusions

This study has shown that increasing OSA severity is associated with lower levels of LH, FSH, free T4, SHBG and total testosterone, with an exacerbating effect in the presence of obesity for the latter. The changes following active treatment for OSA, relative to placebo, include elevation of SHBG and a reduction in TSH production. Both active and placebo intervention for 1 month produced rises in aldosterone and IGF-1 thought to be related to increased physical activity in both groups. The present data confirms OSA as a cause of acquired hypogonadism, independent of the potential compounding factor of concurrent obesity. This suggests dynamic hypothalamo-pituitary-gonadal axis testing prior to treatment of OSA is difficult to interpret and should be delayed until after successful treatment of OSA if possible.

There is a need for a repeat study of extended treatment duration to clarify the changes in IGF-1, thyroid, adrenal and gonadal axes. These data also show neuroendocrine responses to sleep apnoea may be unified by a common pathological response, similar to that seen in other chronic systemic illnesses, with some early responses in IGF-1, TSH and aldosterone analytes supporting reversion back to a more physiological situation.

Conflict of interest statement

No conflicts of interest were expressed by any member of the investigative group.

Acknowledgements

We would like to thank Nadia Payne (Middlesex Hospital, London, UK) for the renin and aldosterone measurements, and the Clinical Biochemistry Department at the John Radcliffe for assistance with other assays.

References

1 Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab* 1989; **68:** 352–8.
2 Parish JM, Shepard JW. Cardiovascular effects of sleep disorders. *Chest* 1990; **97:** 1220–6.
3 Davies RJ, Belt PJ, Roberts SJ, Ali NJ, Stradling JR. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. *J Appl Physiol* 1993; **74:** 1123–30.
4 Fletcher EC, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: the rennin-angiotensin system. *J Appl Physiol* 2002; **92:** 627–33.
5 Grunstein R. Endocrine and metabolic disturbances in obstructive sleep apnea. In: Saunders NA, Sullivan CE, eds. *Sleep and Breathing: Lung Biology in Health and Disease.* New York: Dekker, 1994; 449–89.
6 Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999; **353:** 2100–5.

7 Tarlov AR, Ware JE, Jr, Greenfield S, Nelson EC, Perrin E, Zubkoff M. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *JAMA* 1989; **262:** 925–30.
8 Stradling JR, Barbour C, Pitson DJ, Davies RJO. Automatic nasal continuous positive airway pressure titration in the laboratory, patient outcomes. *Thorax* 1997; **52:** 72–75.
9 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *Br Med J* 1997; **314:** 851–60.
10 Akerstedt T, Palmblad J, de la Torre B, Marana R, Gillberg M. Adrenocortical and gonadal steroids during sleep deprivation. *Sleep* 1980; **3:** 23–30.
11 Semple PD, Beastall GH, Watson WS, Hume R. Serum testosterone depression associated with hypoxia in respiratory failure. *Clin Sci* 1980; **58:** 105–6.
12 Amatruda JM, Harman SM, Pourmotabbed G, Lockwood DH. Depressed plasma testosterone and fractional binding of testosterone in obese males. *J Clin Endocrinol Metab* 1978; **47:** 268–71.
13 Glass AR. Endocrine aspects of obesity. *Med Clin North Am* 1989; **73:** 139–60.
14 Guilleminault C, Simmons FB, Motta J *et al.* Obstructive sleep apnea syndrome and tracheostomy. *Arch Intern Med* 1981; **141:** 985–8.
15 Hirshkowitz M, Karacan I, Gurakar A, Williams RL. Hypertension, erectile dysfunction, and occult sleep apnea. *Sleep* 1989; **12:** 223–32.
16 Sharma AM, Engeli S, Pischon T. New developments in mechanisms of obesity-induced hypertension: role of adipose tissue. *Curr Hypertens Rep* 2001; **3:** 152–6.
17 Rocchini AP. Obesity hypertension, salt sensitivity and insulin resistance. *Nutr Metab Cardiovasc Dis* 2000; **10:** 287–94.
18 Pepperell JC, Ramdassingh-Dow S, Crosthwaite N *et al.* Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; **359:** 204–10.
19 Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea–hypopnea syndrome. *Am J Respir Crit Care Med* 2001; **163:** 344–8.
20 Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol Oxf* 1988; **28:** 461–70.
21 Luboshitzky R, Aviv A, Hefetz A *et al.* Decreased pituitary-gonadal secretion in men with obstructive sleep apnoea. *J Clin Endocrinol Metab* 2002; **87:** 3394–8.
22 Stewart DA, Grunstein RR, Sullivan CE, Handelsman DJ. Neuroendocrine changes in sleep apnea are not related to a pituitary defect. *Sleep Res* 1989; **18:** 308.
23 Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med* 1988; **85:** 775–9.
24 Kittle WM, Chaudhary BA. Sleep apnea and hypothyroidism. *South Med J* 1998; **81:** 1421–5.
25 Skjodt NM, Atkar R, Easton PA. Screening for hypothyroidism in sleep apnea. *Am J Respir Crit Care Med* 1999; **160:** 732–5.
26 Lin CC, Tsan KW, Chen PJ. The relationship between sleep apnea syndrome and hypothyroidism. *Chest* 1992; **102:** 1663–7.
27 Everts ME, de-Jong M, Lim CF *et al.* Different regulation of thyroid hormone transport in liver and pituitary: its possible role in the maintenance of low T3 production during non-thyroidal illness and fasting in man. *Thyroid* 1996; **6:** 359–68.
28 Rapoport D, Rothenburg SA, Hollander CS, Goldring RM. Obstructive sleep apnea (OSA) alters ultradian rhythm of ACTH secretion. *Am Rev Respir Dis* 1989; **139:** A80.
29 Fallo F. Renin–angiotensin–aldosterone system and physical exercise. *J Sports Med Phys Fitness* 1993; **33:** 306–12.
30 Leshem M, Abutbul A, Eilon R. Exercise increases the preference for salt in humans. *Appetite* 1999; **32:** 251–60.
31 Jarrett DB, Greenhouse JB, Miewald JM, Fedorka IB, Kupfer DJ. A re-examination of the relationship between growth hormone secretion and slow wave sleep using delta wave analysis. *Biol Psychiatry* 1990; **27:** 497–509.
32 Quabbe HJ. Hypothalamic control of GH secretion: pathophysiology and clinical implications. *Acta Neurochir Wien* 1985; **75:** 60–71.
33 Melmed S. Acromegaly [see comments]. *NEJM* 1990; **322:** 966–77.
34 Gianotti L, Broglio F, Ramunni J *et al.* The activity of GH/IGF-I axis in anorexia nervosa and in obesity: a comparison with normal subjects and patients with hypopituitarism or critical illness. *Eat Weight Disord* 1998; **3:** 64–70.
35 Gianotti L, Pivetti S, Lanfranco F *et al.* Concomitant impairment of growth hormone secretion and peripheral sensitivity in obese patients with obstructive sleep apnea syndrome. *J Clin Endocrinol Metab* 2002; **87:** 5052–7.
36 Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C, Follenius M. Continuous positive airway pressure treatment. Effects on growth hormone insulin and glucose profiles in obstructive sleep apnea patients. *Horm Metab Res* 1991; 25**:** 375–81.
37 Spiegel K, Follenius M, Krieger J, Sforza E, Brandenberger G. Prolactin secretion during sleep in obstructive sleep apnoea patients. *J Sleep Res* 1995; **4:** 56–62.

Received 24 January 2003; revision received 5 May 2003; accepted 28 May 2003.

Correspondence: Dr Niki Meston, Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU UK. (fax: 44 1865 220348; e-mail: nikimeston@hotmail.com).