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Improved nasal breathing in snorers increases nocturnal growth hormone secretion and serum concentrations of insulin-like growth factor 1 subsequently*

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SUMMARY

In snoring men improved nasal breathing during sleep has been shown to decrease snoring and morning tiredness. The aim was to evaluate whether improved nasal breathing had any effect on growth hormone (GH) secretion, the nocturnal secretion of GH being associated with deep sleep. Forty-two snoring men, mean age 45 years and mean body mass index 26 kg• m-2, slept every night during one month with the Nozovent® nostril dilator.

Before and at the end of the test period, we analysed serum insulin-like growth factor 1 (IGF-1), thyrotropin (TSH), free thyroxine (free T4), free 3,5,3′- triiodothyronine (free T3), cortisol and testosterone in blood sampled at 08:00 h. Fifteen of the 37 snoring men who completed the study experienced a reduction in snoring and were less tired in the morning during the test period. In this group, the mean IGF-1 concentration was significantly increased ($p < 0.05$) after one month. There was no significant difference in mean IGF-1 level between the snorers and a population sample. Likewise, TSH, free T4, free T3, cortisol and testosterone concentrations were within normal limits. Snorers with reduced snoring and morning tiredness due to improved nasal breathing showed an increase in morning IGF-1 concentration which can probably be explained by higher nocturnal GH secretion induced by more deep sleep.

Key words: slow wave sleep, nasal breathing, IGF-1, growth hormone secretion, snoring

INTRODUCTION

The secretion of growth hormone (GH) from the anterior part of the pituitary gland is pulsatile with a serum half-life of 22 minutes. GH secretion is regulated by growth hormone releasing hormone (GHRH) and somatostatin from the hypothalamus with a sleep-wake cycle with a low average GH secretion in the daytime and higher GH secretion during sleep (Holl et al., 1991). The night-time increase in GH secretion is associated with slow-wave sleep (SWS) in sleep stages 3 and 4, with about 70% of the daily secretion occurring in this SWS (Cauter et al., 1992).

In sleep disorders, the sleep architecture can be disturbed, resulting in impaired slow-wave sleep, frequent arousals and sleep stage changes. In the obstructive sleep apnoea syndrome where the sleep is markedly fragmented due to disturbed breathing with repetitive apnoea, Grunstein et al. (1996), have shown that the GH secretion is markedly lower before the breathing is improved with nasal continuous positive airway pressure (CPAP). This treatment improves the sleep architecture and increases slow-wave sleep, resulting in a marked increase in serum GH concentration.

The secretion of GH by the pituitary gland, to some extent, is reflected by the circulating concentrations of insulin-like growth factor 1 (IGF-1) (Melmed, 1990), which correlate with 24-hour mean plasma GH concentrations. The IGF-1 concentration has considerably less within-subject variability than GH (Cauter et al. 1992). Thus serum IGF-1 concentration may be used as an index of GH release. Several other hormones may influence IGF-1 secretion, such as gonadal and thyroid hormones, as may the nutritional state of the individual (Furlanetto, 1990; Hobbs et al. 1993; Nanto-Salonen et al. 1993; Ketelslegers et al. 1995). The major function of the growth hormone is to stimulate growth, but

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it also appears to have a positive effect on human well being, at least applied to GH-deficient patients (Rosén et al. 1994).

One aim of this study was to measure serum IGF-1 in heavy snorers, before and after the air flow through the nose was improved during sleep with a nostril dilator, which increases the air flow through the nose in average 24 % (Petruson, 1988). Improved nasal breathing has been shown to decrease snoring and the number of apnoeas during sleep (Höijer et al. 1992; Petruson, 1990), the number of arousals per hour decrease (Kerr et al. 1992) and less tiredness in the morning has also been observed (Löth & Petruson, 1996).

Another aim of the study was to determine whether other pituitary-related hormones were influenced by improved nasal breathing during sleep in male snorers. TSH, Free T4, free T3, cortisol and testosterone therefore were measured in serum before and after one month of using a nostril dilator.

SUBJECTS AND METHODS

Snorers

From the out-patient waiting-list for snorers at the Department of Otorhinolaryngology, Central Hospital in Skövde, Sweden, 42 men who were willing to test the nostril device for one month were selected. The patients' mean age was 45 years (range 28-62 years), their mean body mass index (BMI) was 26 kg • m^{-2} (range 20-39) and the mean apnoea hypopnoea index (AHI) was 9 per hour (range 2-45).

Five patients dropped out of the study and did not report after one month of using the nostril dilator. In one patient, the blood samples after one month, were lost by the laboratory after sampling in Skövde.

Reference population

As control subjects 197 men from the MONICA population study (MONICA: MONItoring of trends and determinants in CArdiovascular diseases) in Göteborg, Sweden, were selected. This study was designed to measure mortality and morbidity from coronary heart disease and stroke and its relationship to changes in known risk factors in different populations. In the Göteborg population sample from 1990, 1,575 subjects who were randomly selected from 24-64 year age group participated. The mean age of the 786 men in the population sample was 45 years and BMI 25.4 kg • m^{-2} (range 15.5-42.7). For the analyses of hormones 50 samples from each age group were selected at random. A few samples could not be used and in total, 197 men were included (Landin-Wilhelmsen et al., 1994).

Study design

Before the test period started, all snorers answered a questionnaire about morning tiredness. They had to choose between 4 answers: [1] I am not tired in the morning (n=11); [2] I am a bit tired in the morning (n=15); [3] I am rather tired in the morning (n=11); and [4] I am very tired in the morning (n=5). The patients' snoring was scored by his sleeping partner, using a visual analogue scale consisting of a straight line, 100 mm in length which gives a score from 0 = no snoring to 100 = continuous snoring (Löth and Petruson, 1996).

On the first visit, the patients were examined clinically, blood sampling was carried out and the nostril dilator Nozovent® (manufactured by Prevancure Ltd., Box 2116, V. Frölunda, Sweden) that provided the most comfort was determined by choosing between the different sizes (small, medium and large). After one month of continuous night-time use of the nostril dilator, blood samples were taken. The sleeping partner graded the average snoring during the test period and the patient rated his morning tiredness, choosing between three questions: [1] I am more tired in the morning than before; [2] I have not been tired in the morning; [3] I am less tired in the morning now.

After the test period, the patients' sleep was registered for one night at the Department of Otorhinolaryngology, Central Hospital in Skövde, on a static charge sensitive bed (SCSB) (Bio-Matt®, SCSB system delivered by BR Biorec oy, Turku, Finland) with a pulse oximetry (Ohmeda Biox 3740, Louisville, Col). The SCSB bed has a sensitive movement sensor, situated under a normal foam mattress. The signals of body movements are filtered, amplified and enable polygraphic recordings of respiratory movements.

The study was approved by the Ethics Committee at Sahlgrenska University Hospital, Göteborg, Sweden.

Definitions of apnoea / hypopnoea and apnoea / hypopnoea index

The apnoea hypopnoea index (AHI) was calculated from the number of apnoeas and hypopnoea that occurred per hour of sleep. Apnoea and hypopnoea were defined as oxygen saturation fluctuations of more than 4%, when the apnoea was longer than 10 seconds or the respiratory ventilation was reduced (measured as amplitude on the respiratory graph) by at least 50% during the hypopnoea.

Blood sampling

Venous blood samples, were drawn in the morning at 08:00 h after an overnight fast. Serum was separated after centrifugation and stored at −70 C until analysis was performed within two years.

Biochemical assays

Serum IGF-1 was determined by a hydrochloric acid-ethanol extraction radioimmunoassay using authentic IGF-1 for labelling (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), (Landin-Wilhelmsen et al. 1994). Free T4 and free T3 were determined by ligand analogue assays with reagents from Kodak Clinical Diagnostics Ltd. (Amerlex-M, Amersham International plc, Aylesbury, Buckinghamshire, United Kingdom) (Stenlöf et al. 1993). Serum TSH concentrations were determined by immunoradiometric assay (RIA-gnost hTSH. Behringwerke AG, Marburg, Germany). Serum cortisol and total testosterone were analysed by nonextraction radioimmunoassays (Farmos Diagnostica, Turko, Finland, and ICN, Biomedical, Costa Mesa, USA, respectively).

Statistical methods

We calculated values for mean and standard deviation [mean (SD)]. Linear correlations were calculated using Pearson's par-

tial correlation analysis. For statistical calculations analyses using Pitman's two-sided test and Fisher's exact test for paired comparisons were used. A p-value of < 0.05 (two-sided test) was considered statistically significant.

RESULTS

There was no significant difference in mean IGF-1 concentrations between the snorers and a male population sample, when the values were related to age and sex (Landin-Wilhelmsen et al., 1994) (Figure 1). In the snorers there was no correlation between IGF-1 and AHI or BMI.

Fifteen of the 37 snorers who slept with dilated nostrils for one month snored less and experienced less tiredness in the morning. The mean IGF-1 concentration was increased with 10 μg/l after one month ($p < 0.05$). In this group (Group 1) a significant decrease in snoring was also observed (Table 2a,b).

For the group of 21 snorers who did not feel less tired in the morning after one month, there was no difference in IGF-1 level between the two test occasions.

Table 1. Age, body mass index (BMI) and biochemical variables of the snoring men. Blood samples were taken before the study. Results are presented as basal mean values, SD and range.

The mean values of all the snorers before the test (n = 42)

Variable	Mean	(SD)	Range
Age, years	45	(8)	28-62
BMI, kg/m^2	26	(3.7)	22-39
IGF-1, mg/l	225	(58)	122-384
free T3, ρmol/l	6.1	(1.4)	0.7-8.7
free T4, ρmol/l	14.9	(2.1)	10.6-19.4
TSH, mU/l	1.6	(0.8)	0.7-4.0
Cortisol, ηmol/l	375	(105)	174-630
Testosterone, ηmol/l	18	(5)	10-28

Table 2a. When the snorers slept with dilated nostrils for one month it was found that 15 snored less and experienced less tiredness in the morning (Group 1), the other 21 snorers did not feel less tired in the morning (Group 2). The snoring was estimated by the female sleeping partner who had to use a visual analogue scale (VAS) consisting of a straight line, 100 mm in length which gives a score from 0 = no snoring to 100 = continuous snoring. The mean values in the two groups are given as well as the standard deviation in brackets (SD).

	Group 1	Group 2
Age, years	47 (9)	43 (7)
BMI, kg/m^2	27 (3)	26 (4)
AHI	13 (11)	9 (11)
Snoring	87 (10)	76 (24)

Table 2 b. The differences in testvalues (▲) between the two test occasions, before the study and after one month with the dilator, are presented as mean and (SD). The statistical significance is: $p < 0.05$ = *, $p < 0.01$ = ** and $p < 0.001$ = ***.

Variable	Group 1 (n = 15)		Group 2 (n = 21)	
IGF-1, μg/l	10 (36)	*	−16 (34)	N.S.
free T3, ρmol/l	0.1 (0.8)	N.S.	0.0 (0.6)	N.S.
free T4, ρmol/l	0.8 (1.4)	N.S.	0.1 (1.4)	N.S
TSH, mU/l	0.1 (0.7)	N.S.	−0.1 (0.5)	N.S.
Cortisol, ηmol/l	16 (148)	N.S.	40 (161)	N.S.
Testosterone, ηmol/l	0 (3)	N.S.	−1 (3)	N.S.
Snoring (VAS scale)	33 (27)	***	10 (17)	**

Free T4, free T3, TSH, cortisol and testosterone concentrations were within the reference values of the laboratory and did not change during the study (Tables 1 and 2b).

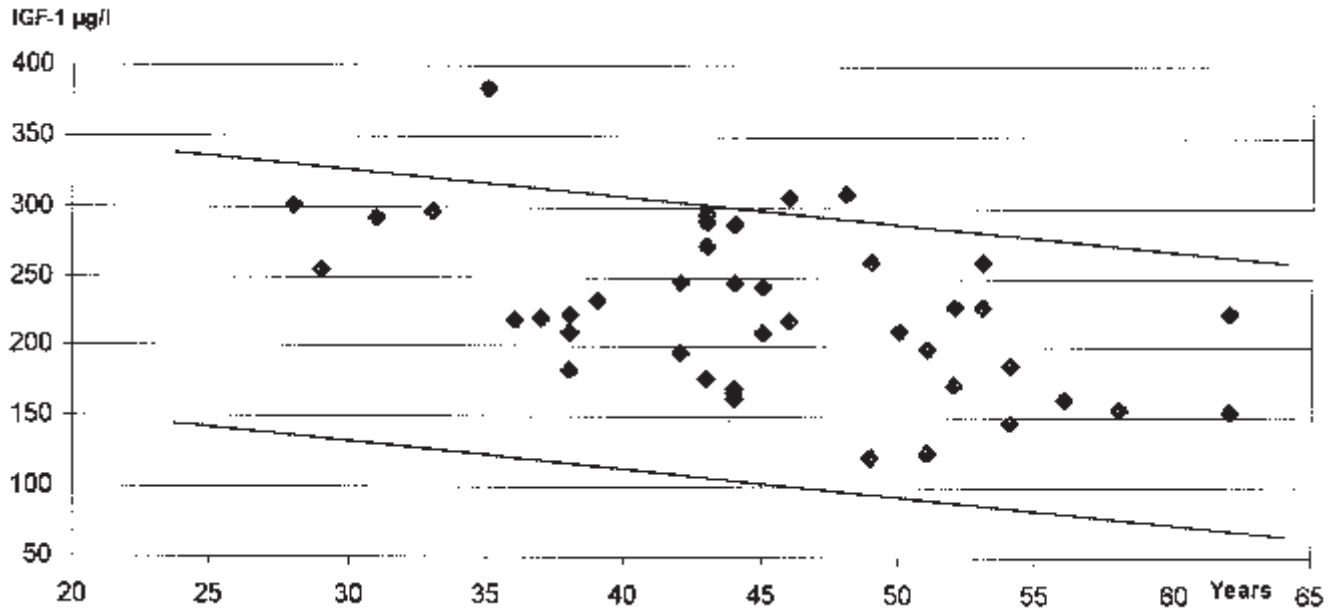

Figure 1. IGF-1 concentrations in 42 male snorers in relation to age. The 95% confidence intervals in a male population sample of 197 men are shown (16).

DISCUSSION

In this study on 36 snorers, we found that 15 of them snored less and felt less tired in the morning when they slept with dilated nostrils for one month. In this group, we noted a significant increase in mean IGF-1 concentration in contrast to what was found in the other 21 snorers who were not less tired in the morning. This indicates that snorers who snored less and felt less tired in the morning may have better sleep and improved SWS, which increases GH secretion during the night, resulting in an elevated formation of IGF-1. It has been known for some years that deep sleep is of importance for the nocturnal secretion of GH, but it is not until recently that it has been shown that improved breathing at night resulting in more deep sleep, increases the secretion of GH (Grunstein et al. 1996; Saini et al. 1993).

The established treatment for obstructive sleep apnoea syndrome, characterised by the repeated cessation of airflow during sleep, is nasal continuous positive airway pressure (CPAP) which is generated by an electro-mechanical blower delivering airflow to a nasal mask secured over the patient´s face. Air is blown into the lungs through the nose. When the correct pressure is used, an increase in the quantity of SWS and a simultaneous increase in the GH-IGF-1 axis has been observed (Grunstein et al. 1989; Saini et al. 1993).

Moriwaki et al. (1997), found in 18 of 24 children who were severe snorers and had hypertrophy of the tonsils and adenoid a significant increase of IGF-1 levels after adenotonsillectomy.

Another way to improve nasal breathing without a machine is to use a nostril dilator, which has been shown to increase nasal airflow significantly (Petruson, 1988). In a study at a sleep laboratory, a significant decrease in the apnoea index (from 18 to 6) was found during the nights on which the nostril dilator was used (Höijer at al. 1992). When nasal airflow was increased in patients with obstructive sleep apnoea syndrome, the number of arousals per hour was significantly reduced and there was a tendency towards increased SWS (Kerr et al., 1992).

Our patients had an average AHI of 9, only 3 had an index above 15 that may indicate a real sleep apnoea syndrome. We did not find any correlation between an elevated AHI and low IGF-1 concentrations, as has been reported in patients with severe sleep apnoea (Grunstein et al. 1989). We believe that it is not the fluctuations in the oxygen saturation in the blood that act on the hypothalamus-pituitary region, but reduced airflow in the upper airway, which results in the impairment of sleep. This is supported by a study of patients with chronic hypoxemia in whom no apparent effect on the secretion of GH was observed (Cornil et al. 1975).

We did not find any correlation between BMI and IGF-1 in the snorers, taking age into account.

When the IGF-1 concentrations in a random population sample (Landin-Wilhelmsen et al., 1994) were compared with the concentrations of IGF-1 in snorers, no difference was found between the groups. This can be explained in part by the occurrence of snoring in the population, in part by the multifactorial regulation of IGF-1 secretion.

Snoring did not appear to influence other pituitary-related hormones, as we found normal concentrations of cortisol, testosterone, TSH, free T4 and free T3 in the snorers. There were no significant differences in the values before and after one month. In summary, those snorers who snored less and were less tired in the morning, due to improved nasal breathing, had a slight but significant increase in the GH-IGF-1 axis which, we believe, was due to a better sleep architecture.

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