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Effect of surgical intervention on serum insulin-like growth factor 1 in patients with obstructive sleep apnoea

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Main Article

Dr H Verma takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To evaluate the effect of surgical intervention on serum insulin-like growth factor 1 levels in patients with obstructive sleep apnoea.

Methods. A prospective study was conducted in a tertiary care hospital of adult patients with obstructive sleep apnoea for whom continuous positive airway pressure therapy failed or was refused. All patients underwent polysomnography and serum insulin-like growth factor 1 evaluation pre-operatively and at three months post-operatively. The site of surgery was determined using Müller's manoeuvre and ApneaGraph AG 200.

Results. Fifteen patients were included with a mean age of 38 years: 11 males and 4 females. The mean pre-operative Apnoea–Hypopnoea Index using polysomnography was 53.7 events per hour, and the mean post-operative Apnoea–Hypopnoea Index at three months was 15.3 events per hour ($p = 0.0001$). The mean pre-operative serum insulin-like growth factor 1 was 160.2 µg/l, while the mean post-operative value was 236.98 µg/l ($p = 0.005$).

Conclusion. In adult patients with obstructive sleep apnoea for whom continuous positive airway pressure therapy fails, site-specific surgical intervention to treat the obstruction leads to an increase in serum insulin-like growth factor 1 levels.

Introduction

Obstructive sleep apnoea (OSA) is a well-established entity characterised by recurrent episodes of partial or complete obstruction of the upper airway. This leads to repetitive oxygen desaturations and frequent arousals from sleep, which disrupts the normal sleep architecture and reduces slow-wave sleep. This can affect the diurnal variations of hormones released from the pituitary gland.[1] Obstructive sleep apnoea is associated with a variety of systemic diseases including cardiovascular disease, systemic hypertension and diabetes mellitus.[2] The derangement of various enzymes and cytokines has been implicated in the aetiopathogenesis of these systemic effects.

Insulin-like growth factor 1 is synthesised by the liver in response to the growth hormone secreted by the pituitary gland. The circulating concentrations of insulin-like growth factor 1 and insulin-like growth factor 1 binding protein-3 are strongly related to diurnal growth hormone secretion. These reflect the mean daily growth hormone levels and seem to correlate well with physiological changes in growth hormone secretion.[3] Insulin-like growth factor 1 serves as the mediator of anabolic and growth-promoting effects of the pituitary growth hormone. It is involved in the metabolism of carbohydrates, fats and lipids; hence, alteration in its levels may be responsible for some of the metabolic dysfunction seen in patients with OSA.

Various hypotheses have been proposed to explain the metabolic dysfunction in OSA. One of them is the dysfunction of the somatotropic axis. The level of serum insulin-like growth factor 1 is lower in patients with OSA than in the normal population and obese individuals. The decreased activity of the growth hormone may predispose to the development of obesity with visceral adiposity. There is also reduced glucose uptake by the cells and increased hepatic production leading to insulin resistance, which is essential for the development of metabolic syndrome.[4–6] Indeed, insulin-like growth factor 1 alteration is associated with an increased prevalence of metabolic syndrome.[7]

In a meta-analysis, Chen *et al.* evaluated the impact of continuous positive airway pressure (CPAP) therapy on insulin-like growth factor 1 levels in patients with OSA.[1] The authors concluded that CPAP therapy was associated with a significant increase in insulin-like growth factor 1 levels. Zhu *et al.* evaluated the role of adenoidectomy and/or tonsillectomy on insulin-like growth factor 1 levels in children with OSA.[8] The authors found a significant increase in insulin-like growth factor 1 levels post-surgery in these children.

The effect of surgical intervention on insulin-like growth factor 1 levels has not been evaluated in adults with OSA. We hypothesised that surgical interventions may lead to an increase in serum insulin-like growth factor 1 levels and conducted a prospective study to evaluate this.

Materials and methods

A prospective study was conducted in the Department of Otorhinolaryngology and Head-Neck Surgery of a tertiary care hospital from January 2019 to December 2020. Ethical clearance was obtained from the Institute Ethics Committee for Postgraduate Research (IECPG-655/19.12.2018, RT-9/23.01.2019). The study included all consecutive adult patients (older than 18 years) with OSA undergoing surgical treatment in the department. Informed written consent was obtained from all patients. The patients who were non-compliant with CPAP, or in whom CPAP therapy had failed, were selected for surgical intervention.

Demographic details were collected for all patients. All patients underwent clinical examination to assess their height, weight and body mass index (BMI). Subjective evaluation was performed using the Epworth Sleepiness Scale.

Overnight polysomnography was performed for the diagnosis of OSA. Apnoea was defined as the complete cessation of airflow for at least 10 seconds, while hypopnoea was defined as either greater than 50 per cent airflow reduction for a minimum of 10 seconds or airflow reduction lower than 50 per cent with associated greater than 3 per cent oxygen desaturation or arousal. The Apnoea–Hypopnoea Index was considered as the total number of instances of apnoea and hypopnoea per hour of sleep. The patients with an Apnoea–Hypopnoea Index of 5 events per hour or more were considered to have OSA. The severity of OSA was classified as mild (Apnoea–Hypopnoea Index of 5–14 events per hour), moderate (Apnoea–Hypopnoea Index of 15–29 events per hour) or severe (Apnoea–Hypopnoea Index of 30 or more events per hour).

Blood samples were taken to assess serum insulin-like growth factor 1 levels in the pre-operative period. Serum was extracted using a centrifuge at 3000 revolutions per minute for 3 minutes. The serum samples were stored in the freezer at −18°C. Serum insulin-like growth factor 1 level was quantified by a chemiluminescence immunoassay technique (sandwich principle) using a Liaison insulin-like growth factor 1 kit and analyser provided by DiaSorin Biotechnology®.

The site of obstruction was determined using Müller's manoeuvre and ApneaGraph® AG 200. The patients underwent site-specific surgery to treat the obstruction, in the hospital.

All patients underwent overnight polysomnography, Epworth Sleepiness Scale evaluation and serum insulin-like growth factor 1 level measurement during the post-operative period and at three-month intervals after surgery. Surgical success was defined as a reduction in the Apnoea–Hypopnoea Index of more than 50 per cent and an Apnoea–Hypopnoea Index of fewer than 20 events per hour on polysomnography. The percentage decrease in Apnoea–Hypopnoea Index was calculated as: {(pre-operative Apnoea–Hypopnoea Index – post-operative Apnoea–Hypopnoea Index) / pre-operative Apnoea–Hypopnoea Index} × 100. The percentage increase in serum insulin-like growth factor 1 levels was calculated as: {(post-operative – pre-operative) / pre-operative value} × 100.

Statistical analysis

Descriptive statistics were used for the demographic data in the form of mean and median values. The pre-operative and post-operative Apnoea–Hypopnoea Index and serum insulin-like growth factor 1 levels were compared using the Wilcoxon signed rank test. A *p*-value of lower than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 20 (2011; IBM, Armonk, New York, USA).

Results

The study included 15 patients with OSA, with a mean age of 38 years (range, 19–57 years), who underwent surgical intervention during the study period. Eleven patients were male and four were female. The mean BMI was 26.8 kg/m^2 (range, 19.2–32.8 kg/m^2). Two patients had mild OSA, four had moderate OSA and nine had severe OSA. The surgical intervention was in the form of a combination of septoplasty, inferior turbinate reduction, tonsillectomy, adenoidectomy or uvulopalatopharyngoplasty, depending on the site of obstruction (Table 1).

The median Epworth Sleepiness Scale score was 18 pre-operatively and 11 post-operatively (Fig. 1). This difference

Table 1. Nature of surgical intervention in the study cases

Case number	Surgery
1	Septoplasty with bilateral ITR
2	Septoplasty with bilateral ITR & expansion pharyngoplasty
3	Septoplasty with bilateral ITR
4	Septoplasty with bilateral ITR with RFA
5	Adenotonsillectomy
6	Septoplasty with bilateral ITR
7	Septoplasty with bilateral ITR with tonsillectomy & expansion pharyngoplasty
8	Bilateral ITR
9	UPPP
10	Septoplasty with right ITR
11	Septoplasty with bilateral ITR
12	Adenotonsillectomy
13	Septoplasty with right ITR with bilateral tonsillectomy
14	Adenoidectomy with UPPP
15	Septoplasty with bilateral ITR & expansion pharyngoplasty

ITR = inferior turbinate reduction; RFA = radiofrequency ablation; UPPP = uvulopalatopharyngoplasty

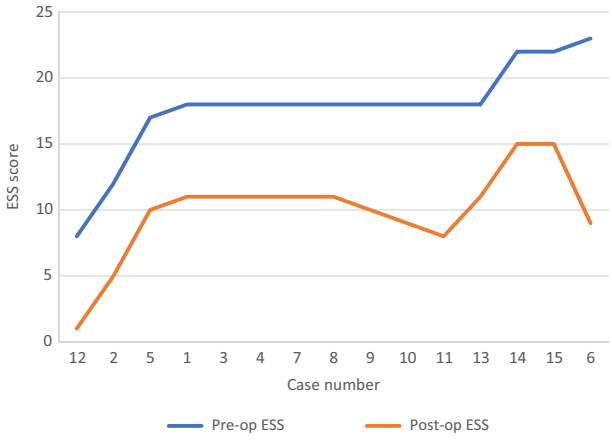

Figure 1. Pre-operative (pre-op) and post-operative (post-op) Epworth Sleepiness Scale (ESS) scores.

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was statistically significant ($p = 0.003$). The mean Apnoea–Hypopnoea Index using polysomnography was 53.7 events per hour (range, 12.6–88.2 events per hour) pre-operatively and 15.3 events per hour (range, 6–44 events per hour) at three months post-operatively. This difference was statistically significant ($p = 0.0001$). The mean serum insulin-like growth factor 1 level was 160.2 µg/l pre-operatively and 236.98 µg/l post-operatively. This difference was also statistically significant ($p = 0.005$). The individual values are depicted in Fig. 2.

Table 2 details the individual percentage changes in Apnoea–Hypopnoea Index and serum insulin-like growth factor 1 levels after surgical intervention. The correlation was not statistically significant (r = 0.19, $p = 0.47$). Surgical success was achieved in 13 of 15 patients as per the defined criteria. The median follow-up period was 14 months (range, 12–18 months). Patients 7 and 15 were followed up for 24 months as they did not have an increase in serum insulin-like growth factor 1 levels post-surgery. Case 7 had a similar Epworth Sleepiness Scale score as during the three months post-surgery. Case 15 had multi-level obstruction and opted for staged surgery. However, case 15 had gained significant weight post-surgery in the three months, which may have influenced serum insulin-like growth factor 1 levels. After two years, she had worsening of symptoms and increased daytime sleepiness, with an Epworth Sleepiness Scale score of 20. She has been counselled for weight reduction and second-stage surgery is planned.

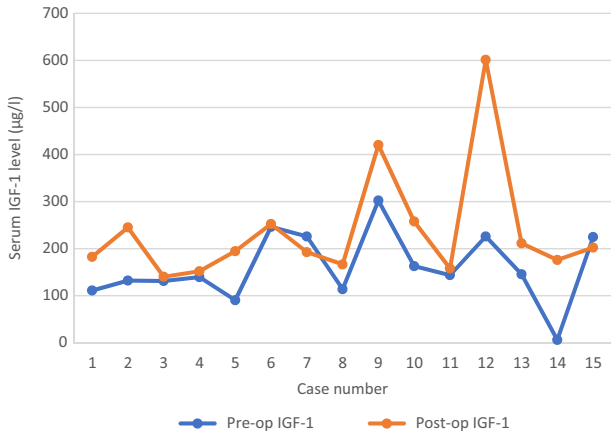

Figure 2. Pre-operative (pre-op) and post-operative (post-op) serum insulin-like growth factor 1 (IGF-1) levels.

Table 2. Percentage change in AHI and serum IGF-1 levels in OSA patients after surgical intervention

Case number	AHI on PSG (events per hour)		% decrease in AHI	% increase in serum IGF-1 levels
	Pre-op	Post-op		
7	82.5	13	84.2	−14.7
15	88.2	18	79.6	−9.9
6	80.8	16	80.2	2.5
3	16.5	7	57.6	6.9
4	88.2	18	79.6	9
11	80	22	72.5	9.9
9	87.2	12	86.2	39
13	67.8	13	80.8	45.2
8	52.6	18	65.8	46.1
10	31.6	12	62	58.2
1	60	8	86.7	64.2
2	56.4	44	22	85.3
5	35.7	6	83.2	114.9
12	12.6	9	28.6	166.1
14	41.5	18	56.6	2695.2

AHI = Apnoea–Hypopnoea Index; IGF-1 = insulin-like growth factor 1; OSA = obstructive sleep apnoea; PSG = polysomnography; pre-op = pre-operative; post-op = post-operative

Discussion

Obstructive sleep apnoea is associated with significantly low levels of serum insulin-like growth factor, which suggests dysfunction of the somatotropic axis in patients with OSA. Ursavas *et al.* demonstrated that the low circulating insulin-like growth factor 1 levels in patients with OSA were correlated with several polysomnography parameters, such as Apnoea–Hypopnoea Index, arousal index, average desaturation and oxygen desaturation index.[9] Grunstein *et al.* highlighted the role of hypoxaemia, which was a more important contributor than sleep fragmentation in the pathogenesis of this hormonal change.[10] Izumi *et al.* found that insulin-like growth factor 1 level in the moderate–severe OSA group was lower than in the no-OSA group (156.8 ± 54.3 µg/l *vs* 225.5 ± 80.5 µg/l; $p = 0.013$).[7] Also, insulin-like growth factor 1 level was negatively correlated with BMI, waist circumference, Apnoea–Hypopnoea Index and sleep duration with oxygen (O_2) saturation of less than 90 per cent, and positively correlated with average and minimum O_2 saturation ($p = 0.027$).

Gianotti *et al.* evaluated the impairment of the growth hormone and insulin-like growth factor 1 axis in patients with OSA.[11] The authors compared 13 male patients with OSA with 15 male obese patients without OSA and with 10 normal patients. The authors found that basal growth hormone and insulin-like growth factor 1 were significantly lower than normal in patients with OSA as compared with others. In addition, the increase in the response of insulin-like growth factor 1 to recombinant humanised growth hormone was significantly less in patients with OSA as compared with others. Hence, the authors concluded that there is an impaired secretion of growth hormone as well as decreased peripheral sensitivity to growth hormone in patients with OSA.

Low serum insulin-like growth factor 1 levels are associated with an increased risk of coronary artery disease.[12,13] A prospective study conducted by Juul *et al.* showed that healthy subjects in the low insulin-like growth factor 1 quartile had an adjusted relative risk of 1.94 (95 per cent confidence interval = 1.03–3.66) for ischaemic heart diseases compared with controls during the 15-year follow-up period.[12] A cross-sectional study covering 218 healthy subjects found that high fasting serum free insulin-like growth factor 1 levels were associated with a decreased presence of atherosclerotic plaques and coronary artery disease.[13] Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome.[14,15] These studies show that the correction of serum insulin-like growth factor 1 and the somatotropic axis in OSA may play a significant role in decreasing the systemic morbidities associated with OSA.

In this regard, multiple studies have evaluated the impact of CPAP therapy on serum insulin-like growth factor 1 levels. A meta-analysis was conducted by Chen *et al.* that included five

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observational studies and one randomised, controlled trial, with a total of 168 patients with OSA using CPAP therapy.[1] The results indicated that CPAP therapy was significantly associated with an increase in serum insulin-like growth factor 1 levels (standardised mean difference = −0.436, $p < 0.0001$).

In OSA patients, growth hormone and insulin-like growth factor 1 secretion are decreased because of a reduction in the amount of slow-wave sleep induced by sleep fragmentation. Hence, a treatment that decreases sleep fragmentation as well as overnight hypoxaemia is expected to increase serum insulin-like growth factor 1 levels. In our cohort of 15 patients with OSA, we found a statistically significant improvement in serum insulin-like growth factor 1 levels after surgical intervention. This implies that the benefit of surgical intervention on serum insulin-like growth factor 1 levels persists even after CPAP failure has occurred.

- Insulin-like growth factor 1 is involved in anabolic and growth-promoting effects of growth hormones
- Alteration in insulin-like growth factor 1 levels may be responsible for some metabolic dysfunction in obstructive sleep apnoea (OSA) patients
- Insulin-like growth factor 1 levels are lower in OSA patients
- In adults with OSA, surgical intervention leads to increased serum insulin-like growth factor 1 levels

To the best of our knowledge, ours is the first prospective study evaluating the change in serum insulin-like growth factor 1 levels in patients with OSA undergoing surgical treatment. We also found that the change in serum insulin-like growth factor 1 levels does not correlate directly with the change in Apnoea–Hypopnoea Index.

Our study does have some limitations. The study sample size is small. There is no concomitant assessment of other elements of the growth hormone and insulin-like growth factor 1 axis. We evaluated the change in serum insulin-like growth factor 1 levels at three months post-surgery; repeated follow-up tests are required to determine whether the impact persists in the long term. Further prospective large-scale randomised, controlled trials are needed to explore the precise impact of OSA treatment on insulin-like growth factor.

Conclusion

In adult patients with OSA for whom CPAP therapy has failed, site-specific surgical intervention to treat the obstruction leads to an increase in serum insulin-like growth factor 1 levels.

Competing interests. None declared.

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