

## SCIENTIFIC LETTERS

## Type 2 diabetes, risk of sleep apnea-hypopnea syndrome, and quality of life associated to sleep breathing disorders



### Diabetes tipo 2, riesgo de síndrome de apnea-hipopnea del sueño y calidad de vida asociada con los trastornos respiratorios del sueño

Our group has recently communicated how type 2 diabetes (T2D) and high levels of fasting plasma glucose (FPG) are independent risk factors for daytime sleepiness and sleep quality, suggesting the role of sleep questionnaires to evaluate the relationship between T2D and sleep breathing disorders.<sup>1</sup> We now provide additional results obtained through the administration of other two specific questionnaires in order to investigate the deleterious effect of T2D and the degree of glycemic control on the risk of having sleep apnea-hypopnea syndrome (SAHS) and quality of life. For this purpose, both questionnaires were administered to a total of 331 patients at the time of a regular visit to the outpatient diabetes unit from Arnau de Vilanova and Vall d'Hebron University Hospitals among February 2012 and December 2014: (i) the Berlin Questionnaire, to measure the risk of having sleep apnea, and (ii) the Quebec Sleep Questionnaire (QSQ) to assess health related quality of life in patients with sleep apnea.

Recruited patients were able to read and recognize the correct meaning of the questions, and also were older than 18 years, of Caucasian origin, and with known T2D for longer than 5 years. In addition, they do not report any nighttime hypoglycemia events or previous episodes of severe hypoglycemia, and a determination of FPG and glycated hemoglobin during the preceding months was available. Subjects with chronic lung illnesses, heart or stroke failure, use of sedatives or alcohol abuse, as well as shift workers, were excluded. Therefore, only data from 135 subjects with T2D were assessed. We designed a case-control study, and one control was selected for every three cases. Then 45 subjects without diabetes and matched to cases by age ( $59.0 \pm 12.0$  vs.  $60.9 \pm 12.6$ ;  $p=0.383$ ), gender (55% of women in each group), BMI ( $29.6 \pm 7.0$  vs.  $30.9 \pm 5.3$ ;  $p=0.192$ ), and smoking status were carefully chosen. In all cases, informed consent was obtained.

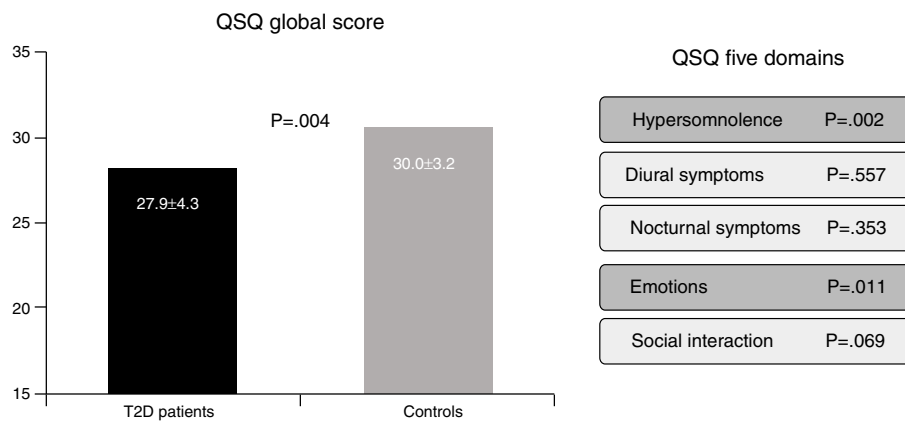
Treatment for T2D was assorted, and comprised metformine alone (20.7%), different oral treatment combinations (13.8%), metformin plus basal insulin (42.9%), and basal plus or basal bolus therapy (19.2%). Only four patients were under diet alone (2.9%), and none subject included in this study was treated with glucagon like peptide-1 analogs.

In the Berlin Questionnaire eleven items cover three domains related to risk of obstructive sleep apnea: (i) snoring and sleep-related symptoms, (ii) awake-time sleepiness and drowsiness, and (iii) hypertension and/or a BMI greater than  $30 \text{ kg/m}^2$ .<sup>2,3</sup> Responses are coded present or absent for each category, and the final score ranges from 0 to 3. Subjects who score  $\geq 2$  are classified as high risk, whereas subjects who score  $< 2$  are classified as low risk. Finally, the QSQ is a valid tool to assess, through 32 questions, how SAHS can be implicated in influencing five health related quality of life domains: hypersomnolence, diurnal symptoms, nocturnal symptoms, emotions and social interactions.<sup>4,5</sup> Lower scores reflect worse subjective sleep quality (Fig. 1).

The risk of SAHS, as defined by the Berlin questionnaire, was present in the 58.8% of the whole population, and this group of "high risk" subjects was associated with lower health related quality of life (QSQ:  $26.9 \pm 4.3$  vs.  $30.2 \pm 3.1$ ,  $p < 0.001$ ). In addition, a higher percentage of patients with T2D in comparison with control subjects were classified as high risk for SAHS (60.0% vs. 40%,  $p=0.015$ ). Furthermore, a lower health related quality of life was present in patients with T2D (QSQ global score:  $27.9 \pm 4.3$  vs.  $30.0 \pm 3.2$ ,  $p=0.004$ ), mainly in domains related with daily somnolence ( $5.6 \pm 1.1$  vs.  $6.1 \pm 0.7$ ,  $p=0.002$ ) and emotions ( $5.8 \pm 1.1$  vs.  $6.3 \pm 0.7$ ,  $p=0.011$ ). However, no differences in diurnal symptoms ( $6.3 \pm 0.8$  vs.  $6.4 \pm 0.8$ ,  $p=0.557$ ), nocturnal symptoms ( $5.1 \pm 1.2$  vs.  $5.3 \pm 1.2$ ,  $p=0.353$ ) nor social interaction ( $6.0 \pm 0.8$  vs.  $6.2 \pm 0.6$ ,  $p=0.069$ ) were detected.

In the univariate analysis, a significant correlation between FPG and glycated hemoglobin was found only with the domain related with emotions ( $r = -0.267$ ,  $p=0.001$  and  $r = -0.182$ ,  $p=0.039$ , respectively). A stepwise regression analysis showed that the presence of T2D (beta =  $-0.185$ ,  $p=0.001$ ) and BMI (beta =  $-0.198$ ,  $p=0.012$ ), but age or gender independently predicted the QSQ global score ( $R^2 = 0.081$ ).

Overall, our results confirm that patients with T2D are a population at risk of SAHS by using the Berlin Questionnaire



**Figure 1** Quebec Sleep Questionnaire (QSQ) global score and five health related quality of life domains according to the presence of type 2 diabetes.

and also provide evidence for implementing a more accurate screening for SAHS in patients with T2D. Some boundaries should be managed when evaluating the results of our work. The former, as a cross-sectional study we cannot draw a causal relationship between T2D and daytime consequences associated to sleep disturbances. However, the problem is clinically relevant since the prevalence of SAHS in subjects with T2D reaches the 40% to 86%, in comparison to the 2–4% in general population.<sup>6,7</sup> Second, we administered to patients with T2D a specific questionnaire to evaluate health-related quality of life in patients with SAHS. We assumed that a great percentage of patients with T2D will experience intermittent hypoxia and sleep disruption.<sup>8–10</sup> For these reason we found remarkable to investigate the association between perceived sleep and life quality in T2D patients. Third, more than half of subjects with T2D were under insulin therapy. Therefore, although no nighttime hypoglycemia episodes were reported, we cannot rule out the occurrence of unawareness events during the sleeping time that could influence our results.

In conclusion, T2D is associated with worse scores in administered questionnaires evaluating the risk of having SAHS, and quality of life associated to sleep breathing disorders. As questionnaires are simple and economic screening instruments that easily can be used and quickly scored in a demanding clinical practice, our findings highlight the importance of screening subjects with T2D for sleep problems, making an appointment to a sleep medicine specialist if appropriate, and suggesting sleep hygiene approaches as part of diabetes care.

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## Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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## References

- Lecube A, Sánchez E, Gómez-Peralta F, Abreu C, Valls J, Mestres O, et al. Global assessment of the impact of Type 2 diabetes on sleep through specific questionnaires: a case-control study. *PLoS One*. 2016;11:e015579.
- Netzer N, Stoohls R, Netzer C, Clark K, Strohl K. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999;131:485–91.
- Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. *Sleep Breath*. 2008;12:39–45.
- Lacasse Y, Godbout C, Series F. Health-related quality of life in obstructive sleep apnoea. *Eur Respir J*. 2002;19:499–503.
- Lacasse Y, Bureau MP, Sériès F. A new standardised and self-administered quality of life questionnaire specific to obstructive sleep apnoea. *Thorax*. 2004;59:494–9.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–5.
- Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. *J Appl Physiol*. 2005;99:1998–2007.
- Sampol G, Lecube A. Type 2 diabetes and the lung: a bidirectional relationship. *Endocrinol Nutr*. 2012;59:95–7.
- Lecube A, Sampol G, Hernández C, Romero O, Ciudin A, Simó R. Characterization of sleep breathing pattern in patients with type 2 diabetes: Sweet Sleep Study. *PLoS One*. 2015;10:e0119073.
- Lecube A, Ciudin A, Sampol G, Valladares S, Hernández C, Simó R. Effect of glycemic control on nocturnal arterial oxygen saturation: a case-control study in type 2 diabetes patients. *J Diabetes*. 2015;7:133–8.

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## Sellar collision tumor involving a primary fibrosarcoma: Clinical, morphological and immunohistochemical study of a case and review of the literature



### Tumor de colisión hipofisario con fibrosarcoma primario: estudio clínico, morfológico e inmunohistoquímico y revisión de la literatura

Collision tumors represent two morphologically different tumors attached to one another at a single anatomical site. While collision tumors have been reported in various organs, the concomitant presence of a pituitary adenoma with a second sellar lesion is an uncommon occurrence. When this does occur, radiation-induced sarcomas may coexist with a pituitary adenoma as result of previous radiation therapy aimed at treating the pituitary adenoma. Of these, fibrosarcomas are the most common, but rhabdomyosarcomas and chondrosarcomas have also been reported. If patients who have undergone previous radiation therapy are excluded from scrutiny, the presence of these two types of tumor in the same patient becomes even rarer.<sup>1</sup>

This report describes the case of a 41-year-old male, without personal or hereditary antecedents of relevance, who was referred to our Neuroendocrinology Unit presenting insidious discomfort and paresthesia in both hands that had developed over the previous 6 months. The patient also reported reduced visual acuity and partial loss of lateral vision over the previous year, accompanied by recurring headaches, which were relieved by analgesic administration.

Confrontation visual field tests found bitemporal hemianopsia. Magnetic resonance imaging (MRI) of the sellar region detected a pituitary mass of heterogeneous signal intensity but with well-defined borders, measuring 28 mm × 39 mm × 22 mm, pressing on the optic chiasm. Hormonal study found slight secondary panhypopituitarism due to tumoral compression (FT4: 0.79 ng/dl [0.90–1.70 ng/dl]; TSH: 2.09 μIU/ml [0.4–4 μIU/ml]; testosterone total 3.1 nmol/L [10–28 nmol/L]; FSH 5.2 mIU/ml [2–8 mIU/ml]; LH 3.2 mIU/ml [2–12 mIU/ml]; cortisol 49.8 ng/ml [50–250 ng/ml]; ACTH 12.8 pg/ml

[8.0–66.0 pg/ml]; IGF-1 89.5 ng/ml, with adequate suppression of GH levels after an oral glucose tolerance test). Diagnosis established a suspected pituitary macroadenoma.

Endoscopic endonasal transsphenoidal resection of the pituitary tumor was performed. Post-operative histopathologic analysis revealed a proliferation of fusiform cells in a lax stroma, with moderate atypia and a proliferation index (Ki-67) of around 10%; vimentin and SMA (smooth muscle actin) were immunophenotype-positive, while other markers showed negative (CD31, CD34, EMA, S100, PGFA, CKAE1/AE3). Islands with an epithelial aspect of pituitary origin were mixed in with the neoplasia, which expressed chromogranin and showed negative for all pituitary hormones (ACTH, GH, PRL, TSH, FSH and LH) (Fig. 1). Histopathological diagnosis identified a collision tumor composed of low-grade mesenchymal spindle cell neoplasm and a non-secreting pituitary adenoma. Histopathologic features and the presence of a small residual tumor observed in post-operative MRI justified fractionated stereotactic radiotherapy, which was clinically well tolerated by the patient. After surgery and radiotherapy, the patient showed a notable clinical improvement, particularly in visual acuity and remained neurologically asymptomatic. In subsequent follow-up examinations, images showed no sign of remains or recurrence of the pituitary tumor. The patient continues to attend the clinic for regular check-ups.

This case presents several notable characteristics. Firstly, the coexistence of two pituitary tumors of different histogenesis. The presence of a collision sellar lesion is a very uncommon event. To date, the concomitance of two different pathologies within the sella have mainly been described in individual case reports; very few surgical series have been published that describe specific combinations of sellar lesions such as a double pituitary adenoma,<sup>2,3</sup> a combination of an adenoma and Rathke's cleft cyst,<sup>4</sup> or a gangliocytoma associated with a pituitary adenoma.<sup>5</sup> In one of the very few case series published, Koutourousiou et al. reported an incidence of 1.46% of collision lesions among a group of 548 patients who underwent transsphenoidal surgery for pituitary adenoma resection. Among these pituitary adenomas with different features, the authors found one case of sarcoidosis, three cases of gangliocytoma, one schwannoma, one case of double pituitary adenoma, and two Rathke's cleft cysts.<sup>6</sup>

Secondly, the present case of a sellar collision tumor is of particular interest due to the discovery of a primary fibrosarcoma in a patient with no history of radiation exposure. This