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Original article

Intermittent hypoxia is an independent marker of poorer glycaemic control in patients with uncontrolled type 2 diabetes

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Abstract

Aim. – This study investigated the association between intermittent hypoxia and glycaemic control in patients with uncontrolled type 2 diabetes (T2D) not treated for sleep apnoea.

Methods. – This was a single-centre cross-sectional study of stable patients with T2D and $HbA_{1c} \geq 7\%$ (53 mmol/mol). Patients underwent overnight pulse oximetry and, if intermittent hypoxia—defined by a 4% oxyhaemoglobin desaturation index ≥ 15—was observed, respiratory polygraphy was performed. All participants completed the Pittsburgh Sleep Questionnaire and Hospital Anxiety and Depression Scale. The association between intermittent hypoxia and poorer glycaemic control (defined by an HbA_{1c} level above the median of 8.5%) was estimated by multivariate logistic regression analysis.

Results. – Out of 145 patients studied, 54 (37.2%) had intermittent hypoxia (with sleep apnoea confirmed in 53). Patients with intermittent hypoxia had 0.7% (7.7 mmol/mol) higher median HbA_{1c} levels than patients without intermittent hypoxia ($P = 0.001$). Intermittent hypoxia was associated with poorer glycaemic control after adjusting for obesity, age at onset and duration of diabetes, insulin requirement, sleep quality and depressive mood (OR: 2.31, 95% CI: 1.06–5.04, model adjusted for body mass index; OR: 2.46, 95% CI: 1.13–5.34, model adjusted for waist-to-height ratio).

Conclusion. – Intermittent hypoxia, a consequence of sleep apnoea, is frequent and has a strong independent association with poorer glycaemic control in patients with uncontrolled T2D.
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Keywords: Diabetes mellitus; Type 2; Glycosylated haemoglobin; Intermittent hypoxia; Sleep apnoea

1. Introduction

Type 2 diabetes (T2D) is associated with vascular complications, which can be reduced by adequate glycaemic control, defined by the American Diabetes Association (ADA) as a level of $HbA_{1c} < 7\%$ (53 mmol/mol) for most adults [1]. Research into the factors that influence glucose control is important for the development of strategies to reduce hyperglycaemia, as has been the case with interventions such as diet and exercise [2,3]. In recent years, other treatable factors have been investigated for their association with poor glycaemic control, including depression [4], and alterations of sleep quantity [5] and quality [6].

Obstructive sleep apnoea (OSA) is a treatable disorder characterized by repeated episodes of collapse of the pharynx during sleep, resulting in intermittent hypoxia (IH) and sleep fragmentation.

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OSA typically causes excessive daytime sleepiness, among other symptoms, and is associated with an increased risk of cardiovascular and all-cause mortality [7]. Upper airways obstruction during sleep can be reversed with the use of continuous positive airway pressure (CPAP), a treatment without significant side-effects that can improve patients' symptoms and quality of life [8]. Patients with OSA are likely to seek medical attention for symptoms when the condition causes significant sleep disturbances. However, most individuals with OSA do not have symptoms [9] and, by remaining undiagnosed, are chronically exposed to the hypoxia–reoxygenation sequence.

OSA is highly prevalent in patients with T2D [10–13]. Also, longitudinal studies have shown that OSA is associated with the development of insulin resistance [14] and T2D [15]. Although the mechanisms involved in this association have not been fully elucidated, experimental studies have shown that chronic IH may cause disturbances of glucose metabolism [16]. The potential effects of OSA on glucose control in patients with T2D is also unclear. The few studies that have addressed whether OSA is associated with poor glycaemic control have found conflicting results [17–19], and the prevalence of OSA in stable patients with uncontrolled T2D is unknown.

Based on these considerations, the present study aimed to investigate the potential association between IH and HbA_{1c} levels in patients with uncontrolled T2D.

2. Methods

2.1. Subjects

This was a single-centre cross-sectional study conducted as part of the recruitment phase for an interventional study addressing the effects of OSA treatment in patients with uncontrolled T2D (NCT01307566). The study was carried out at the General Hospital of Granollers, which serves a population of around 300,000 inhabitants.

Consecutive T2D patients, aged 18 to 70 years, who attended the hospital's diabetes clinic between March 2011 and June 2013 were considered eligible for the study if they had, despite a stable pharmacological treatment regimen for the past 3 months, serum HbA_{1c} levels $\geq$ 7% (53 mmol/mol) and agreed to participate. Exclusion criteria were ongoing treatment with CPAP, non-Caucasian ethnicity, serum haemoglobin levels < 10 g/dL in women or < 11 g/dL in men, haemoglobinopathy, iron deficiency, glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2, pregnancy, breastfeeding, blood transfusion in the last 3 months, usual sleep time < 6 h/night, unusual sleep schedules such as night or shift work, major psychiatric disorders, treatment with steroids, lung disease with chronic respiratory failure, heart failure and alcohol abuse.

The study received the approval of the local ethics committee, and all participants gave their written informed consent.

2.2. Biochemical and general data collection

Age, year of diagnosis of diabetes, presence of complications (retinopathy, nephropathy, neuropathy and coronary, cerebrovascular or peripheral vascular disease) and pharmacological treatment were collected. Multidrug antihypertensive therapy was defined as treatment with two or more antihypertensive drugs at full doses or, alternatively, three or more drugs with at least one at full dose.

The participants' current plasma levels of HbA_{1c} and lipid profile [total cholesterol, high-density lipoprotein (HDL) fraction of cholesterol, and triglycerides] were obtained from the digital clinical records database. Fulfilment of ADA goals for lipid control in patients with diabetes was evaluated [1]. Levels of HDL cholesterol $\leq$ 1.0 mmol/L in men or $\leq$ 1.3 mmol/L in women and levels of triglycerides $\geq$ 1.7 mmol/L were considered undesirable. If the morning urinary albumin-to-creatinine ratio (UACR) had been determined during the last year, this was also recorded; otherwise, urinalysis was repeated. UACR $\geq$ 30 mg/g was considered albuminuria.

2.3. Physical examination

Height, weight and waist circumference at the level halfway between the lower rib and iliac crest were measured, and body mass index (BMI) and waist-to-height ratio (WHR) were calculated. Central obesity was defined as a waist circumference $\geq$ 102 cm in men and $\geq$ 88 cm in women.

Systolic and diastolic blood pressure (BP) was measured with a digital sphygmomanometer after 5 min in a sitting position. The lower of two consecutive measurements was recorded. Off-target BP was defined as a systolic BP $\geq$ 140 mmHg or a diastolic BP $\geq$ 80 mmHg, based on ADA goals for BP [1].

2.4. Evaluation of sleep quality, somnolence and mood

Subjective sleep quality was assessed by the Pittsburgh Sleep Questionnaire, and poor sleep quality was defined as a global Pittsburgh Sleep Quality Index (GPSQI) score > 5. Subjective somnolence was evaluated by the Epworth Sleepiness Scale, which defines hypersomnolence as a score > 10. Mood was assessed by the Hospital Anxiety and Depression Scale, which sets abnormal scores for anxiety and depression at values $\geq$ 8.

2.5. Nocturnal pulse oximetry

Overnight home pulse oximetry was performed by all participants using a Pulsox 300i pulse oximeter, and the data were processed using Data Analysis Software DS-5 (Konica Minolta Sensing, Inc., Osaka, Japan). Recordings lasting < 4 h were discarded. The oxygen desaturation index (ODI) was calculated as the number of dips $\geq$ 4% in oxyhaemoglobin saturation (S_{O_2}) per hour of recording. The mean S_{O_2} and cumulative time with S_{O_2} < 90% (CT90) were also noted. The presence of significant IH was defined as an ODI $\geq$ 15, which determined the subsequent performance of respiratory polygraphy to confirm the suspected OSA.

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