Diabetes & Metabolic Syndrome: Clinical Research & Reviews 8 (2014) 36–44

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original article

Novel sexual dimorphisms of sleep apnea syndrome in diabetes

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ARTICLE INFO

Keywords:
Sleep apnea syndrome
Gender
T2DM
GAD65 antibodies
Microvascular
Ethnicity

ABSTRACT

Background: OSAS, a frequently neglected, yet frequent comorbidity in T2DM, is associated with obesity, metabolic syndrome and central fat. OSAS is better documented in males, and this study explored novel gender dimorphisms in T2DM.
Methods: Cross-sectional study: 815 T2DM (541 males; 274 females) classified into OSAS[−] and OSAS[+] were assessed for cardiometabolic risk factors, glucose homeostasis, micro/macroangiopathies, CV risk, autoimmune thyroid disease (AITD); and GAD65 antibodies.
Results: There was a gender dimorphism in glucose control (worse in females), apolipoprotein B100 (higher in females), with apoB100/apoA1 and log(TG)/HDL-C sexually dimorphic. There was also a marked gender dimorphism in GAD65 positivity, higher (+793%) in OSAS[+] females vs. males. There were clear sexual dimorphisms in macro-/microangioathies, regarding stroke, retinopathy and polyneuropathy. OSAS was not sexually dimorphic regarding age; education; and diabetes duration. There was a significant dimorphism in ethnicity. There were no gender-specific dimorphisms related to OSAS in anthropometrics, nor in hypertension, insulin sensitivity, or hyperbolic product loss rate.
Conclusion: We report a series of novel OSAS-related sexual dimorphisms, concerning GAD65 auto-antibodies; polyneuropathy; atherogenic dyslipidemia [all increased in females]; diabetic retinopathy; North-Caucasian ethnicity; metabolic control; and TIA/stroke prevalence [all lower in females]. These findings raise challenging questions regarding the reciprocal pathophysiology between obstructive sleep disorders and cardiometabolic risk in T2DM.

1. Background

Obstructive sleep apnea syndrome (OSAS) is a frequently overlooked comorbidity of type 2 diabetes mellitus (T2DM). The prevalence of OSAS closely parallels severe obesity and truncal (central) fat accretion. OSAS is also comorbid to the metabolic syndrome (MetS). Sleep fragmentation and intermittent hypoxaemia are associated with insulin resistance (IR), compensatory hyperinsulinemia and impaired β-cell function, all of which characterize the common form of T2DM. OSAS patients are not surprisingly exposed to higher cardiometabolic risk (CMR), due to the frequent coexistence of morbid obesity; high blood pressure (BP); IR; atherogenic dyslipidemia [the combined occurrence of high triglycerides (TG); and low levels of high-density lipoprotein cholesterol (HDL-C)], and hyperactivity of sympathetic nervous system [1–6].

Abbreviations: AD, atherogenic dyslipidemia; AITD, autoimmune thyroid disease; antiTG, anti-thyroglobulin antibodies; antiTPO, anti-thyroid peroxidase antibodies; apoA-I, apolipoprotein A-I; apoB100, apolipoprotein B100; B, β-cell function; BMI, body mass index; BP, blood pressure; B × S, hyperbolic product; CAD, coronary artery disease; CHD, coronary heart disease; CMR, cardiometabolic risk; CPAP, continuous positive airway pressure; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase type 4; DRP, diabetic retinopathy; eGFR, estimated glomerular filtration rate; ESS, Epworth's sleepiness scale; F, female; GAD, glutamic acid decarboxylase; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, Homeostasis Model Assessment; hsCRP, high-sensitivity C-reactive protein; IBT, incretin-based therapies; IR, insulin resistance; IS, insulin sensitivity; LDL-C, low-density lipoprotein cholesterol; LLD, lipid-lowering drug(s); LT, leisure-time; *log*[TG]/HDL-C, ratio of *log*[triglycerides] to HDL-C; M, male; MetS, metabolic syndrome; Non-HDL-C, non-high-density lipoprotein cholesterol; OAD, oral antidiabetic drug(s); OSAS, obstructive sleep apnoea syndrome; PAD, peripheral artery disease; RERA, respiratory effort-related arousals; S, sensitivity; SHBG, sex hormone-binding globulin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TG, triglycerides (triacylglycerols); TIA, transient ischemic attack; TSH, thyroid-stimulating hormone; UKPDS, United Kingdom Prospective Diabetes Study.

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http://dx.doi.org/10.1016/j.dsx.2013.08.002

OSAS carries a higher cardiovascular (CV) risk in nondiabetic populations [7–14]. Since OSAS predominantly affects the male gender, both in nondiabetic and diabetic populations, CMR could be sexually dimorphic beyond the issue of OSAS prevalence according to gender. OSAS presentation could differ between T2DM men and women, the latter being underdiagnosed as a result of lesser awareness and screening for OSAS, with lesser attention given to document the prevalence of this comorbidity and the corresponding CMR of T2DM females, a population in which CV protection provided by the female gender is abolished [15–35].

Previous studies on gender and OSAS focused on dimorphisms in upper airway anatomy or physiology; endocrine regulation; and sleep/polysomnography characteristics [15–17,36]. This study aimed at documenting the sexual dimorphism of OSAS in T2DM. We analyzed the bioanthropometric characteristics, glucose homeostasis determinants, CV risk factors and complications of T2DM patients investigated for the presence of OSAS (OSAS[+]), including standard/emerging CVD risk factors/markers; micro- and macrovascular complications; and absolute CV risk prediction.

2. Methods

This cross-sectional study included 815 adult patients with T2DM, attending the outpatient clinic of St-Luc Academic Hospital in Brussels (Belgium). Diabetes was defined according to the *Expert Committee on the Diagnosis and Classification of Diabetes Mellitus*.

OSAS was suspected in the presence of a positive auto-/heteroanamnesis for habitual snoring, witnessed apneas, and diurnal sleepiness, and/or a pathological daytime sleepiness score [5,11,37,38]. Patients were formally classified into OSAS[−] and OSAS[+] according to the current *International Classification of Sleep Disorders Diagnostic and Coding Manual* (ICSD-2), the diagnostic criteria of OSAS including: A, B, and D or C and D to satisfy the criteria: (A) at least one of the following: (*i*) patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia; (*ii*) patient awakens with breath holding, gasping, or choking; (*iii*) bedpartner reports loud snoring, breathing interruptions, or both during patient's sleep. (B) Polysomnography shows: (*i*) ≥5 scoreable respiratory events (i.e., apneas, hypopneas, or respiratory effort-related arousals (RERAs)) per hour of sleep; (*ii*) evidence of respiratory effort during all or a portion of each respiratory event; or C. Polysomnographic recording showing: (*i*) ≥15 scoreable respiratory events (i.e., apneas, hypopneas or RERAs) per hour of sleep; (*ii*) evidence of respiratory effort during all or a portion of each respiratory event. (D) The disorder is not better explained by another sleep disorder; medical or neurologic disorder; medication use; substance abuse or alcohol [5].

The following sociodemographic; lifestyle and clinical variables were recorded: age; gender; ethnicity; educational level; diabetes duration; family history (early-onset CVD; diabetes mellitus); smoking history; self-reported habitual ethanol intake; menopausal status; self-reported sleep duration; Epworth's daytime Sleepiness Scale (ESS; a >10 score suggestive of excessive daytime sleepiness); leisure-time (LT) exercise duration; LT spent watching screens (television; personal computer or other visual numeric media; as surrogate for LT sedentarity); highest weight ever; and age at maximal weight. Current medications were recorded; oral antidiabetic drugs (OAD), insulin, blood pressure (BP)-lowering drugs, lipid-lowering drugs, aspirin, allopurinol, anxiolytic or antidepressant drugs, and postmenopausal hormone-replacement therapy. Prescription and current use of nocturnal mechanical ventilation with continuous positive airway pressure (CPAP; ongoing or discontinued) were also assessed. In CPAP-treated, the analyzed data are those predating ventilation therapy.

Weight, height, body mass index (BMI) were measured, together with relative/total body fat, skeletal muscle mass and fat-mass index [fat mass (kg)/height^2 (m)] (BodyFat Analyzer, Omron BF 500). Neck circumference, waist circumferences, and conicity index were determined, as surrogates for central/upper body adiposity (*conicity index*: waist circumference (m)/$0.109\sqrt{}$[weight(kg)/height (m)]). Non-alcoholic fatty liver was considered in the presence of ultrasonic hyperreflectivity, in the absence of etiological factors associated with liver steatosis, including excess ethanol intake [11,12].

The presence of a metabolic syndrome (MetS) was defined by a score ≥3/5 for the following items: (*i*) impaired fasting glucose or diabetes; (*ii*) hypertension; (*iii*) enlarged waist; (*iv*) elevated fasting triglycerides (TG); and (*v*) decreased high-density lipoprotein (HDL) cholesterol, according to the *IDF-NHLBI-AHA-WHF-IAS-IASO* harmonized definition [39]. Computer-based Homeostasis Model Assessment (HOMA) of insulin sensitivity and β-cell function was previously detailed (http://www.dtu.ox.ac.uk). Values of insulin secretion (HOMA B; *normal value 100%*) were plotted as a function of insulin sensitivity (HOMA S; *normal value 100%*), defining a hyperbolic product area [B × S] (unit: %^{2}; *normal value 100%*, corresponding to 10^4%^{2}), which represents the true, underlying β-cell function. [B × S] loss rate (% year^{-1}) was obtained by dividing (100%-[B × S]) by each subjects' age at the time of HOMA modelling [40,41].

Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or current treatment with BP-lowering drug(s). Coronary artery disease (CAD) was inferred from medical history (myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography) and systematic review of all procedures, screening (exercise testing, echocardiography) or subclinical disease imaging data in patient's records. Peripheral arterial disease (PAD) was defined by a well-documented medical history of lower-limb(s) claudication and/or clinical or imaging evidence for ischaemic diabetic foot, angioplasty, stenting, revascularization surgery and/or significant lower-limb artery stenosis at Doppler ultrasonography and/or angiography.

The *UKPDS Risk Engine* equation provided absolute 10-year risk estimates for individuals in primary CV prevention regarding: (*i*) *any CAD* (non-fatal/fatal); (*ii*) *fatal CAD*; (*iii*) *any stroke* (non-fatal/fatal); and (*iv*) *fatal stroke*. These were computed from the following: known T2DM duration, age, gender, ethnicity, smoking status, presence vs. absence of atrial fibrillation, current HbA_{1c} level, systolic BP, total cholesterol and HDL-C [42].

The presence of a diabetic retinopathy was established from retinal examination by an experienced ophthalmologist and/or fluorescein angiography. The presence of a diabetic polyneuropathy was diagnosed by clinical examination (knee and ankle reflexes; Semmes–Weinstein monofilament test) and confirmed by lower-limbs electromyography. A diabetic nephropathy was considered in the presence of micro- or macroalbuminuria (urinary albumin excretion 30–299 (micro-) and ≥300 μg mg creatinine^{-1} 1.73 m^2 (macro-), from first-morning urine sample, after exclusion of non-diabetic causes of albuminuria or proteinuria). Estimated glomerular filtration rate (eGFR) was calculated using the *Modification of Diet in Renal Disease* equation [43]. Regardless of (micro)albuminuria, a diabetic nephropathy was also considered in the presence of reduced kidney function, i.e. eGFR <60 ml/min/1.73 m^2). As the latter may not *de facto* be attributable to DM, any eGFR-identified overt nephropathy was considered to represent diabetic nephropathy, unless a confirmed diagnosis of non-specific, non-diabetic nephropathy was made.

HbA_{1c}, fasting lipids (total cholesterol (C), HDL-C, TG; low-density lipoprotein cholesterol (LDL-C), computed using Friedewald's formula, and non-HDL-C (by subtracting HDL-C from total