Sleep and cardiometabolic disturbances in chronic medical illnesses

Thesis abstract

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INTRODUCTION

The pandemic of chronic diseases poses a number of inter- and transdisciplinary challenges for modern medicine. It is essential that comorbid conditions are recognized and managed in a timely fashion and according to evidence based guidelines in patients with chronic medical conditions. This would prevent the further impairment of the patient's quality of life and life expectancy. Eliminating the adverse effects of long-term drug treatments is of great importance in chronic care, as well.

According to the statement of the World Health Organization (WHO) cardiovascular diseases are at the top of the mortality and morbidity statistics in developed countries, and the same applies to metabolic and malignant chronic diseases, as well. Cardiovascular prevention is an outstanding task for public health. For effective prevention it is essential to understand the complex and sometimes bidirectional pathomechanisms that underly cardiovascular chronic comorbidities in metabolic conditions. Cardiovascular autonomic neuropathy and metabolic disturbances play a significant role in the development of cardiovascular disorders. It has been revealed during the last decade that sleep disturbances also have influence on cardiovascular outcomes in cardiometabolic diseases. Based on certain assumptions, sleep disorders can be an interface in the complicated processes between cardiovascular and metabolic disturbances.

Obstructive sleep apnea (OSA) is a form of sleep disordered breathing characterized by episodes of partial or complete closure of the upper airway during sleep with subsequent intermittent hypoxia and sympathetic nervous system activation. OSA is regarded as an independent risk factor for cardiovascular diseases and death. Periodic limb movement during sleep (PLMS) is characterized by periodic episodes of repetitive and highly stereotyped limb movements and also associated with increased cardiovascular morbidity, presumably due to the activating effects of limb movements on the sympathetic nervous system during sleep.

These sleep disorders are two to three times more common in patients with elevated cardiovascular risk, such as in patients with the metabolic syndrome (MetSyn) and after renal transplantation compared to the general population. The potential role of sleep disorders on the cardiovascular risk of these groups of patients has not been studied yet. The impaired carbohydrate metabolism, as the side effect of the corticosteroid pulse therapy used in multiple myeloma may also contribute to an increased cardiometabolic risk.

PURPOSE OF THE STUDY, HYPOTHESES

I. Obstructive sleep apnea and cardiometabolic risk in patients with the metabolic syndrome

The MetSyn is widespread among the adult population in developed nations, and it is associated with two-fold increased risk of cardiovascular events. The prevalence of OSA is very high (50-60 %) in patients with the MetSyn, and it is likely that there is a complex, positive feedback association between them. OSA is regarded as an independent risk factor for cardiovascular diseases. Male patients with OSA are at a higher risk to suffer from coronary heart disease and have increased cardiovascular risk than females with OSA. However it is unknown at present if the presence of OSA increases the cardiovascular risk of patients with MetSyn. The mediating factors between OSA, the MetSyn and cardiovascular diseases are also not exactly known. A potential factor could be the cardiovascular autonomic dysfunction indicated by impaired heart rate variability (HRV), which is a good predictor of cardiovascular mortality and has connection with both OSA and the MetSyn. HRV alterations associated with OSA were shown to be influenced by gender, as well.

The two aims of this cross-sectional study were:

1.) to examine the increase of coronary heart disease risk associated with the severity of OSA in patients with the metabolic syndrome.

I verified the following hypotheses in this study:

- There is an association between the presence of OSA and the higher 10-year coronary heart disease risk in patients with the Metsyn.
- Male patients with OSA have a higher increase in cardiovascular risk compared to female patients.
- The association of OSA and coronary heart disease risk is independent of the severity of MetSyn and the most important comorbidities.

2.) to examine whether comorbid OSA is related to more impaired heart rate variability in male patients with the MetSyn.

I verified the following hypotheses in this study:

- The severity of OSA is associated with more impaired heart rate variability in male patients with the MetSyn.
- This relationship is independent of the most important co-variables.

II. Periodic limb movement disorder during sleep and coronary heart disease risk in patients after renal transplantation

Cardiovascular risk is increased in patients with chronic kidney disease, and it remains elevated after renal transplantation, as well. It is three- to fivefold higher in kidney transplant patients compared to the general population. Moreover sleep disturbances (OSA, PLMS, insomnia) are also more common than in the normal population. It has been recently reported that PLMS is an independent predictor of cardiovascular mortality in dialyzed patients. In kidney transplant recipients no data has been published yet about the association of PLMS and cardiovascular risk.

Therefore our aim was to analyse the association between PLMS and coronary heart disease risk in this patient population.

***I verified the following hypotheses*:**

- More severe PLMS is related to higher coronary heart disease risk in kidney transplant patients.
- This association remains significant even after adjusting for the confounding factors.

III. The effect of dexamethasone pulse therapy on carbohydrate metabolism in multiple myeloma patients

A growing number of evidence suggests that there is a connection between hyperglycemia and cancer mortality. Multiple myeloma is a common hematologic malignancy. The risk of diabetes is doubled in patients with myeloma compared to the normal population. The reasons behind the increased risk of diabetes are unknown, but older age and the glucocorticoid therapy may play a significant role in that. The hyperglycemic effects of glucocorticoids have been described decades ago, but the degree and the dynamics of hyperglycemia are still not clear. There is no published data available on diurnal changes of hyperglycemia associated with high-dose dexamethasone therapy.

Therefore our aim was to compare the glucose metabolism and the characteristics of the continuous interstitial glucose curves during dexamethasone pulse therapy and a steroid therapy-free (control) period in a cross-over study. Glucose metabolism in the two study periods was analyzed separately in patients with and without known diabetes.

I verified the following hypotheses:

- Interstitial glucose values and its variability increase during the dexamethasone therapy compared to the control period.
- The afternoon, late afternoon glucose values are expected to be rise due to the dexamethasone therapy in both patients with and without known diabetes.

METHODS

Ethics

All the three study protocols were approved by the Regional and Institutional Committee of Sciences and Research Ethics of Semmelweis University. All patients received detailed written and verbal information regarding the goals and protocol of the study and written consent for participation was obtained.

I. Obstructive sleep apnea and cardiometabolic risk in patients with the metabolic syndrome

In this study we examined the association between 1.) **OSA and coronary heart disease risk** in patients with the metabolic syndrome and 2.) **OSA and the most important HRV parameters** in male patients with the metabolic syndrome.

Inclusion criteria for both studies

These are cross-sectional studies, in which potentially eligible male individuals with the MetSyn were recruited consecutively. Patients were between 18-80 years of age, who were regularly followed at the diabetes outpatient clinic of the 1st Department of Medicine, Semmelweis University Faculty of Medicine, Budapest. Participants were recruited between May 2008 and June 2010. Diagnosis of the MetSyn was based on the definition of the International Diabetes Federation (IDF) (2005) for Caucasian males: Elevated waist circumference: ≥ 94 cm plus any two of the following four factors: 1.) Elevated triglycerides: ≥ 1.7 mmol/L (150 mg/dL); 2.) Reduced high-density lipoprotein (HDL) -cholesterol: < 1.03 mmol/L (40 mg/dL); 3.) Elevated blood pressure: systolic ≥ 130 or diastolic ≥ 85 mm Hg, or specific treatment for these 1-3 impairments; 4.) Elevated fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL), or previously diagnosed type 2 diabetes.

Exclusion criteria for both studies

Patients were excluded if they: 1.) did not consent to participate; 2.) were previously diagnosed and treated with OSA; 3.) were non-compliant in antihypertensive and/or antihyperglicemic therapy; 4.) suffered from severe mental diseases; 5.) had angina pectoris, myocardial infarction or stroke within 3 month; 6.) had malignant tumorous diseases (life expectancy of less than one year); 7.) had pregnancy. One patient from the enrolled 103 had to be excluded due to technical failure of polysomnography.

Further excludion criteria for OSA and HRV study

Because of the small sample size and the OSA-associated gender differences of HRV, in the current study we did not analyze females from the enrolled 102 patients with successful polysomnography. In addition we excluded those, who 8.) had abnormal resting electrocardiogram (ECG); 9.) had documented cardiac arrhythmias such as atrial fibrillation, atrial flutter, premature atrial and ventricular ectopic beats, or moderate to severe congestive heart failure (New York Heart Association class III–IV). From the 67 studied males 8 patients were excluded due to the 8. and 9. exclusion criteria. Further 7 patients declined to participate in the 24-h ambulatory blood pressure- and HRV monitoring, and 17 patients had to be excluded due to a late noticed technical failure in the patient cable of the ECG. Finally 35 male patients with the MetSyn were included in the final analysis.

Data collection

At the time of the sleep study socio-demographic characteristics were recorded, physical examination was performed, waist circumference, weight and height were measured and body mass index (BMI) was calculated ($BMI=weight/height^2$). Blood samples were obtained (serum triglyceride, HDL-cholesterol, glucose, glycosylated hemoglobin) in the morning between 07:00 AM and 08:00 AM, following an overnight fast. Blood pressure was measured as recommended by American Heart Association: at least two readings were taken with calibrated digital sphygmomanometer on the upper arm in sitting position after about 5 minutes of relaxation. Details of medical history, co-morbidities and medication use were also

recorded. Severity of MetSyn was determined by the number of the fulfilled criteria of IDF definition. In case of our patients with the MetSyn the scores were 3, 4 or 5.

Sleep study, definition of OSA

All patients underwent an overnight sleep study. Recordings were done with SOMNOscreen PSG Tele system (SOMNOmedics GmBH, Germany, CE0494) consisting of 4-channel electroencephalography, electro-oculography, a flow sensor for nasal and oral breath flow, pulse-oximeter, a laryngeal microphone, a 3-channel electrocardiography, two stress-sensitive belts, each for the thorax and the abdomen, a positional sensor for determination of body movement, submental and tibial electromyography. Sleep stages, apneas, hypopnoeas and arousals were manually scored by two somnologists (A.V.L. and O.A.V.) using the standard recommended American Academy of Sleep Medicine (AASM) scoring criteria. OSA severity was defined by apnea-hypopnoea index (AHI), which is calculated as the number of apnea and hypopnoea episodes per total hours of sleep. Patients with OSA were grouped as having mild-moderate (AHI $\geq$5 and <30) or severe (AHI $\geq$30) OSA due to the small sample and clinical considerations.

Assessment of coronary heart disease risk

The ten-year coronary heart disease risk was estimated for all patients using the Framingham score (calculated with low-density lipoprotein (LDL) -cholesterol). The prediction is based on categorical values of patients' gender, age, serum LDL- and HDL-cholesterol concentrations, systolic and diastolic blood pressure, diabetes and smoking.

Assessment of HRV

A 24-hour ECG recording was obtained from each participant during usual daily activities within 3 months of the sleep study and strictly before commencing CPAP (continuous positive airway pressure) therapy. Resting ECG was recorded prior to HRV assessment. HRV was assessed by CardioTens-01 (Meditech Ltd, Budapest, Hungary) device that is a computer-operated ambulatory blood pressure and ECG monitor and complies with the requirements of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation protocols. It records all the RR intervals for 24 hours. Automatic filters were used to continuously restore baseline and to filter background

and muscle noise. Data were analyzed with certified Medibase software program Version 1.42 (Meditech Ltd, Budapest, Hungary). The recording was also edited using visual control. Manual corrections were made to omit ectopic beats, arrhythmic events and noise effects and only normal-to-normal RR intervals (NN intervals) were used for analysis. The ratio of normal beats to total number of beats was >90% for each recordings. The following most commonly used and clearly interpretable time and frequency domain measures were assessed from the HRV software according to the recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: standard deviation of NN intervals (SDNN), high-frequency power (HFP) and the ratio of the power at low- and high-frequencies (LF/HF ratio). To assess the diurnal HRV pattern we analyzed separately the night- (10:00 PM – 06:00 AM) and daytime (06:00 AM – 10:00 PM) periods, and the ratios of the night-time to daytime values (expressed in %).

Statistical methods

Statistical analyses will be undertaken using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL, USA) and statistical significance will be inferred at a 2-tailed $p<0.05$. Data were summarized using proportions, mean±standard deviation (SD) or median [interquartile range (IQR)] as appropriate. Baseline characteristics and HRV parameters were compared among the three OSA subgroups using Pearson's Chi square test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate. Bonferroni corrections were carried out when multiple comparisons were performed. The associations between several co-variables versus OSA severity or HRV were analyzed in bivariate regression analyses. Variables which were associated with AHI or HRV measures at a P level of <0.1 in the bivariate analyses, were included in the multivariate model as covariates. All non-normally distributed variables were transformed before linear regression analyses.

II. Periodic limb movement disorder during sleep and coronary heart disease risk in patients after renal transplantation

Inclusion criteria

For this study potentially eligible patients were selected from all prevalent adult renal transplanted patients (n=1214) who were followed regularly at Department of Transplantation and Surgery, Semmelweis University Faculty of Medicine, Budapest on 31 December 2006.

Exclusion criteria

Applying the exclusion criteria (1.) previous diagnosis of OSA and PLMS 2.) renal transplantation within 3 month; 3.) active and acute pulmonary disorder and acute infection; 4.) hospitalization within 1 month or surgery within 3 month) 1198 patients remained from all patients. And from this base population we randomly selected and approached 150 patients using the simple random sampling strategy offered by SPSS version 15.0. Of the 150 eligible patients 50 (33%) individuals declined to participate. Finally we studied 100 renal transplant recipients.

Data collection

Socio-demographic data, details of medical history such as the date of transplantation, the time elapsed since transplantation, the type and dose of the immunosuppressive therapy were collected at enrolment. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula. The following laboratory data were recorded: haemoglobin (Hb), C-reactive protein (CRP), serum creatinine, blood urea nitrogen (BUN), serum albumin, serum cholesterol, serum triglyceride, serum HDL and LDL-cholesterol and single pool Kt/V (as an indicator for pre-transplant dialysis) were extracted from the medical records. At the time of the sleep study physical examination was performed, anthropometrical data was recorded, blood pressure was measured and transplant physicians completed the modified Charlson Comorbidity Index.

Assessment of coronary heart disease risk and sleep study, definition of PLMS

You may find the description of the assessment of coronary heart disease risk and sleep study above. PLMS was defined by the following criteria: limb movement duration: 0.5–5 s; inter-movement interval: 5–90 s; and separation criteria for limb movements occurring in both legs: more than 5 s between onsets. At least four limb movements were included in one PLMS cycle. The periodic limb movement index (PLMI) was defined as the number of limb movements per hours during sleep. PLMS was defined with PLMI of 15 or more.

Statistical methods

Statistical analyses will be undertaken using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL, USA). Data were summarized using proportions, mean±standard deviation (SD) or median [interquartile range (IQR)] as appropriate. Continuous variables were analysed with the Student's t- or Mann-Whitney-U tests, as appropriate. For categorical variables Pearson's Chi-square tests were used. Multivariate linear regression model was built on bivariate analyses and theoretical considerations. The collinearity of the variables was examined. Variables with skewed distribution were transformed logarithmically to obtain normal distribution.

III. The effect of dexamethasone pulse therapy on carbohydrate metabolism in multiple myeloma patients

Inclusion and exclusion criteria

Participants were recruited consecutively at the haematology outpatient clinic of the 1st Department of Medicine, Semmelweis University Faculty of Medicine, Budapest, Hungary, 18-80 years of age, diagnosed with multiple myeloma and treated with thalidomide-dexamethasone (Thal/Dex) treatment combination. For multiple myeloma diagnosis the International Myeloma Working Group (IMWG) criteria was used. Patients who declined or were not able to participate were excluded.

Data collection, study periods, randomization

Sociodemographic data, details of medical history (especially diabetes risk factors) and resting ECG were recorded at enrolment. Patients received dexamethasone (Dex) treatment 4 weekly for 4 days (40 mg p.o. once a day in the morning between 07:00 and 09:00 h). Outcomes were investigated both during Dex treatment (treatment period) and between the Dex cycles (control period: 13±2 days after the last treatment). The following tests were carried out 1.) fasting laboratory tests: serum glucose, total, HDL-, LDL-cholesterol, triglyceride concentrations; 2.) anthropometrical data: body weight, height (body mass index (BMI) was calculated (BMI=weight/height^2), waist and hip circumference; 3.) blood pressure measurements three times in resting sitting position; 4.) oral glucose tolerance test (oGTT) in patients without known diabetes 5.) continuous glucose monitoring at least 48 h in all patients. Participants were randomly assigned to start the measurements during or between Dex cycles

to reduce any potential carry-over effect. All participants were advised to refrain from consuming any carbohydrate containing food or drink except those provided by the hospital during the study.

Oral glucose tolerance test

OGTT was performed after three days on normal diet (at least 150g carbohydrate per day) and physical activity, in the morning 8–14 hours fast prior to the test. Smoking is not allowed during the test. After fasting plasma sampling patients were instructed to drink 75g of glucose (or 82.5 g glucose monohydrate) in 250-300 ml water. Glucose levels were assessed at 12 min. Glucose tolerance is regarded to normal if fating plasma glucose $\leq$ 6 mmol/L and 2-h postload glucose <7,8 mmol/L. Fasting levels between 6.1 and 7.0 mmol/L and 2-h postload glucose <7,8 mmol/L indicate impaired fasting glycemia. Fasting levels under 7 mmol/L anf 2-h plasma glucose between 7.8 mmol/L and 11.1 mmol/L refer to impaired glucose tolerance. Levels above 11.1 mmol/L at 2 hours confirm a diagnosis of diabetes.

Continuous glucose monitoring

Interstitial glucose values were assessed by Continuous Glucose Monitoring System (Medtronic MiniMed CGMS® System Gold™, Northridge, CA, USA) from the 2nd day of the Dex treatment. The sensor of the CGMS device is a platinum electrode containing glucose oxidase enzyme. Glucose oxidation generates current signals which are recorded by the pager-sized device in every 10 s and averaged per 5 min that means 288 measurements carried out daily. The monitor needs to be calibrated by fingertip self-monitoring blood glucose four times a day.

Statistical analysis

Statistical analyses will be undertaken using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL, USA). Comparisons of baseline characteristics and CGMS data between study periods were done by paired sample Student's t-test, or related samples Wilcoxon signed rank test, as appropriate. For 48 h continuous glucose monitoring data mixed models were built using linear, quadratic, and cubic time terms to describe changes in interstitial glucose values. Known diabetes and treatment period was used as factors and all main effects and time interactions were entered into the first model. Individual terms were then removed from the model to reach the most parsimonious model with the lowest information criteria. Data were organised so that repeated measurements of the hourly mean interstitial glucose values (ie, person-examinations) were nested within participants and the non-independence of the

person-examinations (the same individuals contributed more than one person-examination in the dataset) was taken into account in estimating standard errors.

RESULTS

I. Obstructive sleep apnea and cardiometabolic risk in patients with the metabolic syndrome

1.) Association between OSA and coronary heart disease risk

102 patients with the MetSyn according to IDF definition were included in the final analysis. The mean age was 60 ± 11 (mean±SD) years, two thirds of the participants were male (n=67), and 80 % had diabetes. Largely they were obese, had hypertension, and 72 % of them suffered from at least mild OSA. Most of the clinical parameters (age, prevalence and types of diabetes, treatment intensity in hypertension and diabetes care) of enrolled males were similar to the parameters of enrolled females, although the severity of MetSyn (according to the number of the fulfilled IDF criteria – 4.2±0.7 vs. 3.8±1.0; P=0.024), and the prevalence (80 vs. 55%; p=0,001) and severity of OSA (indicated by AHI - 25[38] vs. 5[18] n/hours of sleep (median [interquartile range]) p=0.001)) were higher in males versus females.

The 10 year Framingham coronary heart disease risk increased both in severe (AHI ≥30; n=31) and mild-moderate OSA (AHI ≥5 és <3; n=24) groups compared to patients without OSA (AHI<5; n=12) (21 and 18% vs. 10%; p=0.019 and 0.033, respectively) in male patients with the MetSyn. We did not find significant differences between the OSA groups (n=16/14/5) in female patients with the MetSyn. The association between OSA and coronary heart disease risk remained significant (β=standardized regression coefficient = 0.267; p=0.030) after adjusting for severity of the MetSyn, duration of diabetes and Charlson comorbidity.

2.) Association between OSA and heart rate variability

In the current study we analyzed the HRV data of 35 males from the enrolled patients of the previous study. The mean (±SD) age of the participants was 57 (± 11) years, the mean (±SD) BMI was 33 (±6) kg/m^2. The sleep study detected OSA in 28 of the 35 participants (80%). Fourteen patients (40%) had severe, 6 (17%) and 8 (23%) had moderate and mild OSA, respectively, while 7 (20%) patients did not have OSA. Age and BMI were not different

between the OSA-groups. MetSyn parameters, the use of medications and most of the macrostructural sleep parameters were similar in the three subgroups; only the AHI and the minimum oxygen saturation were lower in both mild-moderate and severe OSA groups, as expected.

Comparing the most important HRV parameters and its diurnal pattern in the three OSA subgroups, we have found the following results. SDNN (reflecting the overall HRV) over the 24-h period was lower by 30 % in severe-OSA compared to non OSA group (102±28 vs. 144±23 ms; $P^{\text{severe OSA/non OSA}}$=0.008). In terms of diurnal variation of the overall heart rate variability, the night-time, daytime and night/day difference of SDNN values did not differ among the OSA-subgroups. The 24-hour HFP, reflecting the parasympathetic tone, was decreased both in mild-moderate and severe OSA group, but significant difference was found only in mild-moderate OSA group compared to non-OSA group (median [IQR]: 95 [87] vs. 420 [359] ms^2; $P^{\text{mild-moderate OSA-non OSA}}$=0.011). In severe OSA groups less increase was found in HFP values from day to night (decreased relative nocturnal vagal dominance) compared to non OSA group (149 [224] vs. 377 [350] %; $P^{\text{severe OSA/non OSA}}$=0.055). The 24-h LF/HF values, indicating the sympathetic modulation, were similar in the OSA subgroups. The diurnal changes of LF/HF were different for both mild-moderate and severe OSA group: higher night/day LF/HF were found than in non OSA group (89 [94] and 112 [77] vs. 46 [89] %,; $P^{\text{mild-moderate OSA/non OSA}}$=0.032 and $P^{\text{severe OSA/non OSA}}$=0.004, respectively), indicating increased nocturnal sympathetic dominance in the OSA groups.

From the studied HRV parameters 24-h SDNN and night/day LF/HF showed linear associations with AHI ($r_{\text{correlation coefficient}}$=-0.406; P=0.015 and r=0.487; P=0.003, respectively). This association between 24-h SDNN and AHI was not significant any more after the potential confounding factors, when age, duration of diabetes and the severity of MetSyn were added to the multivariate linear regression model (β=-0.225; p=0.188). On the contrary, the associations between daytime LF/HF and night/day LF/HF versus AHI were significant even after adjusting for the factors mentioned above (β= 0.377; p=0.023).

II. Periodic limb movement disorder during sleep and coronary heart disease risk in patients after renal transplantation

There were no significant differences regarding age and gender between participants (n=100) and those who declined (n=50) to participate. The basic characteristics (age, gender, eGFR, haemoglobin, serum albumin) of the 100 participating transplant patients were similar to the characteristics of the total population. The mean age was 51±13 years, the percentage of males was 57%, the prevalence of diabetes was 19% and smoking rate was 20%. 85% of transplant patients took corticosteroids, and 6% of them had at least one transplantation previously. The PLMS (PLMI> 15) frequency was found to be 27%. The two-thirds of the PLMS patients (n=16) had severe limb movement disorder (PLMI$\geq$25). The percentage of males and the microaurosal index were higher among patients with severe PLMS. No other difference was found in socio-demographic and sleep parameters between patients with and without severe PLMS.

A clear trend was observed between PLMI and coronary heart disease risk (Beta=0.157; p=0.090) in renal transplant recipients, after adjusting for gender, serum albumin, haemoglobin concentration, AHI and comorbidity.

III. The effect of dexamethasone pulse therapy on carbohydrate metabolism in multiple myeloma patients

Nine patients were enrolled (one was male). Mean (±SD) age was 69.0±6.7 years, BMI 27.3±4.3 kg/m^2. Two patients had known type 2 diabetes (1 and 15 years of duration, respectively). Mean myeloma duration was 2.9±2.5 years, one patient had stage III, the rest stage I disease.

Fasting plasma glucose were similar during the high-dose dexamethasone therapy and the control period (6.3±1.4 vs. 5.1±0.5 mmol/L; p=0,105), while the post-load glucose values were significantly higher (12.8±4.7 vs. 8.9 ± 3.2 mmol/L; P=0.024) during Dex treatment compared to the control period. Glucose tolerance status determined by the 75g OGTT worsened in 5 participants, while it did not improve in anyone (P=0.063) during Dex treatment compared to the control period (P=0.064). The mean (8.7 ± 4.8 vs. 5.4 ± 1.2 mmol/L; P=0.035) and the standard deviation (1.4 ± 0.5 vs. 0.9 ± 0.6 mmol/L; P=0.010) of interstitial glucose increased one and the half times compared to the values during the control period. The daily maximums occurred more often at late afternoon than during control days (81 vs. 39 %; P=0.002).

According to the mixed model analysis, hourly interstitial glucose values increased linearly by 0.03 [SE] [0.01] mmol/L per hour from 5.0 [0.4] mmol/L at midnight to 5.7 [0.4] mmol/L at 23:00 h in participants with no known diabetes during the control period. During dexamethasone treatment interstitial glucose values followed a cubic trajectory with increasing values from 04:00 h (5.3 [0.4] mmol/L) to 18:00 (7.3 [0.4] mmol/L). Between 18:00 and 22:00 h interstitial glucose values slowly decreased to 6.7 [0.4] mmol/L. While glucose values were significantly higher at midnight (by 0.8 [0.3] mmol/L) and between 12:00 and 22:00 h (all $P<0.05$), night-time and morning values (02:00 to 12:00 h) were similar during the dexamethasone and the control periods (all $P>0.05$). Known diabetes patients had similar interstitial glucose values to participants without known diabetes at midnight ($P>0.05$), however their glucose values increased and decreased following a quadratic curve during the day from 5.0 [0.4] mmol/L at midnight to 7.5 [0.5] mmol/L at 12:00 h. During dexamethasone treatment all glucose values were increased (by a minimum of 7.9 [0.3] mmol/L at 04:00 h to a maximum of 10.5 [1.7] mmol/L at 20:00 h) and followed a cubic trajectory from 13.6 [0.5] mmol/L at midnight to a peak value of 17.5 [0.5] mmol/L at 17:00 h. All participants showed increased interstitial glucose values in the afternoon (16:00-20:00 h) compared to the morning (06:00-10:00 h) and this increase exceeded 1 mmol/L in 7 of 9 participants.

CONCLUSIONS

New results of my work, and answers to the hypotheses:

- The presence and the severity of OSA are associated with higher cardiovascular risk in patients with the MetSyn. The severity of OSA and increased coronary heart disease risk are related to each other independently of MetSyn severity and comorbidities in male patients with the MetSyn, while in female patients this association was not proved.
- The severity of OSA is independently associated with impaired heart rate variability in male patients with the MetSyn.
- The severity of PLMS showed tight correlation with elevated coronary heart disease risk in renal transplant patients, remaining significant in a multivariate linear regression model.
- Elevated late afternoon interstitial glucose values were found in myeloma patients without known diabetes during dexamethasone therapy, while in

patients with known diabetes extreme increases of interstitial glucose developed and remained during the whole day.

Since cardiovascular morbidity is increased in patients with the metabolic syndrome despite of therapeutic attempts, it is essential to explore all potential modifiable risk factors to improve clinical outcomes. OSA, that commonly accompanies the MetSyn, is associated with increased cardiovascular risk in these patients, especially in males. Among the potential underlying pathophysiological mechanisms, OSA-associated impairment of heart rate variability may also play a role. Cardiovascular outcomes of the patients with the metabolic syndrome might be improved by the proper diagnosis and the effective therapy of OSA, but further studies are necessary to confirm this.

Despite the successful transplant, the cardiovascular risk remains high in kidney transplant recipients. PLMS, a common, often asymptomatic sleep disorder, could also contribute to the increased cardiovascular risk. According to one proposed mechanism, periodic limb movement during sleep is associated with arousals, blood pressure and heart rate bursts, which could contribute to the non-dipping phenomenon. Diagnosis (using polysomnography) and the treatment of PLMS might reduce cardiovascular risk of patients after renal transplantation, but further research is necessary to assess this hypothesis.

There is little published data available on the dynamics of dexamethasone pulse therapy induced hyperglycemia. We have demonstrated that patients without previously known diabetes had elevated interstitial glucose values late in the afternoon. Accordingly, the importance of blood glucose monitoring and the possible restriction of carbohydrate intake in the second half of the day need to be emphasized. In patients with pre-existing diabetes, regular glucose monitoring and additional insulin therapy is recommended due to the highly increased glucose values throughout the day.

SUMMARY

Inter-disciplinary effort is required to reduce cardiovascular morbidity and mortality associated with chronic diseases in developed countries. Based on the data of the general population, comorbid sleep disorders may contribute to the cardiovascular outcomes of patients with chronic disorders, although these associations are not well known yet. The side effects of treatments during chronic diseases may also increase the cardiovascular risk of the patients.

Obstructive sleep apnea (OSA), one of the most common sleep disorders, is associated with increased cardiovascular risk. Compared to the general population, the prevalence of OSA is much higher in patients with the metabolic syndrome. Based on our results, comorbid OSA could be associated with an increased estimated coronary heart disease risk and lower heart rate variability in patients with the metabolic syndrome. The most recent publications suggest that the presence of periodic limb movement during sleep (PLMS) also contributes to an elevated risk of cardiovascular diseases. In our cross-sectional study we found an independent relationship between the severity of PLMS and the increased estimated cardiovascular risk. We have also demonstrated that dexamethasone pulse therapy used in multiple myeloma mostly increases the late-afternoon and/or evening glucose values in non-diabetic patients, while patients with known diabetes had substantially increased values during the whole day.

Our studies point out the complex associations between sleep disorders, the cardiovascular and the metabolic system in various patient populations. The diagnosis and the adequate treatment of the sleep disorders, the associated cardiometabolic alterations and the side effects of drug therapy could improve the cardiovascular outcomes of patients with chronic conditions.

PUBLICATIONS OF APPLICANT

Publications related to thesis:

1. Veber O, Wilde A, Demeter J, Tamás G, Mucsi I, Tabák AG. (2014) The effect of steroid pulse therapy on carbohydrate metabolism in multiple myeloma patients: a randomized crossover observational clinical study. J Endocrinol Invest, DOI: 10.1007/s40618-013-0027-8, IF: 1,654
2. Veber O, Lendvai Z, Ronai KZ, Dunai A, Zoller R, Lindner AV, Turanyi CZ, Szocs JL, Keresztes K, Tabak AG, Novak M, Molnar MZ, Mucsi I. (2013) Obstructive Sleep Apnea and Heart Rate Variability in Male Patients with Metabolic Syndrome: Cross-Sectional Study. Metab Syndr Relat Disord, DOI: 10.1089/met.2013.0111, IF: 1,652
3. Lindner A, Fornadi K, Lazar AS, Czira ME, Dunai A, Zoller R, Veber O, Szentkiralyi A, Kiss Z, Toronyi E, Mucsi I, Novak M, Molnar MZ. (2012) Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure. J Sleep Res 21:297-307, IF: 3,361

Publications not related to thesis:

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